EAACI Guideline on Allergen immunotherapy: Prevention of allergy

Draft V6-21.04.2017

Expert panel:

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Short title: EAACI Guidelines on AIT for Allergy Prevention
Keywords: Allergen immunotherapy, allergic diseases, allergy, atopy, prevention, sensitization, AGREE II, asthma, allergic rhinitis

Words: <4500. At present 4077 without tables and boxes

Abbreviations:
AD: Atopic dermatitis (atopic eczema)
AIT: Allergen Immunotherapy
AR: Allergic rhinitis
ARC: Allergic rhinoconjunctivitis
CBA: Controlled before and after study
HDM: House dust mites
OAS: Oral allergy syndrome
RCT: Randomized controlled trial
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
Abstract

Max 250 words – now 248

Allergic diseases are very common and frequently coexist. Allergen immunotherapy (AIT) is a potentially disease-modifying intervention for IgE-mediated allergic disease that may also have important preventive effects. The European Academy of Allergy and Clinical Immunology (EAACI) has developed clinical practice guidelines that aim to provide evidence-based recommendations for the use of AIT for prevention of allergic sensitization, development of early life allergic conditions and development of allergic comorbidities in those with established allergic diseases. These guidelines have been developed using the AGREE II framework, which involved convening a multi-disciplinary expert working group, a systematic review of the underpinning evidence, and external peer-review of draft recommendations. Our key recommendations are that AIT cannot currently be recommended to individuals for the prevention of allergic sensitization or first allergic disease. Children and adolescents up to 18 years with persistent seasonal allergic rhinitis (AR) triggered by grass/birch pollen allergy may benefit from a 3 year course of subcutaneous or sublingual AIT, for the short-term (i.e. <2 years post-treatment) prevention of asthma, but it is uncertain whether this benefit is maintained over a longer period. However, there is no current evidence to suggest that it has a similar preventive effect in children and adolescents with AR triggered by house dust mites or other allergens. There is no evidence that AIT may prevent the development of allergic co-morbidities in those with other allergic diseases. Before initiating AIT, the possible benefits, disadvantages, potential harms and costs should be discussed with the patient/family on an individual basis.
**Introduction**

Allergic diseases are now the commonest chronic diseases and encompass atopic eczema/dermatitis, asthma, allergic rhinoconjunctivitis (ARC), food allergy and venom allergy [1-5]. They frequently start in early childhood and continue throughout adulthood. Allergies cause considerable burden to individuals leading to impaired quality of life [6]. At a societal level, they have additional costs, particularly in terms of healthcare and impact on activities of daily living. The latter may include loss of school days, work absence, presenteeism and early retirement [7;8]. For asthma and ARC, many patients respond well to pharmacotherapy, whereas others do not or need treatment with more than one product. However, many may respond to therapeutic allergen immunotherapy (AIT) reducing symptoms and the need for symptomatic treatment. Management for venom and food allergy is more challenging and often reliant on avoidance strategies and rescue therapy; for these conditions AIT may be a useful adjunctive strategy to avoid considerable personal, healthcare and societal costs.

AIT is considered to be a potentially disease-modifying intervention in IgE-mediated allergic disease, with the potential for preventive as well as therapeutic effects [9-11]. For example, we know that children with allergic rhinitis (AR) have a 3-fold increase risk of developing allergic asthma [12]. Studies assessing the long-term effectiveness of AIT in children with ARC indicate that AIT might reduce the risk of developing asthma [13;14]. There is good evidence for the clinical efficacy of AIT for allergic rhinitis, allergic asthma and severe venom allergy throughout multiple trials and meta-analyses of this treatment (x: SR ARC, SR Asthma, SR venom). We know that AIT can induce immunological changes that result in disease modification [10]. The potential for AIT as a preventive strategy should therefore be considered.

These Guidelines have been developed by the European Academy of Allergy and Clinical Immunology (EAACI) Taskforce on AIT for Allergy Prevention and form part of the EAACI AIT Guidelines. The aim is to provide evidence-based recommendations for the use of AIT for prevention of development of allergic sensitization, first allergic disease and further allergic co-morbidities in those with established allergic disease. These Guidelines do not cover weaning and dietetic strategies, which are considered in the ‘EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy’ [15].
The primary audience for these Guidelines are 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 diseases and healthy individuals at risk of developing allergic diseases.

