**EAACI Guideline on Allergen Immunotherapy - allergic asthma**

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**Short title:** EAACI Guidelines on AIT for allergic asthma

**Key words:**
AGREE II, allergen immunotherapy, allergic diseases, atopy, asthma, asthma control, asthma exacerbations, lung function

**Abbreviations**

AD = atopic dermatitis  
AEs = adverse events  
AGREE = Appraisal of Guidelines, Research and Evaluation  
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  
HCP = healthcare professional  
HDM = house dust mites  
ICS = inhaled corticosteroids  
QoL = quality of life  
RCT = randomised control trial  
SLIT = sublingual AIT  
SCIT = subcutaneous AIT  
SMS = symptom and medication score

**Abstract**

Allergen immunotherapy (AIT) has been used to treat allergic disease for more than 100 years. Despite broad evidence of clinical efficacy AIT remains underused in allergic asthma. Achieving a wider consensus is of utmost importance as AIT is the only treatment that can change the course of allergic disease by inducing allergen-specific immune tolerance.

The European Academy of Allergy and Clinical Immunology has developed clinical practice guidelines that aim to provide evidence-based recommendations for the use of AIT for allergic asthma. These guidelines have been developed by a multidisciplinary expert working group using the Appraisal of Guidelines, Research and Evaluation (AGREE) II framework. A systematic review of the current evidence has been used to generate evidence based clinical recommendations.

The key recommendation is that AIT delivered via subcutaneous or sublingual route is beneficial for mild and moderate allergic asthma, provided that asthma is adequately controlled by pharmacotherapy. AIT has a significant impact on asthma symptoms and medication, with a steroid sparing effect, improves disease specific and generic quality of life (QoL) and specific airways hyperreactivity (AHR). The influence on non-specific AHR and lung function is less prominent. No consistent effects on asthma control and exacerbations have been validated yet in clinical trials. AIT is a safe treatment for well-controlled allergic asthma in children and in adults.

AIT should be integrated in the general frame of asthma management aiming to reduce symptoms, improve QoL and minimize future risk by decreasing exacerbation rate, improving lung function (including AHR) and decreasing adverse reactions to medication (steroid and beta-2 agonists sparing effect). More effective
AIT strategies including novel preparations, adjuvants and alternate routes of administration are underway.

I. Introduction

Asthma represents a major health problem, affecting 300 million people around the globe, with increasing prevalence and an overall projected increase to 400 million within the next 30 years [1-5]. It is the main cause for hospitalization and paediatric emergency and causes significant burden by direct and indirect costs (72.2 billion Euro annual). The major economic impact is due to indirect costs (absenteeism and decreased productivity at the workplace) [6-9].

Asthma is a heterogeneous condition characterized by chronic airway inflammation. Recognisable clusters of visible properties (clinical, inflammatory, morphologic characteristics and unique responses to treatment) are described as asthma phenotypes. Phenotypes do not necessarily provide insight into the underlying pathogenetic mechanisms, which define the disease endotype [10-12]. Endotyping asthma enables its individualised management, including optimised AIT.

Allergic asthma has been extensively studied. It usually starts in childhood and is often accompanied or preceded by allergic rhinitis (AR), atopic dermatitis (AD) and/or food allergy [13]. The proportion of asthma that is allergic varies from 30 to 79% in children [14-16] and from 30 to 60% in adults [17, 18]. Children with severe preschool wheeze or severe asthma are usually allergic [19]. Although type 2-driven inflammation is key in allergic asthma the pathophysiology might be complex involving several endotypes [10, 20]. Assessing the role of atopy in asthma is an important step in asthma evaluation since these patients might benefit from AIT in addition to pharmacological asthma treatment (figure 1 and box 1).

Global Initiative for Asthma (GINA) 2017 guidelines recommend assessment of two domains: symptom control and future risk of adverse outcomes including exacerbations, poor lung function and/or fixed airflow limitation and medication side effects [21]. Achieving control is the major goal currently proposed in asthma management where pharmacological and non-pharmacological treatment is adjusted in a continuous cycle that involves assessment, treatment and review [21].

The rationale for AIT is the modification of the underlying atopic disease mechanisms triggering sustained clinical effect. Effective AIT induces multiple immune-mediated mechanisms, which are sequentially activated leading to allergen-specific tolerance, suppression of inflammation and multifaceted clinical improvement [22, 23]. AIT is currently provided in allergic asthma via the subcutaneous (SCIT) or sublingual (SLIT) route, with alternate routes being currently explored. A limited number of studies have been specifically designed to evaluate AIT in asthma. Most data come from indirect evidence from AIT trials that included patients with both AR and asthma. No consensus has been achieved on the best endpoints, with lung function or asthma exacerbations only occasionally being assessed as primary outcomes.

According to GINA 2017 the benefit of AIT in asthma in reducing symptoms and medication and AHR must be weighed against the risk of side effects, relative inconvenience and its cost incurred by prolonged course of treatment (level D evidence) [21]. GINA 2017 reports SLIT as a possible add-on option for adults with asthma and AR sensitised to house dust mites (HDM) with exacerbations despite low to high doses of inhaled corticosteroids (ICS) provided that their FEV1 is >70% predicted [21]. The current Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [24] 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 of asthma management.
Suggested approach to allergic asthma diagnosis

1. **Asthma diagnosis (symptoms, lung function, AHR)**
2. **Characterize the allergic phenotype**
   - Atopic status (skin prick test, serum specific IgE)
   - Co-morbidities: allergic rhinitis, atopic dermatitis, food allergy
3. **Evaluate the impact of allergic sensitisation on asthma symptoms and control**
   - History
   - Specific AHR
   - Asthma with allergic sensitisation
   - Allergic asthma
     - Regular asthma controller treatment
     - Consider AIT on top of regular asthma controller treatment

Figure 1: Allergic asthma diagnosis and management. Following an accurate asthma diagnosis the investigation of the allergic phenotype includes evidence of sensitisation to a specific allergen. The essential step is the confirmation of the allergic sensitisation as the main driver of asthma symptoms and control.

Box 1: Nomenclature and Terms

- **Anaphylaxis** = immediate systemic reaction often occurring within minutes and occasionally as long as an hour or longer after exposure to an allergen.
- **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 4 degrees of severity
- **Allergic asthma** = typical symptoms of asthma (wheezing, cough, dyspnea, chest tightness) induced upon exposure to an allergen together with the proof of immunological sensitization 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 sensitization to that allergen
- **Asthma control** = evaluated in the past 4 weeks; well controlled asthma has daytime symptoms less than 2/week, no nighttime awakenings, reliever is needed for symptoms less than 2/week and there is no activity limitation due to asthma; 1-2 of these criteria define partially controlled
asthma and 3-4 of these criteria define uncontrolled asthma (GINA 2017)

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

Build-up phase = period of AIT where increasing amounts of the allergen are given until a maintenance dose is reached

CSMS = combined symptom and medication score = standardized method that balances both symptoms and the need for anti-allergic medication in an equally weighted manner

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

Long-term AIT efficacy = Clinical benefit 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)

Monosensitised = IgE reactivity to one allergen or related allergenic molecules

Polysensitised = IgE reactivity to several non-related allergenic molecules; The discrimination between mono- and polysensitised is optimally achieved using purified natural or recombinant allergens

Polyallergic = situation when 2 or more sensitizing allergens are triggers of symptoms.

