EAACI Guidelines on Allergen Immunotherapy: House Dust Mites driven Allergic Asthma

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Short title: EAACI Guidelines on AIT for Allergic Asthma

Key words:
allergen immunotherapy, allergy, asthma, asthma control, asthma exacerbations, GRADE, lung function, safety

Abbreviations
AD = atopic dermatitis/eczema
AEs = adverse events
AHR = airways hyperreactivity
AIT = allergen immunotherapy
AR = allergic rhinitis
ARIA = Allergic Rhinitis and its Impact on Asthma
EAACI = European Academy of Allergy and Clinical Immunology
GINA = Global Initiative for Asthma
GRADE = The Grading of Recommendations Assessment, Development and Evaluation
HCP = healthcare professional
HDM = house dust mites
ICS = inhaled corticosteroids
QoL = quality of life
RCT = randomised control trial
ROB = risk of bias
SLIT = sublingual allergen immunotherapy
SCIT = subcutaneous allergen immunotherapy
SmPC: Summary of product characteristics

ABSTRACT

Allergen immunotherapy (AIT) has been used to treat allergic disease for more than 100 years. AIT remains underused in allergic asthma where, both in adults and children, where treatment

still relies on the use of corticosteroids and bronchodilators, and other controllers recommended to achieve and maintain asthma control, prevent exacerbations, and improve quality of life. However, patients with allergic asthma not adequately controlled on available pharmacotherapy (including biologicals) present an unmet medical need.

The European Academy of Allergy and Clinical Immunology has developed a clinical practice guideline that aims to provide evidence-based recommendations for the use of AIT as an adjunct treatment for allergic asthma. This guideline has been developed by a multi-disciplinary expert working group using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. AIT for allergic asthma was evaluated per allergen and per route: subcutaneous (SCIT) and sublingual (SLIT), separate for drops and tablets and for children and adults. Recommendations are formulated only for house-dust mites (HDM) since for the other allergens there is insufficient evidence.

So far only AIT with HDM SLIT-tablet has demonstrated a robust effect in adults for critical end-points (exacerbations, asthma control and safety). Due to ease of administration at home it represents a highly convenient AIT treatment option as add-on treatment to regular therapy for adults with controlled or partially controlled asthma (conditional recommendation, moderate quality evidence). HDM SCIT and SLIT drops are also recommended for patients with controlled HDM-driven asthma as an add-on to regular asthma therapy to decrease symptoms and medication needs (conditional recommendation, low quality evidence).

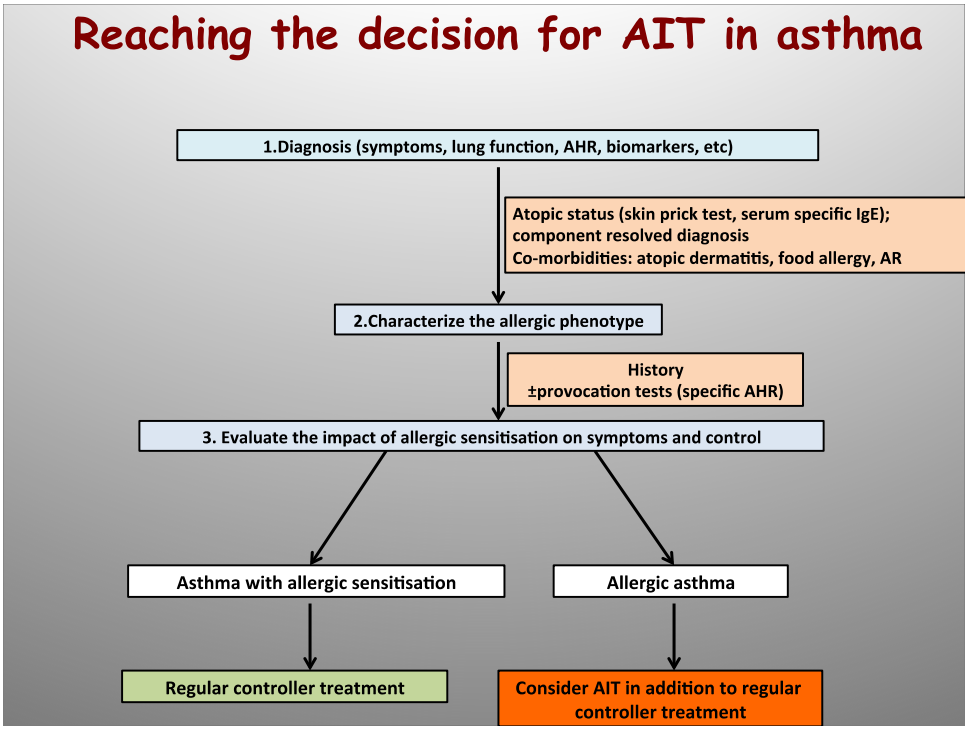
I. Introduction, background

Asthma represents a major health problem, affecting around 350 million people globally, with increasing prevalence and an overall projected increase to 400 million within the next 30 years [1-5]. It is responsible for considerable morbidity (hospitalisation and unscheduled healthcare) as well as direct and indirect costs (72.2 billion Euro annually in the European Union), and in some cases results in death. The major economic impact is due to indirect costs (absenteeism and decreased productivity at the workplace) [6-9].

Assessing the role of allergy in asthma is an important step in asthma evaluation since these patients might benefit from allergen immunotherapy (AIT) in addition to pharmacological asthma treatment (Figure 1 and Box 1). The proportion of asthmatic patients with allergies varies from 30 to 79% in children [10-12] and from 30 to 60% in adults [13-15], depending on the parameter evaluated (sensitisation or clinical allergy). Although type 2-driven inflammation is key in allergic asthma the pathophysiology might be complex with several endotypes [15-19]. Endotyping of asthma enables individualised management, including optimised allergen immunotherapy (AIT).

Figure 1. Allergic asthma diagnosis and management.

An accurate asthma diagnosis includes the proof of evidence and relevance of an allergic sensitisation to a specific allergen. The essential step is the confirmation of allergen exposure in the context of specific allergic sensitisation as the main driver of asthma symptoms and control by history with or without provocation (airway hyperreactivity (AHR)) tests.



Box 1: Nomenclature and Terms

Anaphylaxis = Severe, potentially life-threatening systemic hypersensitivity reaction characterised by being rapid in onset with life-threatening airway, breathing, or circulatory problems and usually, although not always, associated with skin and mucosal changes.

AIT = allergen immunotherapy = procedure inducing tolerance to a specific allergen by repetitive administration of an allergen

AE = adverse event = reaction triggered by AIT administration; can be local or systemic; systemic AE has four degrees of severity

Allergic asthma = typical symptoms of asthma (wheezing, cough, dyspnoea and chest tightness with evidence of reversibility) induced upon exposure to an allergen together with the proof of immunological sensitisation to that allergen

AHR= airway hyperreactivity = exaggerated response of the airways to specific (allergen) and nonspecific stimuli, which results in airway obstruction

AR = allergic rhinitis = inflammation of nasal mucosa induced upon exposure to an allergen together with the proof of immunological sensitisation to that allergen

Asthma control = evaluated in the past four weeks:

- **controlled asthma** has daytime symptoms less than 2/week, no night-time awakenings, reliever is needed for symptoms less than 2/week and there is no activity limitation due to asthma;
- **partially controlled asthma**: failure to meet 1-2 of these criteria;
- **uncontrolled asthma**: failure to meet 3-4 of these criteria (GINA 2018)

Asthma future risk = includes risk of exacerbations, fixed airway obstruction and adverse reactions to medications used to control asthma; lung function measurement is an important part of the assessment of future risk

LR = *local reaction* – inflammatory response confined to the contact site

Long-term AIT efficacy = Clinical benefit at least one year or longer after AIT cessation

QoL = quality of life = the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals (WHO). In studies usually assessed by a standardised validated questionnaire estimating the impact of symptoms on daily activities.

SCIT = *Subcutaneous immunotherapy* = subcutaneous, injectable route of allergen administration

Severe asthma = asthma that requires treatment with high dose inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming ''uncontrolled'' or that remains ''uncontrolled'' despite this therapy (ATS/ERS consensus statement); severe asthma status is valid only after correct diagnosis of asthma and after all comorbidities and adherence to treatment are properly addressed

SLIT = *Sublingual immunotherapy* = sublingual (drops or tablets) route of allergen administration

It is now recognised that house dust mites (HDM), such as *Dermatophagoides (D) pteronyssinus* or *D. farinae*, are the source of the most important indoor allergen associated with asthma worldwide and lead to the development of high-titre allergen-specific IgE. Substantial evidence associates allergic conditions such as asthma, allergic rhinitis (AR), atopic dermatitis (AD) with exposure to HDM or other indoor allergens [20-27]. Data from longitudinal investigations suggest that the development of sensitisation to HDM occurs before polysensitisation [28-30].