**Methods**

Development of the Guidelines has been informed by a formal systematic review and meta-analysis of AIT for prevention [16] with systematic review principles being used to identify additional evidence, where necessary.

These Guidelines were produced using the Appraisal of Guidelines for Research & Evaluation (AGREE II) approach [17;18]. This structured methods for guideline production is designed to ensure appropriate representation of the full range of stakeholders, an exhaustive search for and critical appraisal of the relevant literature, a systematic approach to the formulation and presentation of recommendations, and steps to ensure that the risk of bias is minimized at each step of the process. The process began in April 2015 with detailed face-to-face discussion of the nature of guidelines for clinical practice and a review of approaches to generating these. Then followed a series of face-to-face and WebEx discussions to agree the main aims of the guidelines, target conditions, intended end-users for the recommendations, and ensuring adequate professional and lay representation in the guidelines development process. We elaborate on these various steps below. Key terms are described in Box 1.
**Box 1. Key terms**

<table>
<thead>
<tr>
<th><strong>Allergic diseases</strong></th>
<th>Atopic eczema (AE), food allergy (FA), allergic asthma (AA), allergic rhinitis/conjunctivitis (ARC) at any age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AIT (Allergen immunotherapy)</strong></td>
<td>Repeated allergen exposure at regular intervals to modulate immune response to reduce symptoms and need for medication for clinical allergies and to prevent the development of new allergies and asthma (adapted from European Marketing Agency (EMA)). This is also sometimes known as allergen specific immunotherapy, desensitization and hyposensitization*</td>
</tr>
<tr>
<td><strong>Healthy individuals</strong></td>
<td>Individuals with or without IgE sensitization, but without any manifestations of current allergic disease</td>
</tr>
</tbody>
</table>
| **Prevention** | Prevention of the development of new sensitization or new allergic disease in healthy individuals without sensitizations, in healthy individuals with sensitizations and in those who already have allergic disease.  
  **Short-term prevention**: effect until 2 years post-treatment  
  **Long-term prevention**: effect maintained at least 2 years post-treatment |
| **Sensitization** | Detectable IgE antibodies, either by means of skin prick test or determination of specific-IgE antibody levels in a serum sample |

* Dietary interventions in infants aimed at the prevention of food allergy are not covered in these Guidelines: they form part of the ‘EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy’ [15](ref).
## Box 2: Summary of the aim and outcomes in the supporting systematic review (SR ref)

<table>
<thead>
<tr>
<th><strong>Aim:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>To provide a rigorous overview of current systematic review evidence on the effectiveness, safety and cost-effectiveness of AIT for prevention of allergic disease</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Study outcomes:</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>- Development of the first allergic manifestation in healthy individuals, or of a new allergic manifestation in those with a previous allergic condition (e.g. atopic eczema/dermatitis or allergic rhinitis), assessed over the short term (&lt; 2 years) or the longer term (≥ 2 years) post-treatment</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>- Development of new allergic sensitization(s), spreading of allergic sensitization(s) from one allergen to other non-related allergen(s), spreading of allergic sensitization(s) at molecular level, from one allergenic molecule to other molecules</td>
</tr>
<tr>
<td>- Development of previously non-existent oral allergy syndrome</td>
</tr>
<tr>
<td>- Safety as assessed by local and systemic reactions in accordance with the World Allergy Organization’s grading system of side-effects [19;20].</td>
</tr>
<tr>
<td>- Health economic analysis from the perspective of the health system/payer as reported in studies</td>
</tr>
</tbody>
</table>

### Ensuring appropriate stakeholder involvement

Participants in the EAACI Taskforce on AIT for Prevention represented a range of countries, and disciplinary and clinical backgrounds, including allergists, primary care physicians, allied health professionals, public health and representatives from patient interest organisations. Methodologists took the lead in undertaking the underpinning systematic review and clinical academics took the lead in formulating recommendations for care. Additionally, producers of immunotherapy products were given the opportunity to review and comment on the draft guidelines to allow any omissions or errors in the evidence-base to be highlighted. The Taskforce considered these comments and revised where appropriate.
Systematic reviews of the evidence

The initial full range of questions that were considered important were rationalized through several rounds of iteration to agree on one key overarching question: “What is the effectiveness, safety and cost-effectiveness of AIT for prevention of allergic disease and sensitization in all populations”, which was then pursued through a formal systematic review of the evidence [16;21].