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 only after correct diagnosis of asthma and after all comorbidities and adherence to treatment are properly addressed

Short term AIT efficacy = Clinical benefit under AIT treatment

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

II. Scope, purpose and methodology

These Guidelines have been prepared by the European Academy of Allergy and Clinical Immunology’s (EAACI) Taskforce on AIT for Allergic Asthma and are part of the EAACI AIT Guidelines.

The aim of these Guidelines is to provide evidence-based clinical recommendations for indications and contraindications of AIT in allergic asthma and to identify gaps in knowledge and/or implementation, unmet needs and future perspectives. The primary audience is clinical allergists (specialists and subspecialists) and all healthcare professionals e.g. doctors, nurses, and pharmacists working across a range of primary, secondary and tertiary care settings managing patients with allergic asthma.

The EAACI Taskforce on AIT for Allergic Asthma included a wide range of countries, professional background (allergy, paediatrics, internal medicine, paediatric pulmonology, basic and clinical immunology, primary care) and patient representatives. The broad allergy community, connected specialities and representatives of AIT vaccine manufactures were given the opportunity to review and comment on the draft guidelines, and where appropriate revisions were made.
These guidelines have been developed using the Appraisal of Guidelines, Research and Evaluation (AGREE) II framework, a structured approach to guidelines for public health [25]. Agreement was reached on the search strategy, key questions formulating recommendations and the peer review process. A systematic review of the current evidence conducted by the methodologist [26], complemented by the results of other systematic reviews and by a narrative review for evidence not covered by the systematic review, have been used to generate evidence based clinical recommendations formulated by clinical academics. The key overarching question: “What is the effectiveness, safety and cost-effectiveness of AIT for allergic asthma in all populations?” was pursued through the formal review of the evidence [27]. The primary outcomes considered were effectiveness assessed by symptom score, medication score and symptom and medication score, both during treatment (short-term) and post discontinuation (i.e. at least one year after stop of treatment). Secondary outcomes were asthma control and exacerbations, QoL, lung function (including AHR), safety and health economic analysis from the perspective of the health system/payer (table S1).

We graded the strength and consistency of key findings from the critical appraisal of the evidence published so far to formulate evidence-based recommendations for clinical care using an approach that was adapted from that proposed by the Oxford Centre for Evidence-Based Medicine (Oxford Centre for Evidence-based Medicine) (Box 2). In brief the terms “strong, moderate and weak” were used for recommendations.

Appropriate representation all stakeholders, peer review by invited experts from a full range of organizations, countries, and professional backgrounds and editorial independence were insured. Identifying gaps, barriers and facilitators were an important part of the process. All stakeholders had an opportunity to comment on the draft guidelines publicised on the EAACI Website for a 3-week period 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 these guidelines is planned for 2020, as new evidence will probably emerge during the next 2-3 years.

**Box 2: Assigning levels of evidence and grade and strength recommendations**

<table>
<thead>
<tr>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong> = systematic reviews, meta-analysis, randomised controlled trials</td>
</tr>
<tr>
<td><strong>Level II</strong> = two-groups, non-randomised studies (eg cohort, case-control studies)</td>
</tr>
<tr>
<td><strong>Level III</strong> = one group, non-randomised (eg before and after, pre test and post test)</td>
</tr>
<tr>
<td><strong>Level IV</strong> = descriptive studies that include analysis of outcomes (single-subject design, case-series)</td>
</tr>
<tr>
<td><strong>Level V</strong> = case-reports and expert opinion that include narrative literature, reviews and consensus statements</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grades of recommendation</th>
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<tbody>
<tr>
<td><strong>Grade A</strong> = consistent level I studies</td>
</tr>
<tr>
<td><strong>Grade B</strong> = consistent level II or III studies or extrapolations from level I studies</td>
</tr>
<tr>
<td><strong>Grade C</strong> = level IV studies or extrapolations from levels II or III studies</td>
</tr>
<tr>
<td><strong>Grade D</strong> = level V evidence or troublingly inconsistent or inconsistent studies of any level</td>
</tr>
</tbody>
</table>
III. Current evidence for AIT effectiveness and safety in allergic asthma

The clinical outcome of AIT in allergic asthma can be assessed by a decrease in the severity of symptoms and in the need for concomitant medication. As a result of reciprocal interactions, symptoms and medication should not be analyzed separately and a combined symptom and medication score (SMS) is recommended for AIT trials [28]. SMS has been mostly validated in rhinitis AIT studies [28,29]. Several systematic reviews show a strong effect of SCIT on decreasing asthma symptoms and medications during AIT treatment, both in children and in adults. The evidence for SLIT is less prominent (tables S2 and S3 – supplement). A potential steroid-sparing effect of AIT is of utmost importance to reduce potential side effects of ICS in asthma, in line with the general accepted aim to reduce future risk of treatment related adverse events. No SCIT or SLIT studies reported on the effect of AIT on symptoms or medication after AIT discontinuation. In the EAACI systematic review data pooled from 2 trials showed no evidence of reduction in short-term SMS [26]. Lin et al. brought moderately strong body of evidence that SLIT improved SMS (20 of 41 studies) [30].

The moderate-to-low quality RCTs provided mixed evidence that SLIT is effective in improving asthma control in patients with allergic asthma. One study at low risk of bias found that SLIT did not improve asthma control [31]. In subjects with controlled mild to moderate HDM allergic asthma one-year SLIT treatment allowed reduction in daily ICS dose from individual baseline dose without deterioration in the asthma control [32]. The EAACI systematic review found no evidence to assess whether SCIT is effective in improving asthma control [26].

Several trials report on asthma exacerbations under AIT. The Wang SCIT trial at low risk of bias failed to demonstrate evidence of a reduction in exacerbations in AIT-treated subjects compared with placebo [33]. Two SLIT trials reported a positive effect of AIT on asthma exacerbations, one in the context of reducing the dose of ICS [31,32]. Another SLIT trial failed to demonstrate evidence for SLIT in reducing asthma exacerbations [34].