The rationale for AIT is the modification of the underlying allergic disease mechanisms triggering a sustained clinical effect based on allergen-specific tolerance, suppression of inflammation and multifaceted clinical improvement [31, 32].

AIT is currently administered in allergic asthma via the subcutaneous (SCIT) or sublingual (SLIT) route, the latest with two alternatives: drops and tablets. Other alternate routes are currently under exploration.

A limited number of studies have been specifically designed to evaluate the efficacy and safety of AIT in allergic asthma. Most data come from retrospective subgroup analyses from AIT trials in allergic rhinitis from which patients with concomitant asthma were analysed. No consensus has been achieved on the best clinical endpoints to evaluate the efficacy of AIT in asthma, with asthma control or exacerbations only recently being assessed as primary outcomes.

The Global Initiative for Asthma (GINA) 2018 report recommend assessment of two domains: immediate symptom control and decrease in future risk including exacerbations, progressive loss of lung function and/or fixed airflow limitation and medication side effects. Achieving control of asthma is the major goal currently proposed in asthma management where pharmacological and non-pharmacological strategies are adjusted in a continuous cycle that involves assessment, treatment and review [33].

According to GINA there is potential benefit of AIT in allergic asthma [33]. Even though GINA recognises that SCIT can be effective in patients with mild allergic asthma, only SLIT is recommended in more severe patients, as an alternative to improve asthma control. The current Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [34] give both SCIT and SLIT a conditional recommendation in allergic asthma due to moderate or low quality of evidence. AIT should be integrated in the general frame management of allergic asthma.

II. Scope and purpose of the guideline

This Guideline has been prepared by the European Academy of Allergy and Clinical Immunology's (EAACI) Taskforce on AIT for Allergic Asthma and is part of the EAACI Guidelines on Allergen Immunotherapy.

The aim of this Guideline is to provide evidence-based clinical recommendations for indications and contraindications to AIT as a treatment for allergic asthma and to identify gaps in knowledge and/or implementation, unmet needs and future perspectives.

The document does not address prevention of allergic asthma, which is covered in the EAACI Guidelines on Allergen Immunotherapy Chapter: Prevention of allergy [35] and the potential long-term benefit of AIT (after AIT cessation) that was not evaluated for allergic asthma due to lack of evidence.

The primary audience is clinical allergists, respiratory physicians and paediatricians and other healthcare professionals e.g. doctors, nurses, and pharmacists working across a range of primary, secondary and tertiary care settings managing patients with allergic asthma.

III. How to use these guidelines

1. Disclaimer

   The EAACI guidelines for AIT for allergic asthma are not intended to impose a standard of care. They provide the framework for rational decisions in the management of allergic asthma using AIT by clinicians, patients, third-party payers, institutional review committees and other stakeholders,

   Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting recommendations from these guidelines.

2. Interpretation of strong and conditional recommendations (table 1)

Table 1: Interpretation of GRADE recommendations

Implications	Strong recommendation	Conditional (weak) recommendation

For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognise that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations	Policy making will require substantial debate and involvement of various stakeholders. Documentation of appropriate (e.g. shared) decision-making processes can serve as performance measure.

IV. Methodology

A. Blended approach

1. GRADE assessment of the existing evidence [36,37].
2. Individual assessment of major RCTs and previous meta-analyses
3. Individual assessment of open studies, real-life studies, observational studies, surveys

B. Evaluation of the body of evidence

1. Per major allergen used for AIT for allergic asthma (HDM)
2. Per delivery route (SCIT, SLIT drops, SLIT tablets)
3. Separate for the paediatric and adult populations

C. Clinical questions and outcomes for allergic asthma

The following questions were identified for this guideline:

1. Should HDM SCIT versus no SCIT be used for treatment in paediatric patients with asthma?
2. Should HDM SCIT versus no SCIT be used for treatment in adult patients with asthma?
3. Should HDM SLIT drops versus no SLIT drops be used for treatment in paediatric patients with asthma?
4. Should HDM SLIT drops versus no SLIT drops be used for treatment in adult patients with asthma?
5. Should HDM SLIT tablets versus no SLIT tablets be used for treatment in paediatric patients with asthma?

6. Should HDM SLIT tablets versus no SLIT tablets be used for treatment in adult patients with asthma?

As per GRADE methodology we classified outcomes into critical, important and of low importance according to the classification of asthma outcomes in major RCT asthma trials as requested by the regulatory bodies (table 2)

Table 2: Classification of asthma and AIT related outcomes

Critical	Exacerbations	Number of exacerbations/patients
		Number of patients with at least 1 exacerbation
		Time to first asthma exacerbation upon ICS reduction/withdrawal
	Asthma control	ACQ score
		ACT
		"in-house" definitions
	Corticosteroid sparing effect	% decrease in ICS dose for asthma control
	Safety	Systemic reactions (WAO grading)
Important	Symptom score	"in-house" definitions
	Medication score	"in-house" definitions
	Quality of life	AQLQ
	Lung function	Small airways* (% or absolute improvement of MEF 25, MEF 50, MEF 75, FEF25-75)
		Allergen specific AHR (increase in PD20 allergen)**
	Safety	Local reactions (WAO grading)
Low importance	Lung function	Improvement in FEV_1* (% or absolute)
		Non-specific AHR (increase in PD20 methacholine, histamine)**

Comments:
*As most of AIT trials in asthma enrolled subjects with normal lung function the expected benefit on FEV_1 is of low importance; in comparison the effect on small airways is important given the systemic effects of AIT
** According to the biologic effect the impact on allergen specific AHR is expected to be significant (important outcome) compared to the effect on non-specific AHR (low importance outcome)

D. Evidence review

Evidence summaries for each question were prepared by a methodologist using GRADE Pro GDT (www.gradepro.org). The GRADE approach was specifically used for this guideline to bring it into line with other asthma guidelines [36]. The panel members reviewed the summaries of the evidence and provided feedback when appropriate. Evidence summaries are based on the systematic review conducted for this guideline [37]. In addition, an updated search strategy was performed separate per major allergens (HDM and grass) and delivery routes (SCIT, SLIT drops and SLIT tablets). The methods of the Cochrane Collaboration (www.handbook.cochrane.org) were adopted in order to assess the risk of bias at the outcome level using the Cochrane Collaboration's risk of bias tool [38]. The certainty of the supporting evidence (also called confidence in the estimates of effects or quality of evidence) was assessed by applying the GRADE framework for interventions [39,40]. The certainty of the evidence is categorized as high, moderate, low or very low based on consideration of risk of bias, directness of evidence, consistency and precision of the estimates, and other considerations. Low and very low certainty evidence indicates that the estimated

effects of interventions are very uncertain, and any further research is very likely to influence current recommendations. The GDT GRADEpro (www.gradepro.org) software was used to assess the certainty of evidence. Evidence on values and preferences and cost of AIT was considered as well.

E. Formulating the recommendations:

As per GRADE methodology a summary of judgments is provided for each recommendation. This includes evaluation of the importance of the problem, desirable and undesirable effects, certainty of evidence, values, balance of effects, resources required, certainty of evidence of required resources, cost-effectiveness, equity, acceptability and feasibility.

F. Document revision

Each member of the EAACI allergic asthma AIT guideline task force reviewed the final draft document and approved the document. The document was revised to incorporate the pertinent comments suggested by the external reviewers.

F. Stakeholders involvement

The EAACI task force on AIT for allergic asthma included members from a wide range of countries, professional backgrounds (allergy, paediatrics, internal medicine, pulmonology, basic and clinical immunology, primary care) and patient representatives. The whole allergy community, connected specialities and representatives of AIT vaccine manufactures were given the opportunity to review and comment on the draft guideline, and where appropriate revisions were made.

G. Conflict of interest
In accordance with EAACI policy, everyone who is intellectually involved in the project (i.e., considered for guideline authorship) will disclose all potential COI in writing at the beginning, middle, and end of the project.