Formulating recommendations

We graded the strength and consistency of key findings from the systematic review 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 3) [22]. The adaptation involved providing a summary of the quality of the underpinning evidence and highlighting other potentially relevant contextual information, formulating clear recommendations and making clear the evidence-base underpinning each recommendation, taking into consideration not only possible beneficial effects, but also any possible disadvantages and harms. Experts identified the resource implications of implementing the recommendations, barriers, and facilitators to the implementation of each recommendation, advice on approaches to implementing the recommendations and suggested audit criteria that can help with assessing organizational compliance with each recommendation (see Supporting Information Tables SX,...).
### Box 3. Assigning levels of evidence and grade and strength of recommendations (12)

#### Level of evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Systematic reviews, meta-analyses, randomized controlled trials</td>
</tr>
<tr>
<td>Level II</td>
<td>Two group, non-randomized studies (e.g. cohort, case-control)</td>
</tr>
<tr>
<td>Level III</td>
<td>One-group, non-randomized studies (e.g. before and after, pre-test and post-test)</td>
</tr>
<tr>
<td>Level IV</td>
<td>Descriptive studies that include analysis of outcomes (single-subject design, case-series)</td>
</tr>
<tr>
<td>Level V</td>
<td>Case reports and expert opinion that include narrative literature, reviews and consensus statements</td>
</tr>
</tbody>
</table>

#### Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>Consistent level I studies</td>
</tr>
<tr>
<td>Grade B</td>
<td>Consistent level II or III studies or extrapolations from level I studies</td>
</tr>
<tr>
<td>Grade C</td>
<td>Level IV studies or extrapolations from level II or III studies</td>
</tr>
<tr>
<td>Grade D</td>
<td>Level V evidence or troublingly inconsistent or inconclusive studies at any level</td>
</tr>
</tbody>
</table>

#### Strength of recommendations

<table>
<thead>
<tr>
<th>Strength</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>Evidence from studies at low risk of bias, i.e. high quality</td>
</tr>
<tr>
<td>Moderate</td>
<td>Evidence from studies at moderate risk of bias, i.e. moderate quality</td>
</tr>
<tr>
<td>Weak</td>
<td>Evidence from studies at high risk of bias, i.e. low quality</td>
</tr>
</tbody>
</table>

Recommendations are phrased according to the strength of recommendation: strong: “is recommended”; moderate: “can be recommended”; weak: “may be recommended in specific circumstances” and negative: “cannot be recommended”
Peer review and public comment

A draft of these guidelines was externally peer-reviewed by invited external experts from a range of organizations, countries and professional backgrounds. Additionally, the draft guidelines were made available on the EAACI Website for a 2-week period in May 2017 to allow a broader array of stakeholders to comment. All feedback was considered by the Taskforce and, where appropriate, final revisions were made in light of the feedback received. We will be pleased to continue to receive feedback on these Guidelines, which should be addressed to the corresponding author.

Identification of evidence gaps

The process of developing these Guidelines has identified a number of evidence gaps which are prioritized in Table 5.

Editorial independence and managing conflict of interests

The production of these Guidelines 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. Taskforce members’ conflict of interests were taken into account by the Taskforce Chairs as recommendations were formulated. Methodologists, who had no conflict of interests in this area, checked final decisions about strength of evidence for recommendations.

Updating the guidelines

EAACI plans to update these guidelines using the AGREE II approach in 2022 unless there are important advances before then.

Overarching considerations

These guidelines are based on a comprehensive systematic review evaluating the evidence according to predefined well established methods [16]. As in other systematic reviews, heterogeneity in the populations under study, methods employed and outcomes studied made it challenging to interpret the evidence. It is well known that factors related to the population, such as atopic heredity play a role for the risk of development of allergic disease. In addition, children with sensitization and/or early manifestations of atopic diseases e.g. atopic dermatitis (AD) and food allergy or later...
manifestation such as AR have a higher risk for development of other allergic manifestations such as asthma [23] [12]. The age of the population is important as phenotypic expression may change with age and some manifestations may even disappear spontaneously [24]. The results of individual studies are difficult to compare because studies use different outcome measures, different diagnostic criteria (if any, e.g. the exact definition of asthma, intermittent versus persistent asthma), different methods, and cut-off values for measuring sensitization. Furthermore, the mode of administration and the products used for AIT differ as regards allergens, formulation, strength, dose, and duration of the intervention. Additionally, many studies are small without sufficient power and adjustment for confounders. Where possible, these factors are taken into consideration in the risk of bias and quality assessment in the systematic review on which these guidelines are based.