Lu et al. found no significant differences in lung function (PEF, FEV1 and FVC) between subjects receiving SCIT and the control group [35]. Twenty studies included in SR of Abramson which included the measurement of lung function showed only a trend towards improvement, without statistical significance [36]. EAACI meta-analysis evaluated 25 studies reporting on lung function and showed a favourable response in the overall evaluation and a large beneficial effect on small airways [26]. There are limited numbers of AIT studies using allergen specific bronchial provocation test as primary or secondary endpoint. The marked reduction in allergen-specific AHR to HDM, pollen and animal dander allergens reported by Abramson can be considered as potentially lowering the risk of allergic asthma exacerbations on exposure to the relevant allergen [36]. In the EAACI meta-analysis pooled data from three SCIT studies demonstrated a large effect of AIT [26]. There is
also evidence from several high quality randomised control trials that SCIT is effective in reducing specific AHR [37-44]. Limited, however significant reduction in non-specific AHR are reported both by the Abramson and the EAACI systematic reviews. [26, 36]

The EAACI systematic review showed a large treatment effect for SCIT for improving QoL in allergic asthma [26]. For SLIT the EAACI systematic review was unable to pool data. One SLIT trial at low risk of bias showed no significant improvement in disease-specific QoL [31].

Recent pharmacoeconomic studies demonstrate that AIT in asthma gives value for money, however heterogeneity in methodology limits the data interpretation, and it is difficult to extrapolate the results from one healthcare setting to another [45-49]. More data on cost-effectiveness of AIT in allergic asthma are presented in the supplementary material.

The EAACI systematic review indicated that AIT was associated with a minor increase in the risk of adverse events (AEs), these being seen both with SCIT and SLIT. While severe systemic AEs can occur, these appeared to be uncommon and mainly associated with SCIT. The limited safety data available included in the EAACI SR suggests that local AEs are more common with SLIT, while Kim et al reported that local reactions were frequent with both SCIT and SLIT [26,50]. Real-life data on AIT safety have accumulated both in Europe and US. The survey performed by the American Academy of Allergy, Asthma, and Immunology and American College of Asthma, Allergy, and Immunology from 2008 to 2013 collected data from 28.9 million injection visits and off-label SLIT. Four fatalities occurred under SCIT, systemic AEs were reported in 1.9% patients receiving SCIT and 1.4% of patients receiving off-label SLIT [51]. The European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI) followed 4316 patients and reported a rate of 2.1% for systemic AE (89% with SCIT, 11% with SLIT) [52]. EASSI also recently evaluated prospectively 1563 children (61.5% with asthma) and reported a rate of 1.53% for systemic AEs [53]. Safety of initiation and continuation of AIT during pregnancy analysed in 4 studies totalling 422 women demonstrated no increased incidence of prematurity, hypertension/proteinuria, congenital malformations or perinatal deaths for women continued or initiated on SCIT or SLIT during pregnancy. Among the 10 out of 453 pregnancies who experienced systemic AEs while receiving AIT, none were found to have fetal complications [54].

IV. Clinical recommendations for AIT in allergic asthma

General considerations

According to current evidence, SCIT and SLIT can be recommended in mild and moderate allergic asthma, provided that asthma is adequately controlled by pharmacotherapy. AIT should be integrated in the general frame of asthma management aiming to reduce symptoms, improve quality of life and minimize future risk by decreasing exacerbation rate, improving lung function (including AHR) and decreasing adverse reactions to medication (steroid and beta-2 agonists sparing effect). Before starting AIT benefits and potential harms/disadvantages should be agreed together with the patient (table 1).

In most of the cases a significant clinical benefit on reducing asthma symptoms and medication (with a steroid sparing effect), improvement in QoL and specific AHR can be expected (tables 2,3,4,5). A smaller benefit is expected for improving lung function and non-specific AHR while the impact on asthma control and exacerbation needs further evaluation (tables 6, 7, 8, 9, 10).

AIT may be stopped if there is no impact after a year of therapy (IV D, weak recommendation based on the number, size, or quality of individual studies). The decision depends on the frequency and duration of exposure to the allergen.
### Table 1 - Benefits and potential harms/disadvantages of AIT in allergic asthma

<table>
<thead>
<tr>
<th>Population</th>
<th>Benefits</th>
<th>Potential harms/disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children with mild/moderate asthma</td>
<td>Decreased symptoms and medication score with a steroid sparing effect. Improvement in QoL. Improvement of specific AHR. Possible effect on small airways and non-specific AHR. Possible effect on asthma exacerbations and control.</td>
<td>Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years. Frequency of visits in the clinic (SCIT). Risk for adverse events. Costs.</td>
</tr>
<tr>
<td>Adults with mild/moderate asthma</td>
<td>Decreased symptoms and medication score with a steroid sparing effect. Improvement in QoL. Improvement of specific AHR. Possible effect on small airways and non-specific AHR. Possible effect on asthma exacerbations and control.</td>
<td>Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years. Frequency of visits in the clinic (SCIT). Risk for adverse events. Costs.</td>
</tr>
<tr>
<td>Asthma and rhinitis</td>
<td>Simultaneous tolerance induction for the one airways disease.</td>
<td>Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years. Frequency of visits in the clinic (SCIT). Risk for adverse events. Costs.</td>
</tr>
<tr>
<td>Asthma and atopic dermatitis</td>
<td>Possible beneficial effect for adults sensitised to HDM.</td>
<td>Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years. Frequency of visits in the clinic (SCIT). Risk for adverse events. Costs.</td>
</tr>
</tbody>
</table>

**Clinical recommendation for AIT to reduce symptoms and medication in allergic asthma**

AIT significantly reduces asthma symptoms and medication during treatment, with more evidence available for SCIT compared to SLIT and differences between individual allergens (tables 2,3). There are not enough data to formulate recommendations for AIT in reducing asthma symptom or medication long term (after treatment cessation) or for the combined symptom and medication score.