H. Other considerations

Appropriate representation of all stakeholders, peer review by invited experts from a full range of organisations, countries, and professional backgrounds and editorial independence were ensured. Identifying gaps, barriers and facilitators was an important part of the process. All stakeholders had an opportunity to comment on the draft guideline publicised on the EAACI Website for a 3-week period (November 2018) to allow any omissions or errors in the evidence-base to be highlighted.
The development of AIT for Allergic Asthma was funded and supported by EAACI. The funder did not have any influence on the guideline production process, on its contents or on the decision to publish.
The review of this guideline is planned for 2022 but will be brought forward if there are any prior major developments in the evidence.

V. Evaluation of the body of evidence

1. GRADE assessment of the existing evidence

The summary of evidence (SOF) and evidence profiles are presented in annexe A (supplementary online material)

2. Individual assessment of major randomised trials and previous meta-analysis

A. HDM SCIT

Wang et al. investigated children and adults with HDM allergic asthma and reported exacerbations defined by the number of courses of oral corticosteroids required to restore asthma control. No significant difference was found between the SCIT and placebo groups. A difference in favour of SCIT for decreased exacerbation frequency and severity as well as overall symptoms measured with a self-evaluation questionnaire [41] was observed.

AIT with mite allergoid added to pharmacotherapy decreased the dose of ICS needed to maintain disease control in children with asthma [42].

The minimal ICS dose for asthma control was evaluated as the secondary outcome for HDM SCIT versus placebo in 146 adult patients with asthma. The only statistically significant ICS dose decrease was observed in the highest dose SCIT group. While average Asthma Control Test (ACT) scores increased in all dose groups, the only statistically significant change was recorded for the medium SCIT dose [43].

Three small size prospective DBPC trials assessed efficacy and safety of AIT in adults with allergic asthma [44-46]. In two trials allergen specific AHR evaluated with bronchial allergen provocation (BAP) was the main outcome, and symptom and medication scores were secondary outcomes. In the study of Basomba, clinical scores were the primary outcomes [46]. All trials reported a significant increase in BAP PD_{20} FEV_1 and improvement in symptom and medication scores. One trial reported significant improvement in quality of life as well (AQLQ) [44]. BAP was not influenced by a placebo effect.

In a study evaluating 42 children with HDM allergic asthma SCIT significantly improved their BAP PD_{20} FEV_1. Interestingly, BAP differentiated between responders (60.7%) and non-responders. Although all SCIT treated children reported subjective improvement in their symptoms, only the responders required less medication after SCIT [47].

B. HDM SLIT drops

In the systematic review of Normansell, a wide but varied reporting of largely un-validated asthma symptom and medication scores precluded meaningful meta-analysis. A general trend suggested SLIT benefit over placebo, but variation in scales made the results difficult to interpret [48]. Compalati identified 12 randomized, placebo-controlled studies that assessed HDM SLIT in patients with AR or asthma (382 patients with AR and 476 with allergic asthma) and reported significant benefit of SLIT for symptom scores and decrease in rescue drug use [49]. Kim et al. evaluated 7 studies for symptom score and 6 with reported medication score. The strength of evidence was high for improving asthma symptoms and moderate for reducing asthma medication [50]. However, most of the studies included small numbers of patients: Yukselen 11 SLIT vs 10 placebo, Lue 10 children on SLIT and 10 on placebo, Pajno 24 children/12 on SLIT, Hirsch 30 children, Tari 58 children with both rhinitis and asthma, Bahçeciler 15 children with rhinitis and asthma. The larger studies included, were by Niu et al. which included 97 children, 49 on SLIT and by Ippoliti et al. including 86 children, 47 on SLIT. The meta-analysis of Liao included 11 studies with a total of

454 children with asthma/rhinitis, ranging from 15 to 109 patients. A significant reduction in symptom score but not in medication score was found [51].

In the study of Wang, which included 484 asthmatic adults, 308 on SLIT, no benefit of SLIT for mild asthma was reported. A subsequent *post hoc* analysis by asthma severity revealed significant clinical benefits in actively treated subjects with moderate, persistent asthma at baseline, with better achievement of well-controlled asthma and totally controlled asthma, a higher percentage of patients with an ACQ score < 0.75 and a greater mean reduction in ICS use [52].

The incidence of exacerbations was similar between active and placebo groups and no effect was observed on lung function or on the quality of life (QoL) [53].

C. HDM SLIT tablets

Pham-Thi et al showed in 111 children, 55 on AIT, no additional benefit of SLIT tablets to improve lung function or decrease symptoms or medication use [54].

Clinical efficacy of SLIT-tablet in asthma has been evaluated in adults in three DBPC randomised trials [55, 57, 58]. Each trial had a different asthma related end-points: ICS dose decrease, average asthma symptom score and time to first asthma exacerbation upon ICS dose decrease.

The study of Mosbech et al [55] included subjects with controlled (ACQ <1) and partially controlled (ACQ 1-1.5) mild to moderate asthma and a history of HDM AR. The primary end-point was the lowest ICS dose needed to maintain asthma control. The daily ICS dose was decreased from 462 μg at baseline to 258 μg, compared to an 81 μg reduction observed for subjects receiving placebo. A *post hoc* analysis showed that subjects with a daily ICS dose of 400–800 μg and partly controlled asthma at randomisation experienced a significantly better treatment benefit in terms of ICS dose decrease, AQLQ and ACQ compared to the rest of the trial population [56].

One study evaluated HDM asthma as secondary endpoint in allergen exposure chamber. The doses of both twelve and six SQ-HDM for 24 weeks resulted in a statistically significant improvement vs. placebo in reported average adjusted symptom score during allergen challenge, with higher efficacy of the 12 SQ-HDM dose [57].

In the study of Virchow et al [58] the primary end point was time to first moderate or severe asthma exacerbation during a 6-month ICS reduction period. After 7–12 months of treatment with the HDM SLIT-tablet or placebo, daily ICS use was reduced to 50% for 3 months, followed by complete ICS withdrawal for 3 months for the remaining subjects who had not experienced an asthma exacerbation during the previous study phases. The trial included 834 adults with HDM not well-controlled allergic asthma (ACQ score of 1–1.5) and HDM AR, with a need for daily ICS treatment equivalent to budesonide 400–1200 micrograms. There was a significant risk reduction in the time to first asthma exacerbation versus placebo, as observed by hazard ratios of 0.69 and 0.66 for six SQ-HDM and 12 SQ-HDM, respectively. Treatment with 12 SQ-HDM resulted in a 34% risk reduction compared to placebo. However, the effect was driven by a decrease in moderate asthma exacerbations accounting for more than 90% of the exacerbations reported.

Combined clinical safety data from the SQ-HDM tablet trials indicate that it is well tolerated, and the observed safety and tolerability profile corresponds with the observed profile for other SLIT products.

As a result of these trials the HDM SLIT tablet is recommended for HDM-induced allergic asthma not well controlled by ICS and associated with mild to severe HDM-induced AR, when the patients' asthma status is carefully evaluated before the initiation of treatment. GINA 2018 recommends SLIT with HDM as an add-on therapy (Evidence B) in patients with exacerbations despite taking Step 2 therapy to decrease mild and moderate asthma exacerbations.

3. Individual assessment of open studies, real-life studies, observational studies, surveys

A recent prospective, multi-centre non-interventional study evaluated 220 patients (117 adults, 103 children) with HDM allergy receiving SCIT with allergoid preparation. Organ-specific key symptoms and the use of concomitant anti-allergic medication were assessed at baseline and after 12 and 24 months. 63% of adults and 64% of children had bronchial symptoms and they decreased significantly at 12 and 24 months in parallel with the use of symptomatic medication. During the 24-month study period, AEs were observed in 3.4% adults and in 6.8% children, all local AEs related to the study drug (erythema, swelling, and pain at the injection site). Serious AEs were reported in three adults and one child: a grade-II anaphylactic reaction (one adult) controlled by oral antihistamines (no hospitalisation) classified as "definitely," three others as not (2) or possibly (1) drug-related [59].