Using AIT for prevention of development of new allergic disease or sensitization requires a high level of safety, especially in healthy individuals. However, if AIT is indicated due to treatment of an allergic disease that has already developed, and the preventive effect is regarded as an additional effect, then the safety profile should be considered in that context.

Strategies to prevent development of a new sensitization or of a new allergic disease by AIT may vary for different populations at different stages in life. It may thus be relevant for those planning pregnancy to take measures such as AIT to reduce the likelihood of their child becoming allergic. Strategies for healthy infants and young children with early manifestations such as AD, older children with manifest allergic disease such as AR, healthy adolescents/adults and adolescents/adults with already developed allergic disease need to be pursued.

In order to recommend AIT for the prevention of allergic diseases, evidence is required that there is a relevant and substantial beneficial effect on outcomes for the individual. Furthermore, safety aspects, quality of life, evaluation of health economics and other factors should be taken into consideration. Thus, an optimal balance between benefits, harms, costs and other possible disadvantages should be achieved (Table 1).
1 AIT for prevention: Evidence and clinical recommendations

2 AIT for short- and long-term prevention of development of new allergic disease

3 AIT for prevention of allergy in the offspring of allergic individuals

This topic has not been included in the protocol or in the systematic review. However, after finalizing
the systematic review, we found one low quality case-control study including 194 children of parents
subjected to and completing AIT at least 9 months before birth, who were compared with 195 controls
[25]. This study found that the odds ratios of any allergic disease and asthma was significantly lower
in children with one or both parents with allergy after AIT compared with those having parents with
allergy but without AIT (odds ratio: 0.73, 95% confidence interval 0.59-0.86). The authors hypothesise
that AIT in allergic parents might reduce the risk of allergies in their offspring, but this remains to be
established.

Based on the very scarce and very low quality evidence, we cannot recommend AIT for allergic
adult’s for prevention of allergic disease in their offspring (Table 2)

4 AIT in healthy individuals: Short- and long-term preventive effects

Two RCTs, one of high [26] and one of low quality [27], investigated the possible effect of AIT in
healthy individuals on the risk for development of their first allergic disease among infants with family
history of allergic diseases and asymptomatic adults sensitized to Japanese cedar pollen,
respectively. Meta-analysis [16] did not demonstrate a short-term preventive effect of oral HDM AIT
and Japanese cedar pollen SLIT in these two trials [26;27]. No data on long-term effects was
identified. Based on the results from the systematic review [16] there is no high quality evidence to
recommend use of AIT for the prevention of first allergic disease in healthy individuals (Table 2).

5 AIT in individuals with AD: Short- and long-term preventive effects

One medium quality RCT investigated the effects of 12 months of daily SLIT on prevention of asthma
and new sensitizations in children with AD and sensitization to one or more food allergens [28]. The
investigators included early immunological changes as a stopping rule and, as these a priori
immunological changes were not met,, recruitment was terminated and the trial reduced to pilot study
status. After 48 months of follow-up, there were no differences in asthma prevalence between the two
groups [28].
Based on the results from the systematic review [16], we cannot recommend AIT for prevention of development of first allergic disease in individuals with AD (Table 3).

**AIT in individuals with AR: Short- and long-term preventive effects**

The systematic review [16] identified six RCTs investigating the short-term preventive effect (i.e. up to two years post-treatment) of AIT on development of asthma in individuals with allergic rhinitis. These RCTs included three SCIT studies (one of high [29], one of medium [30] and one of low quality [31]), one medium quality on oral AIT [32] and one high quality SLIT study [33]. Three of these [29;30;32] were small studies with a trend towards less development of asthma in the AIT group but no significant differences. The remaining three studies [31;33;34] showed a significant reduction of development of asthma in the AIT groups as compared to the control groups. Meta-analysis [16] demonstrated a significant preventive effect of AIT on the development of asthma up to two years post-treatment in patients with AR. Subgroup analyses showed that AIT with either SLIT or SCIT was beneficial for those aged <18 years but not ≥18 years and for pollen AIT but not for HDM AIT.