### Table 2: Recommendations for AIT in allergic asthma to reduce asthma symptoms during treatment

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergen</td>
<td>Recommendation</td>
<td>Level of Evidence</td>
<td>Notes</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDM AIT</strong></td>
<td>Recommended to reduce symptoms in allergic asthma</td>
<td>I</td>
<td>Moderate based on results from well-designed, well-conducted studies included in several SR with some inconsistency between studies. See evidence below for individual allergens, patient’s sensitisation pattern, asthma severity and route of administration.</td>
<td>[26, 36, 50, 55]</td>
<td></td>
</tr>
<tr>
<td><strong>Grass AIT</strong></td>
<td>Recommended to reduce symptoms in allergic asthma</td>
<td>I</td>
<td>Strong based on consistent results from well-designed, well-conducted studies included in several SR.</td>
<td>[26, 35, 56, 57]</td>
<td></td>
</tr>
<tr>
<td><strong>Cat AIT</strong></td>
<td>Recommended in specific circumstances to reduce symptoms in allergic asthma</td>
<td>I</td>
<td>Strong based on the number, size, or quality of individual studies. Safety and extract quality concerns might downgrade the level of the recommendation to very weak.</td>
<td>[26, 58-60]</td>
<td></td>
</tr>
<tr>
<td><strong>Dog AIT</strong></td>
<td>Recommended in specific circumstances to reduce symptoms in allergic asthma</td>
<td>IV</td>
<td>No direct evidence, expert opinion extrapolated from other allergens. Can be considered in occupational exposure.</td>
<td>[61, 62]</td>
<td></td>
</tr>
<tr>
<td><strong>Tree AIT</strong></td>
<td>Recommended in specific circumstances to reduce symptoms in allergic asthma</td>
<td>I</td>
<td>RCT data but weak based on the limited number or size of studies. If seasonal symptoms are severe/impacting QoL, the strength of recommendation can be upgraded to moderate.</td>
<td>[26, 63]</td>
<td></td>
</tr>
<tr>
<td><strong>Mold AIT</strong></td>
<td>Recommended in specific circumstances to reduce symptom x</td>
<td>I</td>
<td>Weak to moderate based on very limited number or size of studies. Safety and extract quality concerns Data from RCT available only for Alternaria.</td>
<td>[64, 65]</td>
<td></td>
</tr>
<tr>
<td><strong>AIT</strong></td>
<td>Recommended in mild/moderate asthma to reduce symptoms</td>
<td>I</td>
<td>Strong based on consistent results from well-designed, well-conducted studies included in several SR.</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td><strong>AIT</strong></td>
<td>Recommended for moderate/severe allergic asthma to reduce symptoms</td>
<td>I</td>
<td>Moderate based on the number, size, or quality of individual studies. Safety concern might decrease the level of recommendation to weak.</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td><strong>AIT</strong></td>
<td>Recommended in monosensitised allergic asthma to reduce symptoms</td>
<td>I</td>
<td>Strong based on consistent results from well-designed, well-conducted studies included in several SR.</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td><strong>AIT</strong></td>
<td>Recommended for polysensitised monoallergic asthma to reduce symptoms</td>
<td>I</td>
<td>Moderate based on the number, size, or quality of individual studies. One relevant allergen for AIT has to be demonstrated to induce relevant symptoms (history, provocation test).</td>
<td>[26, 66]</td>
<td></td>
</tr>
<tr>
<td><strong>AIT</strong></td>
<td>Recommended in specific circumstances for polysensitised polyallergic asthma to reduce symptoms</td>
<td>IV</td>
<td>Very weak based on expert opinion.</td>
<td>[67-71]</td>
<td></td>
</tr>
<tr>
<td><strong>SCIT</strong></td>
<td>Recommended in allergic asthma to reduce symptoms</td>
<td>I</td>
<td>Strong based on consistent results from well-designed, well-conducted studies included in</td>
<td>[26, 35, 36, 50, 55]</td>
<td></td>
</tr>
</tbody>
</table>
SLIT can be recommended for allergic asthma to reduce symptoms. Several SR have been conducted, with results from well-designed, well-conducted studies included in several SR with between-study inconsistency. Patients' preferences or safety considerations can upgrade the strength of recommendation to strong.

Table 3: Recommendations for AIT in allergic asthma to reduce asthma medication during treatment

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT can be recommended alongside other effective treatment options in children with allergic asthma to reduce medication</td>
<td>I</td>
<td>B</td>
<td>Moderate based on results from well-designed, well-conducted studies included in several SR with some inconsistency between studies</td>
<td>See evidence below for individual allergens, patient's sensitisation pattern, asthma severity and route of administration</td>
<td>[26, 36, 50, 55]</td>
</tr>
<tr>
<td>Allergen</td>
<td>AIT may be recommended under specific circumstances in adults with allergic asthma to reduce medication</td>
<td>Level</td>
<td>Strength</td>
<td>Reason</td>
<td>References</td>
</tr>
<tr>
<td>----------</td>
<td>-------------------------------------------------</td>
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<td>---------</td>
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<td>------------</td>
</tr>
<tr>
<td>HDM</td>
<td>Weak based on the inconsistency between studies.</td>
<td>I</td>
<td>B</td>
<td>[26, 36,50,55]</td>
<td></td>
</tr>
<tr>
<td>Grass and trees</td>
<td>Weak based on the limited number or size of studies.</td>
<td>I</td>
<td>B</td>
<td>[26, 58-60,63]</td>
<td></td>
</tr>
<tr>
<td>Molds</td>
<td>Weak based on the limited number or size of studies</td>
<td>I</td>
<td>B</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>Cat and dog</td>
<td>Very weak based on expert opinion</td>
<td>IV</td>
<td>D</td>
<td>Can be considered in occupational exposure</td>
<td></td>
</tr>
<tr>
<td>AIT is recommended in mild/moderate allergic asthma to reduce medication</td>
<td>Strong based on consistent results from well-designed, well-conducted studies included in several SR</td>
<td>I</td>
<td>A</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>AIT can be recommended in moderate/severe allergic asthma to reduce in medication score</td>
<td>Moderate based on the number, size, or quality of individual studies.</td>
<td>I</td>
<td>B</td>
<td>Safety concern might decrease the level of recommendation to weak</td>
<td>[26]</td>
</tr>
<tr>
<td>AIT can be recommended in monosensitised allergic asthma to reduce medication</td>
<td>Moderate based on the number, size, or quality of individual studies.</td>
<td>I</td>
<td>B</td>
<td>[26]</td>
<td></td>
</tr>
<tr>
<td>AIT can be recommended for polysensitised monoallergic asthma to reduce medication</td>
<td>Moderate based on the number, size, or quality of individual studies.</td>
<td>I</td>
<td>B</td>
<td>One relevant allergen for AIT has to be demonstrated to induce relevant symptoms (history, provocation test)</td>
<td>[26, 66]</td>
</tr>
<tr>
<td>AIT might be considered for polysensitised polyallergic asthma to reduce medication</td>
<td>Very weak based on expert opinion</td>
<td>IV</td>
<td>D</td>
<td>[67-71]</td>
<td></td>
</tr>
<tr>
<td>SCIT is recommended in allergic asthma to reduce medication</td>
<td>Strong based on consistent results from well-designed, well-conducted studies included in several SR</td>
<td>I</td>
<td>A</td>
<td>[26, 35, 36, 50, 55]</td>
<td></td>
</tr>
<tr>
<td>SLIT can be recommended in allergic asthma to reduce the</td>
<td>Moderate based on results from well-designed, well-conducted studies</td>
<td>I</td>
<td>B</td>
<td>Patient’s preference or safety considerations can upgrade the strength of recommendation to</td>
<td>[26, 50, 72-76]</td>
</tr>
</tbody>
</table>
medication included in several SR with some inconsistency between studies

Clinical recommendation for AIT in allergic asthma to improve asthma control and reduce long-term risk

There are no consistent effects of AIT on asthma control and exacerbations thus no recommendation can be made for SCIT. There is weak evidence for HDM SLIT for achieving asthma control and moderate evidence for decreasing exacerbations (tables 4,5). Assessing asthma control and exacerbations in addition to symptom and medications score as primary end-point was identified as a significant gap in AIT trials (table 14).