Several studies assessed the immunological and functional effects of HDM SCIT in adults with mild allergic asthma that provide indirect evidence on the efficacy of SCIT. Alvarez performed inhaled allergen challenges at the beginning (T0) and after 1 year of treatment (T12). The day before and 24 h after the allergen provocation, patients were challenged with methacholine (Mch) and blood and sputum samples were obtained. Dose-response curves to Mch were evaluated in terms of Mch-PD_{20}, slope (Mch-DRS) and level of plateau. Blood and sputum eosinophils and serum levels of eosinophil cationic protein (ECP) and intercellular adhesion molecule-1 (ICAM-1) were measured. At T12, previous to the allergen challenge, the active group showed higher values of both FEV_1 and Mch-PD20 and lower values of Mch-DRS. At T12, before the allergen challenge, serum ECP levels increased in the placebo group and blood eosinophils showed a trend towards lower numbers in the active one. The immediate response and the changes in Mch-DRS values, sputum eosinophils and serum ECP levels, following the allergen challenge were attenuated in the active group [60].

A sub-analysis by Trebuchon of 736 paediatric patients included in a previous retrospective, observational, multicentre study reported a significant decrease in symptoms and medications with HDM SLIT drops [61]. In a prospective, open, parallel-group, controlled study the efficacy of 3 year of SLIT in addition to pharmacotherapy (62 children) compared with pharmacotherapy alone (28 children), Ozdemir and colleagues reported significant decreases in the dose and duration of ICS treatment in the SLIT group with 52.4% of subjects able to discontinue ICS [62]. Di Rienzo reported in 60 children, 35 with SLIT versus standard treatment significant long-lasting effect on symptoms and medication use at the end of 4-5-year SLIT [63].

A health-economic, piggy-back analysis of SCIT was conducted based on a RCT that enrolled 65 children and adolescents with controlled allergic asthma. Both costs and cost-effectiveness of HDM SCIT were evaluated based on total medication costs, incremental medication costs and treatment effects (measured as lung function). A

bootstrap analysis was performed to validate the results. A steady decline in medication costs could be observed in the SCIT group one year after treatment start compared to the control group. This cost trend became statistically significant 3 years after SCIT started. The calculated potential savings in the SCIT group correlated with an improved lung function. The distribution of the bootstrap results revealed that the probability of SCIT having a superior effectiveness compared to the control group is around 90% [64].

HDM SLIT-tablet cost-effectiveness was evaluated in HDM allergic asthma uncontrolled by ICS. SLIT plus pharmacotherapy was estimated to generate 6.16 quality-adjusted life years (QALYs) per patient at a cost of €5658, compared with 5.50 QALYs at a cost of €2985 for placebo plus pharmacotherapy. This equated to an incremental cost of €2673, incremental QALYs of 0.66 and an incremental cost-effectiveness ratio (ICER) of €4041. The ICER was, therefore, substantially lower than the €40,000 willingness-to-pay threshold per QALY adopted for the analysis. Deterministic sensitivity analyses indicate the results are most sensitive to the utility score of SLIT during years 2 and 3 of treatment [65].

Another observational, retrospective, and multicentre study carried out in Spain on 419 adult patients diagnosed with HDM AR and/or asthma showed a significant decrease in all quantified resources after a single year of SCIT. Direct costs were decreased by 64% and indirect costs by 94%. Estimated savings for the public National Health System if using SCIT were 5.7 times the cost of immunotherapy [66].

VI. Recommendations

We present recommendations for AIT in allergic asthma only for HDM since it is the major allergen for allergic asthma and it has the most solid evidence.

HDM SCIT

Question: Is HDM SCIT recommended for children and adults with allergic asthma?

Recommendations

1. HDM SCIT is recommended for children and adults with controlled HDM – induced asthma as the add-on treatment to regular therapy to decrease symptoms and medication use

   Conditional recommendation, low quality evidence

2. HDM SCIT is recommended for adults with controlled HDM-induced asthma as the add-on treatment to regular therapy to decrease allergen specific AHR and to improve QoL.

   Conditional recommendation, low quality evidence

Values and preferences
This recommendation places a higher value on the safety of intervention with SCIT and a lower value on the benefit of decreasing symptom and medication use and decreasing allergen specific AHR

Remarks
1. There is significant heterogeneity of HDM SCIT studies: different preparations (extracts and modified forms like allergoid), different delivery systems like a

liposome-encapsulated allergen, protocols included DBPC or non-DBPC studies, different end-points, etc.

2. No single HDM SCIT study evaluated as its primary outcome the exacerbations of asthma or control because they were performed before GINA guidelines indicated these endpoints as primary goals for asthma management. However decreased symptoms and medication use can be considered as a surrogate for asthma control. The decrease in specific AHR might lead to less allergen-driven asthma exacerbations. Of note the number of studies that demonstrated a significant effect on the early and most importantly on the late phase of allergen induced bronchial reaction are very limited.
3. There is limited evidence on potential direct or indirect cost-saving effect by adding HDM SCIT to regular asthma treatment
4. Asthma control and lung function should be assessed regularly (preferably before each SCIT injection); a minimum 30 minutes observation at the office is recommended; SCIT should be administered by healthcare professionals (HCPs) with proper training in AIT, under proper conditions to manage severe bronchospasm or a systemic anaphylactic reaction

Table 3: Judgement of HDM SCIT in decreasing asthma symptoms and medication in children or in adults as add-on treatment to regular asthma therapy in controlled asthma

Importance	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Desirable effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable effects	Large	**Moderate**	Small	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
Certainty of evidence of resources required	**Very low**	Low	Moderate	High			No included studies
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	No included studies
Equity	Decreased	Probably decreased	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Feasibility	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Due to lack of evidence no recommendation can be provided for the use of HDM SCIT to decrease exacerbations, improve asthma control and lung function or to decrease non-specific AHR

HDM SLIT drops

Question: Are HDM SLIT drops preparations recommended in children or adults with allergic asthma?

Recommendations

1. HDM SLIT drops are recommended for children with controlled HDM allergic asthma as an add-on treatment to decrease symptoms and medication use

   Conditional recommendation, low quality evidence

Values and preferences

This recommendation places a high value on decreasing asthma symptoms and medication as well as on the ease of administration at home with potential of decreased resource utilisation

Remarks

1. Asthma control and lung function should be assessed regularly
2. The subgroup of patients with moderate asthma might have a better benefit but SLIT should be carefully monitored at a specialised centre
3. In children the potential benefits could include the corticosteroid sparing effect or the improvement in small airways disease obstruction

Table 4: Judgment of HDM SLIT (drops) in decreasing asthma symptoms and medication in children while added to regular asthma treatment for controlled asthma

Importance	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know

Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of resources required	Very low	Low	Moderate	High			**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Decreased	Probably decreased	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Due to lack of evidence no recommendation can be provided for the use of HDM SLIT drops to decrease exacerbations, improve asthma control and or to decrease specific and non-specific AHR

HDM SLIT tablets

Question: Are HDM SLIT tablets recommended for children and adults with allergic asthma?

Recommendations

HDM SLIT tablets are recommended for adults with controlled and partially controlled HDM-induced asthma as an add-on treatment to regular therapy to decrease exacerbations and to improve asthma control.

Conditional recommendation, moderate quality evidence

Values and preferences

This recommendation places the high value on decreasing asthma exacerbations and improving or maintaining asthma control while decreasing the inhaled corticosteroid use and on the ease of administration at home with potential decreased resource utilisation

Remarks

Asthma control and lung function should be assessed regularly; patients with partially controlled asthma or with a history of severe asthma exacerbations during the last 12 months should be carefully monitored in specialised centres

Table 5: Judgment of HDM SLIT tablets for decreasing asthma exacerbations and improving asthma control while added to regular asthma treatment

Importance	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Desirable effects	Trivial	Small	**Moderate**	Large		Varies	Don't know
Undesirable effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	Low	**Moderate**	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			No known undesirable outcomes
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
Certainty of evidence of resources required	Very low	Low	Moderate	High			**No included studies**
Cost-effectiveness	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	Favours the intervention	Varies	**No included studies**
Equity	Decreased	Probably decreased	**Probably no impact**	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Feasibility	No	Probably no	Probably yes	**Yes**		Varies	Don't know

Due to lack of evidence no recommendation can be provided for the use of HDM SLIT tablets for children or for adults to improve asthma lung function or quality of life or to decrease specific and non-specific AHR.

VII. Safety, precautions, contraindications

AIT is a safe adjunct treatment for controlled allergic asthma in children and adults. Most of the safety data are derived from AR studies enrolling patients with asthma and with FEV_1 > 70% predicted. Limited data for adverse events are available for patients only with allergic asthma or for patients with moderate or severe asthma.