Further, one large-scale real life retrospective non-randomized controlled before-after (CBA) study [35] investigated the short-term effect of AIT in patients with AR and reported a preventive effect of AIT on the progression from AR to asthma overall, and in those receiving SCIT but not SLIT.

For the long-term preventive effect (i.e. two or more years post-treatment) the systematic review identified two low quality SCIT RCTs [36;37] in patients with AR. Both showed a significantly lower risk for developing asthma in the SCIT groups as compared to the controls, up to seven years post-treatment [36], and two years post-treatment [37]. A large yet unpublished high quality RCT [38] explored the effect of a three-year course of SLIT tablets on the prevention of asthma in 812 mono-allergic children with AR and grass pollen allergy. Based on data available in EudraCT [39] this study failed to demonstrate the preventive effect of AIT on the development of asthma diagnosed by very strict criteria including reversibility to beta-2-agonists (OR=0.91; 95%CI 0.58 to 1.41)[38;39] two years post-treatment. It was, however, also reported that the number of subjects with asthma symptoms or asthma medication usage at the end of the five-year trial period in the SLIT group was significantly lower than in the placebo group (OR 0.66; 95%CI [0.45; 0.97] ; P=0.036). As published in the systematic review [16], meta-analysis showed no overall evidence of reduction in the long-term (i.e. at least 2 years post-treatment) risk of developing asthma. However, the studies may suggest a long-
term effect as regards development of asthma symptoms and medication but we need more data and more studies to confirm if this is the case.

The studies on asthma prevention in AR included patients with a history of AR and need for medication combined with documented pollen allergy for at least one previous season. There is no published information on severity thus subjects may have had a milder disease than those included in studies on efficacy of AIT. However, based on baseline descriptions of the populations in these studies, it is reasonable to assume that most of the patients included have persistent and not intermittent symptoms.

As discussed in another manuscript of this series of guidelines on AIT (ref: AR SR + Guideline)), patients with AR and pollen allergy also may benefit from AIT in reducing AR symptoms and need for medication for their AR. Thus, AIT is recommended for treatment of patients with moderate-to-severe pollen induced AR if not optimally controlled on antihistamines and nasal corticosteroids.

There are however also potential harmful effects, disadvantages and costs associated with the treatment, but these seem to be outweighed by the beneficial effects for this group of patients (Table 1) giving a favorable risk benefit profile.

In addition, there is moderate to high quality evidence indicating that AIT (SCIT or SLIT) can be recommended for short-term prevention (up to two years post-treatment) of asthma in children with moderate - severe AR and pollen allergy who are sub-optimally controlled despite appropriate pharmacotherapy, though there is no robust data indicating that this benefit persists after two years post-treatment. However, AIT may be considered in patients with milder AR disease given that it is able to modify the natural history including a long-term effect and the preventive effect as regards development of asthma on the progression of disease unlike pharmacotherapy.

The indication and initiation of AIT should be preceded by a discussion of the possible benefits, harms and disadvantages, and costs as well as the mode of AIT (SCIT vs SLIT) with the patient / family on an individual basis (Table 4).

**AIT for prevention of development of new allergic sensitization**

The systematic review identified three high quality RCTs [26;40;41], one moderate [42] and two low quality [33;43] RCTs that investigated the short-term effects of AIT on the risk of developing new
sensitizations. One high quality RCT [26] on oral HDM AIT for healthy infants at high risk of developing allergic disease found a significant reduction in sensitization to any common allergen in the active group compared with the placebo group at the end of the trial but no difference in HDM sensitization between the AIT and control groups [26]. The other two high quality RCTs found no effect of SLIT in adult patients allergic to peach [40] post-treatment and after SLIT with grass pollen or HDM extract in mono-sensitized children [41]. Three additional RCTs of medium to low quality [33;42;43] found a significantly lower incidence of new sensitizations among children and adults with AR treated with SLIT [33;43] and SCIT [42] as compared to controls.

Meta-analysis showed an overall reduction in the risk of allergic sensitization but the sensitivity analyses, excluding the two low quality studies by Marogna [33;43], failed to confirm this risk reduction [16].

The inconsistent evidence found in RCTs was also reflected in the included low quality CBA studies with three finding a lower occurrence of new sensitizations among AIT treated subjects compared with controls [44-46] with one study reporting higher occurrence in the AIT group compared with controls [47] and three studies reporting no differences between groups [48;49] [50].