Table 4. Recommendations for AIT in allergic asthma to improve asthma control

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recommendation can be made for or against using SCIT to improve asthma control</td>
<td>IV</td>
<td>D</td>
<td>Weak, inconsistent evidence</td>
<td></td>
<td>[77]</td>
</tr>
<tr>
<td>SLIT may be recommended in specific circumstances in allergic asthma to improve asthma control for:</td>
<td>I</td>
<td>B</td>
<td>Weak based on the limited number or size of studies or heterogeneity in evaluation of asthma control*</td>
<td></td>
<td>[31-34, 78-79]</td>
</tr>
<tr>
<td>Children and adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moderate asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Asthma control was measured in various heterogenous ways

Table 5: Recommendations for AIT in allergic asthma to reduce asthma exacerbations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>No recommendation can be made for or against using SCIT to decrease asthma exacerbations</td>
<td>IV</td>
<td>D</td>
<td>Weak, inconsistent evidence based on 2 RCTs</td>
<td></td>
<td>[80]</td>
</tr>
<tr>
<td>SLIT can be recommended in allergic asthma to decrease asthma exacerbations</td>
<td>I</td>
<td>B</td>
<td>Moderate based on results from well-designed, well-conducted studies with some inconsistency between studies and heterogeneity in definition of exacerbations*</td>
<td></td>
<td>[31-34, 81,82]</td>
</tr>
<tr>
<td>Children and adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-moderate asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Exacerbations were defined in various heterogenous ways

The AIT studies evaluating the impact of AIT on lung function are of limited size and moderate to low quality, with heterogeneity in assessing the end-points and provide inconsistent results thus the strength of recommendations is weak (table 6). However the EAACI systematic review and other studies showed a significant effect on small airways.

Table 6: Recommendations for AIT in allergic asthma to improve lung function in asthma

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
No recommendation can be made for or against using AIT to improve PEF or FEV1 in allergic asthma

SLIT may be recommended in special circumstances for allergic asthma to improve FEF25-75 in:
- Children
- Mild-moderate asthma
- HDM, grass and Parietaria pollen

SCIT can be useful alongside other effective treatment options in allergic asthma to decrease allergen specific AHR. There are not enough data to provide recommendations for SLIT and allergen specific AHR and for AIT and non-specific AHR (table 7).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key References</th>
</tr>
</thead>
</table>
| SCIT is recommended in allergic asthma to reduce the allergen specific AHR for:  
- Children and adults  
- Mild-moderate asthma  
- HDM, cat or dog dander, birch, grass and Artemisia pollen, Cladosporium | I | A | Strong based on consistent results from well-designed, well-conducted studies included in several SR | | [26] |
| No recommendation can be made for or against using SLIT to reduce the allergen specific AHR in allergic asthma | I | B | Weak based on very limited number of studies | | [84,85] |
| AIT may be recommended in specific circumstances in allergic asthma to decrease non-specific AHR for:  
- Children and adults  
- SCIT and SLIT  
- Mild-moderate asthma  
- HDM, cat and dog dander, birch, grass and Parietaria pollen, Alternaria | I | B | Weak based inconsistent results with limited number and size and moderate/low quality of studies | | [26] |

SCIT can be useful alongside other effective treatment options in allergic asthma to improve quality of life. There are not enough data to provide recommendations for SLIT (table 8).

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCIT can be useful alongside other effective treatment options in allergic asthma to improve quality of life.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SCIT can be recommended alongside other effective treatment options in allergic asthma to improve QoL in:
- Children and adults
- Mild-moderate asthma
- HDM and Alternaria

No recommendation can be made for or against using SLIT to improve asthma QoL

V. Safety and contraindications

AIT is a safe treatment for well-controlled allergic asthma in children and in adults (table 9).

<table>
<thead>
<tr>
<th>Statement</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Rate ratio</th>
<th>Strength of statement</th>
<th>Key References</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT delivered by any route (SCIT and SLIT) has a small risk of adverse events (AE) in children and in adults</td>
<td>I</td>
<td>A</td>
<td>1.74 (95% CI 1.38, 2.2) overall 2.22 (95% CI 1.48, 3.33) for SCIT 1.49 (95% CI 1.13, 1.98) for SLIT</td>
<td>Moderate based on results from well-designed, well-conducted studies included in several SR with between-study inconsistency</td>
<td>[26, 51,52,53]</td>
</tr>
<tr>
<td>SCIT has a small risk of systemic AEs</td>
<td>I</td>
<td>A</td>
<td>1.92 (95% CI 1.19, 3.09)</td>
<td>Moderate based on results from well-designed, well-conducted studies included in several SR with between-study inconsistency</td>
<td>[26, 51,52,53]</td>
</tr>
<tr>
<td>SLIT has a small risk of systemic AEs</td>
<td>IV</td>
<td>D</td>
<td>1.39 (95% CI 0.67, 2.92)</td>
<td>Weak based on 2 studies included in the SR and results of 2 surveys</td>
<td>[26, 51,52,53]</td>
</tr>
<tr>
<td>SCIT may increase the risk of local AEs</td>
<td>I</td>
<td>A</td>
<td>0.96 (95% CI 0.74, 1.24)</td>
<td>Weak; in the SR the risk is suggested but not confirmed</td>
<td>[26]</td>
</tr>
<tr>
<td>SLIT can increase the risk of local AEs</td>
<td>I</td>
<td>A</td>
<td>6.45 (95% CI 3.67, 11.31)</td>
<td>Moderate based on results from well-designed, well-conducted studies included in several SR with between-study inconsistency</td>
<td>[26,50]</td>
</tr>
</tbody>
</table>

Severe or uncontrolled asthma is the major independent risk factor for both nonfatal and fatal adverse reactions and is therefore a major contraindication for both SLIT and SCIT. Other contraindications and precautions are listed in table 10.
Table 10: Contraindications and precautions for AIT in patients with allergic asthma