Uncontrolled asthma is the major independent risk factor for both severe and fatal adverse reactions and is therefore a major contraindication for both SLIT and SCIT. Patients with severe but controlled asthma may be eligible for AIT in selected cases. Other contraindications and precautions are listed in Table 6 and 7. The Summary of Product Characteristics (SmPC) should also be checked for product specific contraindications that may differ between preparations.

Table 6 Contraindications and precautions for AIT in patients with allergic asthma		
	Remarks	Key reference
AIT is contraindicated in uncontrolled asthma	Due to safety concerns.	Epstein 2016 [67], Calderon 2017 [68], Rodriguez del Rio 2017 [69], Normansell 2015 [48], Pitsios 2015 [70], Cox 2011 [71], Lockey 2001 [72], Bernstein 2004 [73]
HDM SLIT may be considered with caution in partially controlled asthma	AIT might be beneficial especially in patients with partly controlled asthma with studies demonstrating improved asthma control and quality of life [55]. HDM SLIT in adults with asthma not well controlled by ICS (ACQ >1.5) or combination products did not increase the risk of major AEs [58]; however, FEV_1 less than 70% of predicted value or hospitalisation due to asthma within 3 months before randomization were key exclusion criteria.	Mosbech 2014 [55] Virchow 2016 [58]
AIT should not be initiated in pregnancy (but can be continued in pregnancy)	Safety of initiation and continuation of SCIT and SLIT during pregnancy analysed in 4 studies totalling 422 women demonstrated no increased incidence of prematurity, hypertension/proteinuria, congenital malformations or perinatal deaths during pregnancy and no foetal complications following systemic AEs while receiving AIT [74]	Pitsios 2015 [70] Oykhman 2015 [74].
AIT should not be initiated in patients with active autoimmune disorders (AID)	The CONSIT survey reported on patients undergoing AIT with AID. Major problems were infrequent [69]	Pitsios 2015 [70] Rodriguez del Rio 2017 [69]
AIT should not be initiated in patients with active malignancies		Pitsios 2015 [70]
AIT may be considered with caution in patients with controlled asthma under treatment with beta-blockers (BB) or ACE inhibitors (ACEI)	Only in specialised settings due to increased refractoriness to treatment of anaphylaxis with epinephrine. The CONSIT survey reported on patients undergoing AIT under BB or ACEI. Major problems were infrequent [69]	Rodriguez del Rio 2017 [69]
AIT is not recommended in patients with immune deficiencies, active infections and infestations and uncontrolled diseases like diabetes, inflammatory bowel dsease, gastric ulcer etc.	The CONSIT survey reported on patients with immune deficiencies or under immune suppressants receiving AIT. Major problems were infrequent [69]	Pitsios 2015 [70] Rodriguez del Rio 2017 [69]

Table 7: Recommendations for risk management of AIT in allergic asthma	
SCIT for allergic asthma	Signed informed consent Supervised administration by a healthcare professional (HCP) trained in the evaluation of patients with allergic conditions in a setting facilitating proper management of systemic reactions. Assessment of the patient's current health status before the administration of SCIT to determine whether there have been any recent changes in the patient's health that may require modifying or withholding treatment (e.g., uncontrolled/symptomatic asthma or exacerbation of allergy symptoms. Observation for at least 30 minutes after injection. Patient education for management and reporting late reactions.
Home based SLIT for allergic asthma	Signed informed consent Supervised initiation by a HCP trained in the evaluation of patients with allergic conditions in a setting facilitating proper management of systemic reactions Observation for at least 30 minutes after the first dose. Patient education and written instructions on how to recognize and manage adverse reactions and when to contact the HCP for adverse reactions, treatment gaps, or other events that may affect treatment (e.g. new medication or illness), how to manage missed doses and the situations when they should withhold SLIT. In cases of oral inflammation, such as mouth ulcers, lichen planus, stomatitis aphthosa or dental extractions, administration of SLIT should be temporarily discontinued until there is complete healing of the oral cavity. Dental flossing and gum hygiene can be associated with gum bleeding. It is recommended that the patient delay the administration of SLIT for a few hours after cessation of

	gum bleeding. It is suggested to resume SLIT 24 hours after a dental cleaning procedure. Recommendations for when to withhold SLIT dose to avoid potential situations when systemic allergic reactions may be more likely should also be provided. Regular follow-up care with a HCP trained in the evaluation of patients with allergic conditions to monitor safety [104, 105].

VIII. Special considerations

A. Provocation tests for selecting patients with allergic asthma for AIT or efficacy assessment

In AIT trials allergen provocation tests with mites are sometimes used as inclusion criteria or to measure the efficacy of AIT [47]. Based on the concept of "united airways" nasal and conjunctival allergen provocations can be performed under some circumstances, especially in high risk patients [75, 76]. The drawback of provocation testing is that it may not reflect natural exposure. Standardisation and availability for daily practice (including safety issues) are still to be refined [75].

B. Duration of AIT

Although there is evidence for efficacy after the first year of AIT [77,78], the current practice is three years of treatment for both SCIT and SLIT. For asthma there appears not to be an additional benefit for five years of therapy compared to three years [79,80].

C. Categories not covered by recommendations

This guideline formulated recommendations only for HDM. For all the other allergens including polysensitised and polyallergic patients, more data from studies with asthma as primary population are needed.

D. Biomarkers

To date, there are no biomarkers sufficiently predicting response to allergen immunotherapy that can be used to decide on initiation or cessation of AIT in allergic asthma.

E. Combination with biologics

Few trials have been performed with pre-administration or co-administration with omalizumab to either improve safety of SCIT up-dosing [81] or its efficacy [82,83]. Evidence is lacking to recommend co-administration of biologics and AIT for allergic asthma.

IX. Discussion

A. Unmet needs for AIT in asthma

Measuring outcomes

Most of the clinical trials of AIT in asthma evaluated clinically relevant parameters such as symptom and medication scores (with an emphasis on the corticosteroid sparing effect). Limited number of trials have used established asthma outcomes such as validated asthma control questionnaires (eg ACQ), lung function parameters besides FEV_1, or exacerbation rates (generally defined by requirement for oral corticosteroids) and showed negative or mixed results. There is a clear need for better designed studies of AIT in allergic asthma using harmonised and validated clinical outcomes and respiratory physicians should be included in the trial design.

Lung function (with a special focus on small airways), number of exacerbations or decreased need for controller medication should be considered as primary endpoints. Co-primary end-points such as corticosteroid- sparing and decrease of exacerbations should also be considered.

Methodological difficulties

Several challenges were encountered in developing this guideline.

Firstly, we faced different patient population (paediatrics vs adults), different allergens with significant variations in standardisation and potency and routes for AIT. Thus, a decision was made to formulate separate research questions for each patient population and AIT interventions according to biological plausibility and pharmacological effects.

Secondly, guideline panel members identified multiple outcomes to appreciate desirable and undesirable effects of AIT. Although, guideline panel members rated the importance of the outcomes, additional work needs to be continued to define patient-important outcomes for allergy patients.

Thirdly, multiple RCT reported findings using different approaches. For instance, while some RCTs reported findings in mean and standard deviation, other reported results as median and interquartile ranges. Ideally a meta-analysis should have access to individual patient data. To summarize all the body of evidence data were transformed using validated approaches and available data.

B. Barriers- facilitators, gaps and audit criteria

A subgroup of patients with asthma with related allergy may benefit most from AIT. The important prerequisite for a successful treatment is to select the group of patients responding to this cause-directed therapy. The major barriers and facilitators as well as audit criteria are presented in Table 8. Generally, a holistic approach to patients is required with joint commitment of various stakeholders to offer the patients optimal care [84,85,86].