The systematic review on long-term (i.e. at least two years post-treatment) preventive effects on prevention of new sensitivities identified one medium [51] and one low quality RCT [51] showing no preventive effect of SCIT among children with moderate-to-severe asthma followed into adulthood [51] and SCIT in adults with ARC three years post-treatment [52]. Another low quality RCT [37] found that patients with AR treated with HDM SCIT less frequently developed new sensitizations compared with controls two years post-treatment [37].

Meta-analyses of these studies [16] showed no evidence of a reduction in the long-term risk of allergic sensitization.

The seven low quality CBA studies investigating long-term preventive effects of AIT found inconsistent results, one study found no difference in onset of new sensitizations between intervention and control group [53], four studies showed reduced onset of new sensitizations in the AIT groups [45;54-57] and one found a significantly higher occurrence of new sensitization among AIT treated compared with controls [58].
The development of new sensitivities may impose a higher risk for development of new symptomatic allergies and it therefore might be relevant to try to prevent the development of new sensitizations. However, this has not been investigated sufficiently. Based on the present evidence, there is no high quality evidence to recommend the use of AIT for either the short- or the long-term prevention of development of new sensitizations in healthy individuals, children with atopic predisposition (Table 2), children with AD / food allergy (Table 3) nor in children and adults with AR / asthma (Table 4).
1 **Table 1. Benefits and harms / disadvantages of AIT in different populations**

<table>
<thead>
<tr>
<th>Population</th>
<th>Benefits</th>
<th>Harms / disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy +/- sensitization</td>
<td>Possible preventive effect</td>
<td>Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequency of visits in the clinic (SCIT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk for adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Costs</td>
</tr>
<tr>
<td>Children with atopic dermatitis</td>
<td>Possible preventive effect not documented</td>
<td>Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frequent visits in the clinic (SCIT)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risk of adverse events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Costs</td>
</tr>
<tr>
<td>Patients with allergic rhinitis</td>
<td>Documented beneficial effect on symptoms and reduction in medication, short - and long-term</td>
<td>Daily intake of tablets/drops (SLIT/oral) or regular injections (SCIT) for 3 years</td>
</tr>
<tr>
<td></td>
<td>Possible preventive effect</td>
<td>Frequency of visits in the clinic (SCIT)</td>
</tr>
<tr>
<td></td>
<td>Short term</td>
<td>Risk for adverse events</td>
</tr>
<tr>
<td></td>
<td>Long term?</td>
<td>Costs</td>
</tr>
</tbody>
</table>
## Table 2. AIT for prevention: recommendations for healthy individuals

<table>
<thead>
<tr>
<th>Recommendations for healthy individuals all ages</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT is not recommended in adult allergic patients for prevention of onset of allergic diseases in their offspring</td>
<td>IV-V</td>
<td>D</td>
<td>Weak recommendation: Based on results from 1 low quality study</td>
<td></td>
<td>Bozek A, 2016</td>
</tr>
<tr>
<td>AIT is not recommended for prevention of onset of allergic diseases in healthy individuals with or without sensitization</td>
<td>I</td>
<td>A</td>
<td>Weak recommendation: Based on 1 high and 1 low quality RCTs</td>
<td>One RCT with infant and one with adult population</td>
<td>Zolkiipli 2015, Yamanaka 2015</td>
</tr>
<tr>
<td>AIT is not recommended for prevention of new sensitizations in healthy children</td>
<td>I</td>
<td>B</td>
<td>Weak to moderate recommendation: Based on results from 2 high quality RCTs</td>
<td>One RCT with infant and one with preschool population</td>
<td>Zolkiipli 2015, Szepfalusi 2014</td>
</tr>
<tr>
<td>AIT is not recommended for prevention of new sensitizations in healthy adults</td>
<td>V</td>
<td>D</td>
<td>Expert opinion. No studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. AIT for prevention: recommendations for individuals with early life atopic manifestations, e.g. atopic dermatitis or food allergy