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Authors recommendations (level of certainty)</th>
<th>Other considerations</th>
<th>Key reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT is contraindicated in poorly controlled asthma</td>
<td>IV/V</td>
<td>D</td>
<td>Strong based on safety concerns</td>
<td>Due to safety concerns performance of RCT studies in poorly controlled asthma is not recommended</td>
<td>[51-53,74, 87-91]</td>
</tr>
<tr>
<td>AIT should not be considered in children and adults with severe asthma</td>
<td>IV/V</td>
<td>D</td>
<td>Very weak due to gaps in the chain of evidence</td>
<td>Individual differences between allergens should be considered with mites inducing less SRs compared to grass and probably molds and animal dander</td>
<td>[51-53,74, 87-91]</td>
</tr>
<tr>
<td>AIT should not be initiated in pregnancy (but can be continued in pregnancy)</td>
<td>IV/V</td>
<td>D</td>
<td>Very weak due to gaps in the chain of evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIT should not be initiated in patients with active autoimmune disorders</td>
<td>IV/V</td>
<td>D</td>
<td>Very weak due to gaps in the chain of evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIT should not be initiated in patients with active malignancies</td>
<td>IV/V</td>
<td>D</td>
<td>Very weak due to gaps in the chain of evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIT may be considered with caution in asthmatic patients under treatment with beta-blockers or ACE inhibitors</td>
<td>IV/V</td>
<td>D</td>
<td>Very weak due to gaps in the chain of evidence</td>
<td>Only in specialised settings.</td>
<td></td>
</tr>
<tr>
<td>AIT is not recommended in patients with immune deficiencies, active infections and infestations and uncontrolled diseases like diabetes, IBD, gastric ulcer etc</td>
<td>IV/V</td>
<td>D</td>
<td>Very weak due to gaps in the chain of evidence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Recommendations around risk management when administering AIT in allergic asthma are detailed in table 11 ((level IV/D, weak recommendation).

| Table 11: Recommendations for risk management of AIT in allergic asthma |
|---------------------------------------------------------------|-------------------------------------------------------------|
| SCIT for allergic asthma                                      | 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 and written instructions on how to recognize and manage adverse reactions and when to contact the HCP for adverse reactions, treatment |
| Home based SLIT for allergic asthma                           | 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    |
|                                                              | Consider an adrenaline (epinephrine) auto-injector and training in how to use the device |
|                                                              | Patient education for management and reporting late reactions |
gaps, or other events that may affect treatment (e.g., new medication or illness) and how to manage missed doses and the situations when they should withhold SLIT.

In cases of oral inflammation, such as mouth ulcers, lichen planus, or dental extractions, administration of SLIT should be temporarily discontinued until there is complete healing of the oral cavity.

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 is also recommended.

In spite of some case reports suggesting that AIT might be associated with the development of autoimmunity [92], the evidence from long-term observational studies in patients with asthma does not confirm this hypothesis [93]. In total, 1,144 patients with allergic asthma and/or AR, were observed up to 20 years after immunotherapy and compared to a control group consisting of 1,154 allergic patients with only symptomatic treatment. No significant differences in the prevalence of autoimmune diseases was observed between the groups [93], however due to lack of data AIT is not recommended in patients with active autoimmune diseases.

VI. Special considerations

Polysensitized patients, allergen mixes and multiple vaccines

The majority of patients with allergic asthma seen by specialists are polysensitized. However, polysensitization does not necessarily mean that all sensitivities are clinically significant. In Europe the one or two most important sensitivities are typically treated. In contrast, in the United States mixtures including many or most of the sensitizing allergens are administered [94]. Related allergen mixes proved efficacy in polysensitized patients [95]. An alternative to allergen mixes for both SLIT and SCIT is the administration of multiple allergen extracts at different occasions or locations [96-98].

A literature survey identified 13 studies simultaneously using 2 or more distinct allergen extracts (11 SCIT, 1 SLIT and 1 SCIT and SLIT) [99]. In studies with adequate information, administration of 2 extracts by means of either SCIT or SLIT was effective. In studies using multiple allergens, 3 studies showed clear efficacy, whereas in the other 2 studies, lack of efficacy might have been due to inadequate doses of extract or omission of clinically relevant allergens in the treatment regimen. It is concluded that simultaneous administration of more than 1 allergen extract is clinically effective. However, more studies are needed, particularly with more than 2 allergen extracts and with SLIT [99].

For polysensitised patients with allergic asthma we recommend either mono-allergen immunotherapy or multiple vaccines pending on the burden of allergen of symptoms (level IV/D, weak recommendation). If a mixture of related allergens is used the AIT product characteristics should include the following: high efficacy and optimal safety profile, standardized production, and documented presence and titration of the major allergen.

Allergens not included in the systematic review and rare allergens

Several forms of ragweed SCIT and SLIT were tested mainly in patients with AR, with or without seasonal asthma [100-102]. We recommend SCIT or SLIT with ragweed natural extracts in patients with allergic asthma with proven symptoms induced by weeds (level IV/D, weak evidence). There are not enough data to formulate a recommendation for AIT with other allergens such as Bermuda grass, cockroach, laboratory animals (mouse, rat, rabbit) or latex. AIT in such cases can be considered on an individual basis pending on the burden of asthma symptoms.
induced exposure to the relevant allergens. For more details on these rare allergens see supplementary material.

**Recombinant allergens for AIT in allergic asthma**

The use of recombinant allergens for immunotherapy is a very promising approach. Murine models of allergic airway inflammation have provided important proof of concept findings. For example, using a murine model of birch pollen allergic asthma, both sublingual recombinant Bet v 1a or epicutaneous immunotherapy with a hypoallergenic recombinant Bet v 1B2 suppressed lung inflammatory responses such as eosinophil recruitment, type 2 cytokine levels and AHR[103,104].

While a number of studies have examined the use of recombinant birch pollen allergen in humans, none of these published studies have focused specifically on asthma patients, although typically 30-40% of the study populations being tested in these studies have asthma. Future studies on recombinant allergens need to specifically focus on sensitized asthma patients.

Based on the current evidence we cannot make recommendations on the use of recombinant allergens for allergic asthma

**Preseasonal versus continuous schedules**

There is only one study directly comparing SLIT administered pre-coseasonal or continuous in a 2-year prospective, randomized, double-blind, placebo-controlled trial including children allergic to grass pollen with rhinitis and concomitant asthma. Both protocols were effective compared with placebo and showed similar decreases for combined SMS and all secondary endpoints (medication, ocular and asthma scores) [105].

Based on the current evidence we cannot make recommendations on the choice of preseasonal versus continuous schedules for AIT in allergic asthma. The use of either schedule depends on doctors and patients preference

**Novel adjuvants and alternative routes for AIT in asthma**

The use of novel adjuvants and alternative routes of administration have brought a lot of attention over the last years [106,107]. Although there are still few studies demonstrating the benefits of novel adjuvants or alternative routes of administration in large cohorts of patients in the context of asthma, promising alternatives have been reported in preclinical mouse models and humans [108-111] Novel adjuvants with demonstrated clinical efficacy and security in human clinical trials for AIT in asthma include Toll-like receptors (TLRs) agonists, viral-like particles (VPLs) and 1,25-dihydroxy vitamin D3 [108-111]. Further clinical trials should show whether these or other alternative routes could improve efficacy, safety and patient compliance for AIT in asthma.

Based on the current evidence we cannot make specific recommendations on adjuvant use or for alternative routes in AIT in allergic asthma.