Table 8: Barriers, facilitators and audit criteria for AIT in asthma

Recommendation: SCIT and SLIT can be recommended in children and adults with controlled allergic asthma where clinically relevant sensitization is proven

Barriers	Facilitators	Audit criteria	Resource implications
Insufficient evidence for allergens beside HDM	Large RCTs or real life studies	Updated AIT indications based on new evidence.	Joint efforts and harmonisation of different stakeholders
Insufficient evidence for the paediatric population	Large RCTs focused on paediatric population	Updated AIT indications based on new evidence.	Revised, realistic paediatric investigation plan (PIP)
Differences in the evidence for efficacy and safety between different AIT products due to product quality and standardisation and study designs	Better product standardization. Harmonisation of production process and study design. Head-to-head comparison between products.	Proportion of patients treated with products for which there is product specific evidence of efficacy and safety	Joint efforts and harmonisation of different stakeholders
The application of AIT in asthma is limited due to efficacy and safety concerns	Higher quality large phase 3 DBPC trials with validated outcome measures, patient centred outcomes and post-marketing data	Proportion of patients with allergic asthma successfully treated with AIT Proportion of patients treated with AIT for asthma who suffer from an adverse event	Joint efforts and harmonisation of different stakeholders

Definition of asthma as a lower airways condition, ignoring the frequent association with AR and/or AD and disease endotypes	Revised definition of asthma to include the one airways disease concept and asthma endotypes	Proportion of patients prescribed AIT for the one airways disease (AR and allergic asthma) Proportion of patients with allergic asthma treated according to their endotype	More research for better understanding of the disease mechanism and implementing a new disease taxonomy
Low awareness and knowledge of AIT potential by the general public and healthcare professionals outside allergy speciality, e.g. paediatricians, respiratory physicians, ENT, dermatology, primary care physicians,	Joint commitment and coordinated actions among academia, patient organisations, regulators, industry to find solutions that properly answer the health expectations of the allergic patients	Proportion of patients prescribed AIT for allergic asthma	Alignment between various stakeholders
Availability and affordability	Pharmacoeconomics studies and implementation of better reimbursement policies	Prescription and reimbursement rate	Change in priority perception of healthcare system
Improved patient selection	Better selection of responders using diagnostic tools for accurate identification of clinically relevant patient's sensitization profile	Proportion of patients who do not benefit from AIT	More research in disease mechanisms and diagnostic tools
Adherence to AIT	Educational programmes, more convenient AIT regimens	Proportion of patients who drop-out from AIT	Allocation of funds for education. Harmonisation between stakeholders
Outcomes reporting in individual RCTs	Randomised controlled trials reported findings as, for instance, median and interquartile rank.	Transform data using properly formulas and approaches	Harmonisation between researchers.

Table 9: Gaps in evidence for AIT in allergic asthma and plan to address

Gaps in evidence	Plan to address	Priority
Identifying and standardising relevant outcome measures (control, exacerbation)	Investigate and validate optimal outcome measures in adults and children.	High
Stratification of patients (driving allergen, adherence, severity)	Well-designed RCT, example for personalised medicine	High
Determining long-term efficacy of AIT in allergic asthma (after treatment cessation)	Well-designed RCT and real-life studies focusing on long-term efficacy of AIT in asthma	High
Cost-effectiveness of AIT in allergic asthma	Sectoral and generalised cost-effectiveness analysis Long-term perspective as AIT can modify the disease and thereby influence long-term cost	High
Alignment of studies with guidance from regulatory bodies.	Work in partnership with regulatory bodies to continually review trial methodology and outcomes.	High
Identification of clinically relevant biomarkers of sensitisation beyond SPT/IgE in order to select responders to AIT	Proof of concept studies evaluating patient selection based on provocation tests and/or biomarkers including components and other measures	High
Impact of allergic multi- morbidities (allergic rhinitis, atopic dermatitis, etc)	Studies evaluating the global effect of AIT on allergic multi- morbidities	High
Impact of multi-morbidity (autoimmunity, diabetes, obesity, smoking) and the impact of age (>60 and <5) and age of onset (early onset (childhood; < 18 years); adult onset (between 18 and 40 years) or late onset (> 40 years).	Well-designed RCT and real-life studies focusing on AIT in asthma with co-morbidities	Medium

Impact of severity of asthma including suboptimal lung function	Well-designed RCT and real-life studies focusing on AIT in asthma stratified by severity, including severe and uncontrolled asthma	High
Impact of observational period after AIT dose on safety	Well-designed RCT and real-life surveys assessing impact of different observational periods	Medium
Validation of different regimens (pre-seasonal, perennial), mode of up dosing, duration	RCTs and real-life studies testing different approaches in AIT in terms of duration, allergen, regimen	Medium

C. AIT positioning in the context of general asthma management

The administration of AIT does not interfere with or substitute for pharmacological asthma treatment as recommended by various asthma guidelines. It should be considered only when asthma is driven by allergy and is controlled providing the perspective of stepping-down controller treatment while decreasing the future risk of asthma exacerbations and drug-related adverse events. More safety data are required to support this approach. Another option that needs further exploration is whether adding AIT to pharmacological treatment in partially controlled asthma can facilitate achieving asthma control (Figure 2).

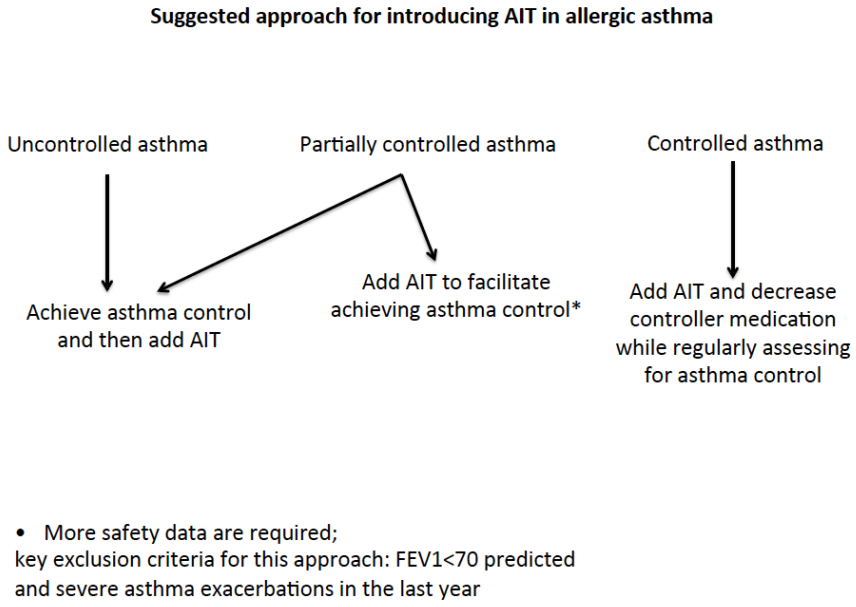


Figure 2: Integration of AIT in the stepwise management of allergic asthma based on asthma control. *AIT is recommended for controlled asthma with the expectation to be able to step-down controller treatment while maintain asthma control, given the fact, that an allergen is identified as relevant trigger. For partially controlled asthma adding AIT while stepping-up pharmacological treatment might facilitate achieving asthma control. Due to safety concerns AIT should not be used for uncontrolled asthma. Caution is necessary if treatment decisions are made in patients with severe controlled asthma*.

X. Key points and conclusion

The treatment of allergic asthma both in adults and children still relies on the use of corticosteroids and bronchodilators, and other controllers recommended to achieve and maintain asthma control and to prevent exacerbations, loss of lung function and improve quality of life. The addition of the first AIT product approved specifically for asthma, the HDM SLIT tablet, has fuelled optimism for the potential benefits of AIT in

some patients with allergic asthma, especially if appropriate responder phenotypes can be identified. However, in some countries, due to the lack of reimbursement for AIT, economic constraints may render these options inaccessible at present.

Conclusion. Key points

1. Patients with allergic asthma not adequately controlled on available pharmacotherapy present an unmet medical need.
2. AIT targets the underlying mechanisms in allergic asthma by modifying the immunological response to allergen towards tolerance.
3. AIT may add to the anti-inflammatory action of ICS to promote asthma control and decrease the risk of exacerbations.
4. Success of AIT in asthma is based on proper selection of patients with allergic sensitisation with symptoms driven by specific allergen exposure.
5. To date, only AIT with HDM SLIT-tablet has shown robust effect in adults on critical end-points (exacerbations, asthma control and safety). Due to ease of administration at home, SLIT-tablet represents a highly convenient AIT treatment option.
6. It is important to explore the short and long-term health economic effect by AIT in asthma due to its potential disease modifying effect