<table>
<thead>
<tr>
<th>Recommendations for individuals with early atopic manifestations</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT is not recommended in children with atopic dermatitis for the prevention of onset of later allergic manifestations</td>
<td>I</td>
<td>B</td>
<td>Weak recommendation: Based on 1 small medium quality study</td>
<td></td>
<td>Holt P 2013</td>
</tr>
<tr>
<td>AIT is not recommended for the prevention of onset of other allergic manifestations in individuals at all ages with other early atopic manifestations e.g. food allergy</td>
<td>V</td>
<td>D</td>
<td>Expert opinion. No studies</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4. AIT for prevention: recommendations for school age children, adolescents and adults with allergic rhinitis or asthma

<table>
<thead>
<tr>
<th>Recommendations for individuals with manifest allergic disease(s), e.g. allergic rhinitis</th>
<th>Evidence level</th>
<th>Grade of recommendation</th>
<th>Strength of recommendation</th>
<th>Other considerations</th>
<th>Key references</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A 3 year course of AIT (SCIT or SLIT) can be recommended for short-term (i.e. &lt; 2 years post treatment) prevention of the onset of asthma in children and adolescents with AR and grass/birch pollen allergy who are sub-optimally controlled despite appropriate treatment with antihistamines / nasal corticosteroids</strong></td>
<td>I</td>
<td>A</td>
<td>Moderate recommendation: Based on consistent significant results from 2 medium (Möller1986, Novembre) and 2 low quality (Möller2002, Marogna2008) RCTs and some CBA studies</td>
<td>The indication should be discussed with the patients / families including the asthma preventive effect as well as the effect on AR and risk of adverse effects, costs and preferences</td>
<td>Möller1986, Möller2002, Novembre2004, Marogna2008</td>
</tr>
<tr>
<td><strong>No recommendation can be made in favor for or against the use of AIT (SCIT or SLIT) for the long-term (≥ 2 years post treatment) prevention of the onset of asthma in children and adolescents with AR and grass/birch pollen allergy</strong></td>
<td>I</td>
<td>B</td>
<td>Weak recommendation: Based on consistent results from 2 low quality RCTs, non-significant results from 1 high quality RCT (Valovirta2016), and the meta-analyses being not significant</td>
<td>The study by Valovirta not yet published</td>
<td>Jacobsen2007, Song2015, Valovirta2017</td>
</tr>
<tr>
<td><strong>No recommendation can be made in favor for or against the use of AIT (SCIT or SLIT) for short-term (i.e. &lt; 2 years post treatment) or long-term (i.e. ≥ 2 years post treatment) prevention of the onset of asthma in children and adolescents with AR and allergy to HDM or other allergens except for birch/grass pollen</strong></td>
<td>I</td>
<td>B</td>
<td>Weak recommendation: Based on inconsistent results from 1 low (Marogna2008) and 1 high quality RCTs (Grembiale2002)</td>
<td>Only HDM, parietaria and mix of these and grass/birch pollen investigated</td>
<td>Marogna2008, Crimi2004, Grembiale2002</td>
</tr>
<tr>
<td><strong>AIT (SCIT or SLIT) is not recommended for short-term (i.e. &lt; 2 years post treatment) or long-term (i.e. ≥ 2 years post treatment) prevention of the onset of asthma in adults with AR and HDM or pollen allergy</strong></td>
<td>I</td>
<td>B</td>
<td>Weak recommendation: Based on 1 small medium quality study</td>
<td></td>
<td>Crimi 2004</td>
</tr>
<tr>
<td><strong>AIT is not recommended for prevention of new sensitizations, either in children or adults with allergic rhinitis and/or asthma</strong></td>
<td>I</td>
<td>B</td>
<td>Weak recommendation: Based on inconsistent results from 4 low, 2 medium and 3 high quality RCTs</td>
<td></td>
<td>SR</td>
</tr>
</tbody>
</table>
Safety

The systematic review only included safety data from studies on the preventive effect of AIT and it is therefore not complete with this regard. However, the safety issues are fully covered by other systematic reviews and guidelines in this AIT guideline series (AR SR and Guideline). Fatalities are very rare and not described for SLIT. The safety profile for the present purpose is not regarded as being different from AIT for treatment of AR. Due to its better safety profile SLIT might be a better choice for prevention than SCIT.

Cost-effectiveness

The systematic review did not identify any studies investigating the cost-effectiveness of AIT for the prevention of allergy.

Summary, gaps in the evidence and future perspectives

This guideline on AIT for prevention of allergy has been developed as part of the EAACI AIT Guidelines project. The recommendations in this guideline are based on a thorough systematic review performed by a group of experienced and independent methodologists and have been developed by a multidisciplinary collaboration in an EAACI Task Force representing a range of countries and disciplines and clinical backgrounds.