**Combination with biologics**

A few trials have been performed with pre-administration or co-administration with omalizumab to either improve safety of SCIT up-dosing [112] or improve efficacy of SCIT [113,114]. 248 asthmatics not controlled by ICS received rush SCIT (cat, dog, HDM) combined with placebo or omalizumab. Adding omalizumab reduced the systemic AEs rate from 26.2% to 13.5% and 87.3% of subjects on omalizumab reached the maintenance dose of SCIT versus 72.1% of placebo patients [112].

Co-administration of omalizumab and SCIT with a depigmented grass pollen–rye pollen extract was investigated in 140 patients with seasonal AR and mild-to-moderate allergic asthma incompletely controlled by pharmacotherapy. Significant difference for AIT and omalizumab co-administration was noted for reducing symptom severity and improving asthma control and quality of life [113]. The combination had no prolonged effect during treatment with AIT only [114]. A slight
increase in FEV1 in patients formerly treated with the omalizumab/SIT combination therapy was shown in the second year of observation which should encourage further evaluation of long-term effects of omalizumab [114].

A recent trial in AR patients evaluated the induction of sustained tolerance to allergen when anti-IL-4 was combined with a suboptimal course of SCIT grass pollen using the allergen-induced skin late-phase response (LPR) and exploratory immune monitoring as surrogate markers of therapeutic response. Both treatment arms led to a substantial and sustained reduction of the LPR with no additional suppression with addition of anti-IL-4. However the combination anti-IL-4/SCIT compared with SCIT alone led to a sustained reduction in allergen-specific IL-4-producing cell counts [115].

Evidence is lacking to recommend co-administration of biologics and AIT for allergic asthma.

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

Nonspecific bronchial provocation tests with metacholine/histamine and specific challenges that utilize allergen extracts assist in identifying AHR, a major feature of asthma. To validate AHR the most adequate provocation test is the bronchial challenge, although nasal and conjunctival allergen provocations are performed under some circumstances, especially at higher risk groups [116,117]. In AIT trials allergen provocation tests (cat, mites and grass pollen) are sometimes used as inclusion criteria or to measure the efficacy of AIT[118-121]. The drawback of provocation testing is that it may not reflect natural exposure [116].

We cannot make recommendations on the use of provocation tests for patient selection or efficacy assessment.

**Biomarkers and AIT for allergic asthma**

Many studies on AIT report on potential biomarkers for measuring efficacy or useful for responders to AIT. In type-2 asthma sputum or blood eosinophilia or serum can be correlated with response to ICS or targeted interventions such as anti-IgE, anti IL-5 or anti IL-4,13 [10-12,20]. Some in vivo, ex vivo or in vitro parameters correlate with the clinical efficacy of AIT (Table 12). It may be assumed that AIT biomarkers described for AR or food allergy might predict response to AIT in allergic asthma as well, but none of them is validated or qualified [10,122].

Based on current evidence for biomarkers in AIT for allergic asthma we cannot formulate any recommendation for their use in routine practice, with the exception of course of specific IgE to allergen.

<p>| Table 12: Biomarkers of allergen immunotherapy efficacy |</p>
<table>
<thead>
<tr>
<th>Methodology</th>
<th>Parameter/test</th>
<th>Documented changes during AIT*</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vivo</td>
<td>Skin prick tests; late cutaneous response</td>
<td>Decrease in early and late skin reactivity</td>
<td>[40, 61, 123-126]</td>
</tr>
<tr>
<td></td>
<td>Nasal allergen provocation test</td>
<td>Decrease in nasal sensitivity to allergen challenge</td>
<td>[127-129]</td>
</tr>
<tr>
<td></td>
<td>Conjunctival allergen provocation test</td>
<td>Decrease in conjunctival sensitivity to allergen challenge</td>
<td>[123, 130]</td>
</tr>
<tr>
<td></td>
<td>Bronchial allergen provocation test</td>
<td>Decrease in bronchial sensitivity to allergen challenge</td>
<td>[38, 42-43, 49,61]</td>
</tr>
<tr>
<td>Ex vivo (in biological fluids)</td>
<td>Immunoglobulins: s-IgE, s-IgG1, s-IgG4, s-IgA</td>
<td>Early increase and progressive decrease in s-IgE; increases in s-IgG1, s-IgG4 in serum and s-IgA at mucosal sites, together with the increase of their blocking capacities; Higher s-IgE/s-IgE ratio correlated with AIT efficacy</td>
<td>[43, 121, 122, 124-126, 126, 131-132]</td>
</tr>
<tr>
<td></td>
<td>s-IgE/s-IgE ratio</td>
<td>Increase in IL-10 and TGF-β</td>
<td>[133, 134]</td>
</tr>
<tr>
<td></td>
<td>Allergen-specific T cell responses</td>
<td>Increase in IL-10 and TGF-β</td>
<td>[128, 135-138]</td>
</tr>
</tbody>
</table>
The presented changes were replicated in the majority but not all studies. s-IgE, s-IgG1, s-IgG4, s-IgA; specific IgE, IgG1, IgG4, IgA; t-IgE; total IgE

**Background**

**asthma treatment: ICS versus no ICS**

There is no evidence that background ICS may influence the outcome of AIT, however they should be used as first line asthma controllers to ensure the maximum safety of AIT.

**AIT in allergic asthma with allergic co-morbidities**

Allergic asthma and AR frequently co-exist and share similar triggers and similar pathophysiology [24]. Patients with asthma and AR will have benefits following AIT from both the upper and lower airways, thus the association of AR is a recommendation for AIT in well-controlled allergic asthma (level I/A, strong recommendation).

The association with AD is mentioned in five AIT for allergic asthma studies. In three studies, the presence of AD is a descriptive parameter for the study population [44, 77, 152]. In one study, patients with severe AD were excluded, however no definition of severe AD is provided. [153] In another AIT study for dog allergic patients symptoms of AD were recorded in the active and placebo group [143]. Only one study reported that patients *had the subjective impression, that also AD improved during AIT for asthma* [154]. No study reported however that adverse effects in patients with AD were more frequent under AIT.

Food allergy is not mentioned as comorbidity or as exclusion criterion.

Our recommendation is that neither AD nor food allergy are contraindications for AIT in asthma (level IV/D, weak recommendation).