REFERENCES

1. Lai C, Beasley R, Crane J, Foliaki S, Shah J, Weiland S. Global variation in the prevalence and severity of asthma symptoms: phase three of the International Study of Asthma and Allergies in Childhood (ISAAC). *Thorax* 2009;**64**:476-483.
2. Ellwood P, El Sony A, El-Tigany M, Enarson D, Garay J, García-Marcos L, et al. The Global Asthma Report 2011. Paris, France: The International Union Against Tuberculosis and Lung Disease. In.; 2011.
3. Burney P, Perez-Padilla R. The global burden of chronic respiratory disease in adults. *Int J Tuberc Lung Dis* 2015;**19**:10-20.
4. Sembajwe G, Cifuentes M, Tak S, Kriebel D, Gore R, Punnett L. National income, self-reported wheezing and asthma diagnosis from the World Health Survey. *Eur Respir J* 2010;**35**:279-286.
5. Chinn S, Jarvis D, Burney P, Luczynska C, Ackermann-Liebrich U, Anto J, et al. Increase in diagnosed asthma but not in symptoms in the European Community Respiratory Health Survey. *Thorax* 2004;**59**:646-651.
6. Masoli M, Holt S, Beasley R. Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;**59**:469-478.
7. Bahadori K, Doyle-Waters M, Marra C, Lynd L, Alasaly K, Swiston J, et al. Economic burden of asthma: a systematic review. *BMC Pulm Med* 2009;**9**:24.
8. Sullivan P, Ghushchyan V, Campbell J, Globe G, Bender B, Magid D. Measuring the cost of poor asthma control and exacerbations. *J Asthma* 2017;**54**:24-31.
9. Tavakoli H, FitzGerald J, Chen W, Lynd L, Kendzerska T, Aaron S, et al. Ten-year trends in direct costs of asthma: a population-based study. *Allergy* 2017;**72;**291-299.
10. Tran T, Zeiger R, Peters S, Colice G, Newbold P, Goldman M, et al. Overlap of atopic, eosinophilic, and TH2-high asthma phenotypes in a general population with current asthma. *Ann Allergy Asthma Immunol* 2016;**116**:37-42.
11. Arabkhazaeli A, Vijverberg S, van Erp F, Raaijmakers J, van der Ent C, Maitland van der Zee. Characteristics and severity of asthma in children with and without atopic conditions: a cross-sectional study. *BMC Pediatr* 2015;**15**:172.
12. Ballardini N, Bergstrom A, Wahlgren C, van Hage M, Hallner E, Kull I, et al. IgE antibodies in relation to prevalence and multimorbidity of eczema, asthma, and rhinitis from birth to adolescence. *Allergy* 2016;**71**:342-349.
13. Gibson P. Inflammatory phenotypes in adult asthma: clinical applications *The Clinical Respiratory Journal* 2009;**3**:198-2016

14. Knudsen TB, Thomsen SF, Nolte H, Backer V. A population-based clinical study of allergic and non-allergic asthma. J Asthma 2009;46(1):91-4.
15. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? Thorax 1999;54(3):268-72
16. Lotvall J, Akdis C, Bacharier L, Bjermer L, Casale T, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;**127**:355-360
17. Agache I, Akdis C, Jutel M, Virchow J: Untangling asthma phenotypes and endotypes. *Allergy* 2012;**67**:835-846
18. Agache I, Akdis C. Endotypes of allergic diseases and asthma: An important step in building blocks for the future of precision medicine. *Allergol Int* 2016;**65**:243-252
19. Muraro A, Lemanske R, Hellings P, Akdis C, Bieber T, Casale T, et al. Precision medicine in patients with allergic diseases: Airway diseases and atopic dermatitis-PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2016;137:1347-1358
20. Smith JM, Disney ME, Williams JD, Goels ZA. Clinical significance of skin reactions to mite extracts in children with asthma. *Br Med J.* 1969;2(5659):723-6.
21. Soto-Quiros M, Avila L, Platts-Mills TA, Hunt JF, Erdman DD, Carper H, et al. High titers of IgE antibody to dust mite allergen and risk for wheezing among asthmatic children infected with rhinovirus. *J Allergy Clin Immunol.* 2012;129(6):1499-1505
22. Platts-Mills TA, Erwin EA, Heymann PW, Woodfolk JA. Pro: The evidence for a causal role of dust mites in asthma. *Am J Respir Crit Care Med*. 2009;180(2):109-13; discussion 120-1.
23. Sylvestre , Jégu J, Metz-Favre C, Barnig C, Qi S, de Blay Fl. Component-Based Allergen-Microarray: Der p 2 and Der f 2 Dust Mite Sensitization Is More Common in Patients With Severe Asthma. *J Investig Allergol Clin Immunol* 2016;26:141–143
24. Dzoro S, Mittermann I, Resch-Marat Y, Vrtala S, Nehr M, Hirschl AM, et al. House dust mites as potential carriers for IgE sensitization to bacterial antigens. *Allergy*. 2018;73(1):115-124
25. Banerjee S, Resch Y, Chen KW, Swoboda I, Focke-Tejkl M, Blatt K, et al. Der p 11 is a major allergen for house dust mite-allergic patients suffering from atopic dermatitis. *J Invest Dermatol.* 2015;135(1):102-109
26. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. *Allergy*. 2018;73(4):765-798
27. Miller JD. The Role of Dust Mites in Allergy. *Clin Rev Allergy Immunol.* 2018 Jun 23. doi: 10.1007/s12016-018-8693-0. [Epub ahead of print]
28. Posa D, Hofmaier S, Arasi S, Matricardi PM. Natural Evolution of IgE Responses to Mite Allergens and Relationship to Progression of Allergic Disease: a Review. *Curr Allergy Asthma Rep.* 2017;17(5):28
29. Posa D, Perna S, Resch Y, Lupinek C, Panetta V, Hofmaier S, et al. Evolution and predictive value of IgE responses toward a comprehensive panel of house dust mite allergens during the first 2 decades of life. *J Allergy Clin Immunol.* 2017; 139(2):541-549
30. Silvestri M, Rossi GA, Cozzani S, Pulvirenti G, Fasce L.l. Age-dependent tendency to become sensitized to other classes of aeroallergens in atopic asthmatic children. Ann Allergy Asthma Immunol 1999.;83(4):335-40
31. Jutel M, Agache I, Bonini S, Burks A, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;**136**:556-568
32. Jutel M, Agache I, Bonini S, Burks A, Calderon M, Canonica W, et al. International Consensus on Allergen Immunotherapy II: Mechanisms, standardization, and pharmacoeconomics. *J Allergy Clin Immunol* 2016;**137**:358-368
33. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2018. Available from: www.ginasthma.org
34. Bousquet J, Khaltaev N, Cruz A, Denburg J, Fokkens W, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**:8-160

35. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. *Pediatr Allergy Immunol.* 2017;28(8):728-745
36. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343-73
37. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. *Allergy*. 2017;72(12):1825-48
38. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-6.
39. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64(4):383-94
40. Higgins J, Altman D, Sterne J. Chapter 8: Assessing risk of bias in included studies. In: Higgins J, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions Version 510 (updated March 2011): The Cochrane Collaboration*. Available from www.handbook.cochrane.org.; 2011
41. Wang H, Lin X, Hao C, Zhang C, Sun B, Zheng J, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy* 2006;**61**:191-197
42. Zielen S, Kardos P, Madonini E: Steroid-sparing effects with allergen-specific immunotherapy in children with asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2010;**126**:942-949
43. Jutel M, Rudert M, Kreimendahl F, Kuna P. Efficacy and tolerability of a house dust mite allergoid in allergic bronchial asthma: a randomized dose-ranging trial. *Immunotherapy*. 2018 Aug 9. doi: 10.2217/imt-2018-0087. [Epub ahead of print]
44. Ameal A, Fernandez S, Miranda A, Carmona M, Rondon M, Reina E, Garcia-Gonzalez J. Double-blind and placebo-controlled study to assess efficacy and safety of a modified allergen extract of Dermatophagoides pteronyssinus in allergic asthma. *Allergy* 2005;**60**:1178-1183
45. Garcia-Robaina C, de la Torre F, Fernandez-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of Dermatophagoides pteronyssinus and Dermatophagoides farinae in a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2006;**118**:1026-1032
46. Basomba A, Tabar A, de Rojas D, Garcia B, Alamar R, Olaguibel J, et al. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. *J Allergy Clin Immunol* 2002;**109**:943-94
47. Rosewich M, Arendt S, El Moussaoui S, Schulze J, Schubert R, Zielen S. Bronchial allergen provocation: a useful method to assess the efficacy of specific immunotherapy in children. *Pediatr Allergy Immunol*. 2013;24(5):434-40
48. Normansell R, Kew K, Bridgman A. Sublingual immunotherapy for asthma. *Cochrane Database Syst Rev* 2015(8):CD011293
49. Compalati E, Passalacqua G, Bonini M, Canonica G. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy* 2009;**64**:1570-1579
50. Kim J, Lin S, Suarez-Cuervo C, Chelladurai Y, Ramanathan M, Segal J, et al. Allergen-specific immunotherapy for pediatric asthma and rhinoconjunctivitis: a systematic review. *Pediatrics* 2013;**131**:1155-1167
51. Liao W, Hu Q, Shen LL, Hu Y, Tao HF, Li HF, Fan WT. Sublingual Immunotherapy for Asthmatic Children Sensitized to House Dust Mite: A Meta-Analysis. *Medicine (Baltimore).* 2015;94(24):e701.
52. Wang L, Yin J, Fadel R, Montagut A, de Beaumont O, Devillier P. House dust mite sublingual immunotherapy is safe and appears to be effective in moderate, persistent asthma. *Allergy* 2014;**69**:1181-1188
53. Devillier P, Fadel R, de Beaumont O. House dust mite sublingual immunotherapy is safe in patients with mild-to-moderate, persistent asthma: a clinical trial. *Allergy* 2016;**71**:249-257