**VII. Dissemination and implementation: barriers, facilitators, audit criteria** (66 words)

The data on the efficacy and safety of AIT in allergic asthma provide an incentive to use AIT in a much larger number of patients with allergic asthma than currently indicated. The major barriers and facilitators as well as audit criteria are presented in table 13. In general a holistic approach to patients is required with joint commitment of various stakeholders to offer the patients the optimal care [155, 156, 157].
Table 13: Barriers, facilitators and audit criteria for AIT in asthma

<table>
<thead>
<tr>
<th>Barriers</th>
<th>Facilitators</th>
<th>Audit criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of asthma as a lower airway condition, ignoring the frequent association with AR and disease endotypes</td>
<td>Revised definition of asthma to include the one airways disease concept and asthma endotypes</td>
<td>Increased prescription of AIT for the one airways disease (AR and allergic asthma)</td>
</tr>
<tr>
<td>Low awareness of AIT potential by the general public and healthcare professionals outside allergy speciality, eg paediatricians, pulmonologists, ENT, dermatology, primary care physicians</td>
<td>Joint commitment and coordinated actions among academia, patient organisations, regulators, industry to find solutions that properly answer the health expectations of the allergic patients</td>
<td>Increased prescription of AIT in allergic asthma</td>
</tr>
<tr>
<td>The application of AIT in asthma is limited due to efficacy and safety concerns</td>
<td>Higher quality large phase 3 DBPC trials with patient centered outcomes and postmarketing data</td>
<td>AIT is included in general asthma guidelines (GINA, national guidelines)</td>
</tr>
<tr>
<td>Availability and affordability</td>
<td>Pharmacoeconomics studies and implementation of better reimbursement policies</td>
<td>AIT included in national health programmes</td>
</tr>
<tr>
<td>Improved patient selection</td>
<td>Better selection of responders using diagnostic tools for accurate identification of clinically relevant patient’s sensitization profile</td>
<td>Lower rate of AIT failures</td>
</tr>
<tr>
<td>Adherence to AIT</td>
<td>Educational programmes, more convenient AIT regimens</td>
<td>Lower rate of drop-outs</td>
</tr>
</tbody>
</table>

VIII. Evidence gaps and unmet needs

**Measuring outcomes**

Most of the clinical trials of AIT in asthma evaluated clinically relevant parameters such as symptom and medication score (with an emphasis on the corticosteroid sparing effect) and lung function. A standardized and globally harmonized method for analysing the clinical efficacy of AIT products in RCTs is required, as recently highlighted by the EAACI Position Paper for AIT in AR [28]. According to the European Medicine Agency clinical trials on AIT in asthma start as add on therapy, which has to be considered in the evaluation of the primary endpoint (e.g. evaluation in the context of a stepwise reduction of controller medication). Lung function, number of exacerbations or reduced need for controller medication should be considered as primary endpoints in addition to the symptoms and medication scores.

**AIT positioning in the context of general asthma management (controller, biologics, avoidance)**

The application of AIT does not interfere or substitute the pharmacological treatment for asthma as recommended by various asthma guidelines. It should be applied only when asthma is well controlled providing the perspective of stepping-down controller treatment while decreasing the future risk of asthma exacerbations and drug-related adverse events.

The concept of AIT complements the biologics use in asthma in several aspects including the possibility of early implementation aiming at achieving prevention and disease-modifying effects. AIT and biologics target different asthma subpopulations with AIT addressing early and/or milder cases and biologics for more severe long-duration asthma.

Given that effective allergen avoidance is hardly achievable in real-life AIT offers the opportunity to achieve tolerance to common allergens.

The AIT for allergic asthma working group identified several gaps in evidence (table 14)

Table 14: Gaps in evidence for AIT in allergic asthma and plan to address

<table>
<thead>
<tr>
<th>Gaps in evidence</th>
<th>Plan to address</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Establishing and standardising the optimal outcome measures</td>
<td>Investigate and validate optimal outcome measures in adults and</td>
<td>High</td>
</tr>
</tbody>
</table>
Poor alignment of studies with guidelines from regulatory bodies. Work in partnership with regulatory bodies to continually review trial methodology and outcomes. High

How to assess clinically relevant 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

How to evaluate the impact of comorbidities (autoimmunity, diabetes, obesity, smoking) and the impact of age (>45) Well-designed RCT and real-life studies focusing on AIT in asthma with co-morbidities Medium

Safety: LF level cut-off and observation period after dose Well-designed RCT with LF level cut-off and observation period as primary end-point High

When to start RCTs and real-life studies testing different approaches in AIT in terms of duration and allergen Medium

Validation of different regimens (preseasonal, perennial), mode of updosing RCTs and real-life studies testing different regimens Medium

Optimal dose for SCIT in asthma Mechanistic studies High

Optimal dose of SLIT in asthma Mechanistic studies High

Discussion and future perspectives

The major aim of this guideline is to provide recommendations according to the evidence for efficacy and safety of AIT in the targeted patients populations (box 3). Since AIT remains underused the possible approaches to increase its application in the asthma treatment are also outlined. Low awareness, limited access to specialist care, the reimbursement policy, long duration, and often unjustified concerns regarding safety and effectiveness are the main reasons of the limited (less than 10% of eligible patients) utilization in asthma treatment worldwide. Among allergy specialists there is practically no controversy about the importance of AIT in the treatment of allergic asthma however indications and contraindications in subgroups defined by disease severity, age groups, concomitant diseases, sensitization pattern etc. are of utmost importance. The small number of even lack of RCT in these modalities poses the major problem for making recommendations. Constant monitoring of clinical evidence is necessary to improve and develop a comprehensive consensus report to harmonize, disseminate, and implement the best AIT practice in order to provide the optimal patient’s care.

There is room for improving as far as prescription, efficacy and safety are concerned. The molecular-based diagnosis and endotyping allergic asthma would certainly improve patient selection for AIT. Recent advances in immunology and bioengineering such as cloning of allergen proteins and genetic engineering enable the use of novel vaccines for AIT with increased efficacy and safety. Work is ongoing for new routes of administration such as the intralymphatic and epicutaneous routes. However, the quality level of evidence is variable and includes conceptual studies in experimental models, proof-of-concept clinical studies with a limited number of subjects and large-scale multicentre clinical studies are further needed.

Box 3: Key points for AIT in allergic asthma

When should AIT be considered in asthma = well controlled asthma under pharmacotherapy where relevant clinical sensitization is proven

What is the expected benefit = a decrease in symptom and medication score with improved
quality of life and with a potential steroid sparing effect allowing step-down in well controlled asthma; potential benefit in reducing the risk of exacerbations and improving lung function and decrease in AHR.

*What products should be used* = well characterised vaccines with proof of efficacy; eg HDM, grasses and trees.

*Which route should be used* = both SCIT and SLIT depending on patient preference, costs and adherence to treatment.

*How is AIT integrated with asthma regular treatment* = AIT should be additional to asthma controller treatment.

**Conclusion**

This guideline combines the best scientific evidence with expert opinion aiming at providing the practical resource for all stakeholders dealing with AIT for allergic asthma including patients, health care professionals, competent authorities, and industry. The data of systematic reviews and expert consensus provide sufficient rationale for the increased use of AIT in the treatment of asthma as well as to foster well-designed clinical and translational research in this field.

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