54. Pham-Thi N, Fadel R, Combebias A, Andre C. Assessment of sublingual immunotherapy efficacy in children with house dust mite-induced allergic asthma optimally controlled by pharmacologic treatment and mite-avoidance measures. *Pediatr Allergy Immunol* 2007;**18**:47-57
55. Mosbech H, Deckelmann R, de Blay F, Pastorello E, Trebas-Pietras E, Andres L, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *JACI* 2014;**34**:568-575
56. de Blay F, Kuna P, Prieto L, Ginko T, Seitzberg D, Riis B, Canonica GW. SQ HDM SLIT-tablet (ALK) in treatment of asthma--post hoc results from a randomised trial. Respir Med. 2014;108(10):1430-7
57. Nolte H, Maloney J, Nelson HS, et al. Onset and dose-related efficacy of house dust mite sublingual immunotherapy tablets in an environmental exposure chamber. *J Allergy Clin Immunol.* 2015;135:1494–1501
58. Virchow J, Backer V, Kuna P, Prieto L, Nolte H, Villesen H, Ljørring C, et al.Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. *JAMA* 2016;**315**:1715-1725
59. Mahler V, Klein C, Sager A, Zimmermann J. House dust mite-specific immunotherapy with two licensed vaccines: Outcome under clinical routine conditions. *Immun Inflamm Dis.* 2017;5(2):132-140
60. Alvarez MJ, Echechipía S, García B, Tabar AI, Martín S, Rico P, et al. Liposome-entrapped D. pteronyssinus vaccination in mild asthma patients: effect of 1-year double-blind, placebo-controlled trial on inflammation, bronchial hyperresponsiveness and immediate and late bronchial responses to the allergen. *Clin Exp Allergy.* 2002;32(11):1574-82.
61. Trebuchon F, Lhéritier-Barrand M, David M, Demoly P. Characteristics and management of sublingual allergen immunotherapy in children with allergic rhinitis and asthma induced by house dust mite allergens. *Clin Transl Allergy*. 2014;4:15
62. Ozdemir C, Yazi D, Gocmen I, Yesil O, Aydogan M, Semic-Jusufagic A, et al. Efficacy of long-term sublingual immunotherapy as an adjunct to pharmacotherapy in house dust mite-allergic children with asthma. *Pediatr Allergy Immunol*. 2007;18(6):508-15.
63. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, et al.Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy. 2003;33(2):206-10
64. Reinhold T, Ostermann J, Thum-Oltmer S, Brüggenjürgen Bl. Influence of subcutaneous specific immunotherapy on drug costs in children suffering from allergic asthma. *Clin Transl Allergy* 2013, 3:30
65. Hahn-Pedersen J, Worm M, Green W, Andreasen JN, Taylor M.Cost utility analysis of the SQ(®) HDM SLIT-tablet in house dust mite allergic asthma patients in a German setting. *Clin Transl Allergy.* 2016 ;6(1):35.
66. Garcia-Robaina JC, Polanco Sánchez C, Estella Pérez E. Savings associated with high-dose hypoallergenic house dust mite immunotherapy in rhinitis and/or asthma patients in Spain. *Clinicoecon Outcomes Res.* 2016;8:235-41
67. Epstein T, Liss G, Murphy-Berendts K, Bernstein D. Risk factors for fatal and nonfatal reactions to subcutaneous immunotherapy: National surveillance study on allergen immunotherapy (2008-2013). *Ann Allergy Asthma Immunol* 2016;**116**:354-359.
68. Calderon M, Vidal C, Rodriguez Del Rio P, Just J, Pfaar O, Tabar AI, et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. *Allergy* 2017;**72**:462-472.
69. Rodriguez Del Rio P, Vidal C, Just J, Tabar A, Sanchez-Machin I, Eberle P, et al. The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): A paediatric assessment. *Pediatr Allergy Immunol* 2017;**28**:60-70
70. Pitsios C, Bilò M, Gerth van Wijk R, Pfaar O, Sturm G, Rodriguez del Rio, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy* 2015;**70**:897-909.
71. Cox L, Esch R, Corbett M, Hankin C, Nelson M, Plunkett G. Allergen immunotherapy practice in the United States: guidelines, measures, and outcomes. *Ann Allergy Asthma Immunol* 2011;**107**:289-299.

72. Lockey R, Nicoara-Kasti G, Theodoropoulos D, Bukantz S. Systemic reactions and fatalities associated with allergen immunotherapy. *Ann Allergy Asthma Immunol* 2001;**87**:47-55.
73. Bernstein D, Wanner M, Borish L, Liss G, Immunotherapy Committee AAoAA, Immunology. Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *J Allergy Clin Immunol* 2004;**113**:1129-1136.
74. Oykhman P, Ellis A.: Allergen immunotherapy in pregnancy. *Allergy Asthma Clin Immunol* 2015;**10**:11-31
75. Agache I, Bilo M, Braunstahl G, Delgado L, Demoly P, Eigenmann P, et al. In vivo diagnosis of allergic diseases--allergen provocation tests. *Allergy* 2015;**70**:355-365.
76. Choi I, Kim S, Won J, Park M. Usefulness of House Dust Mite Nasal Provocation Test in Asthma. *Allergy Asthma Immunol Res* 2017;**9**:152-157
77. Yukselen A, Kendirli S, Yilmaz M, Altintas D, Karakoc G: Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. *Asian Pac J Allergy Immunol* 2013;**31**:233-241
78. Yukselen A, Kendirli S, Yilmaz M, Altintas D, Karakoc G. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int Arch Allergy Immunol* 2012;**157**:288-298
79. Stelmach I, Sobocińska A, Majak P, Smejda K, Jerzyńska J, Stelmach W. Comparison of the long-term efficacy of 3- and 5-year house dust mite allergen immunotherapy. *Ann Allergy Asthma Immunol* 2012; 109: 274-278
80. Arroabarren E, Tabar AI, Echechipía S, Cambra K, García BE, Alvarez-Puebla MJ. Optimal duration of allergen immunotherapy in children with dust mite respiratory allergy. *Pediatr Allergy Immunol.* 2015;26(1):34-41
81. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba G, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;**125**:383-389.
82. Kopp M, Hamelmann E, Zielen S, Kamin W, Bergmann K, Sieder C, et al. Combination of omalizumab and specific immunotherapy is superior to immunotherapy in patients with seasonal allergic rhinoconjunctivitis and co-morbid seasonal allergic asthma. *Clin Exp Allergy* 2009;**39**:271-279.
83. Kopp M, Hamelmann E, Bendiks M, Zielen S, Kamin W, Bergmann K, et al. Transient impact of omalizumab in pollen allergic patients undergoing specific immunotherapy. *Pediatr Allergy Immunol* 2013;**24**:427-433.
84. European Innovation Partnership on Active and Healthy Ageing, Mechanisms of the Development of Allergy, Global Alliance against Chronic Respiratory, Bousquet J, Addis A, Adcock I, Agache I, Agusti A, Alonso A, et al. Integrated care pathways for airway diseases (AIRWAYS-ICPs). *Eur Respir J* 2014;**44**:304-323.
85. Papadopoulos N, Agache I, Bavbek S, Bilo B, Braido F, Cardona V, et al. Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin Transl Allergy* 2012;**2**:21.
86. Jutel M, Angier L, Palkonen S, Ryan D, Sheikh A, Smith H, et al. Improving allergy management in the primary care network--a holistic approach. *Allergy* 2013;**68**:1362-