The guideline provides evidence based recommendations for the use of AIT for prevention of new allergic disease(s) and new allergic sensitization(s) in all populations. The guidelines should provide help to all healthcare professionals as regards evaluation of AIT for prevention of allergic disease/sensitization, and when to refer which individuals to further evaluation. The main results are summarized in box 4.

There are many areas, for which there is no evidence or no high quality evidence representing gaps in the current evidence as indicated in Table 5. Thus, for the possible preventive effect of AIT in healthy individuals or in children with early atopic manifestations such as atopic dermatitis or food allergy as well as for the possible long-term effect in children with AR there is a lack of evidence. Also, we did not find studies related to spreading of allergic sensitization(s) at the molecular level, nor did we identify studies exploring the development of new oral allergy syndrome (OAS) or health economic
analyses of AIT used for prevention. In addition, there is a lack of evidence as regards patient selection (e.g. optimal age and characteristics) for preventive AIT or for the optimal allergen preparation, mode and duration of AIT administration; there is a need for standardized relevant outcomes including Quality of life (QoL) for future studies.

The current evidence does not allow differentiation between SCIT and SLIT; therefore, this choice has to depend on availability, patients / families preferences, and other considerations such as safety and costs. Studies, which demonstrate a preventive effect upon which we have based our recommendations, included three-year courses of perennial AIT.

Based on current evidence, AIT can be recommended for the short-term prevention of development of asthma in children and adolescents with AR and pollen allergy, primarily birch and grass, however it is not documented whether this effect is a postponement or whether it can be extended to the longer-term (i.e. at least two years post-treatment). AIT should in particular be considered for those with moderate-severe AR as it has been shown to be effective in controlling this condition in addition to the preventive effect on the short-term development of asthma (ref AR SR and guideline). Furthermore, some patients with less severe AR may prefer AIT due its long-term and asthma preventive effect or to avoid side effects of other treatments.

Children and adolescents included in the prevention studies did not necessarily fulfil the criteria for recommendations for AIT for treatment of AR as well as they did not necessarily meet the ARIA criteria for moderate/severe symptoms. At present, the indications for AIT for prevention of allergic disease are the same as for treatment of AR (i.e. documented IgE-mediated disease caused by the relevant allergens and not sufficiently controlled by antihistamines and nasal corticosteroids).

Contraindications are the same as for treatment of AR. The asthma preventive effect may in the future influence the threshold for AIT by reducing the level of severity of AR required for the indication of AIT in children and adolescents with AR and pollen allergy, especially grass pollen allergy. Therefore, based on the preventive effect, it may be relevant to discuss AIT as a relevant treatment option for children and adolescents up to 18 years of age with less severe but persistent AR due to pollen allergy and need for medication during the relevant season. During and after AIT patients should receive relevant pharmacological treatment as needed. At this moment, there is no high quality evidence to support this approach for HDM allergic patients with AR.
For implementation of these guidelines there is a need to ensure that primary care healthcare professionals recognise AIT as a treatment option for some allergic diseases and have clear guidelines to aid patient selection for referral to specialist care. Patients and patient organizations need to be aware of AIT as a treatment option. Political awareness should be increased to ensure sufficient availability, knowledge, competences, skills and resources in the health care system by demonstrating total economic benefits of such therapy by exploration of its positive impact on economic productivity.
### Table 5. Gaps in the evidence

<table>
<thead>
<tr>
<th>Gaps</th>
<th>Plan to address</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT for the prevention of new allergic sensitizations</td>
<td>RCTs</td>
<td>Low</td>
</tr>
<tr>
<td>- spreading from one allergen to related and unrelated allergen(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- spreading at molecular level, from one allergenic molecule to other molecules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIT for prevention of first allergic disease</td>
<td>RCT</td>
<td>Medium</td>
</tr>
<tr>
<td>AIT for prevention of AR / asthma in children and adults with AD / food allergy</td>
<td>RCTs</td>
<td>Medium</td>
</tr>
<tr>
<td>AIT for prevention of the Oral Allergy Syndrome</td>
<td>RCT</td>
<td>Low</td>
</tr>
<tr>
<td>AIT for prevention of asthma in children with AR - long term effect</td>
<td>RCTs</td>
<td>High</td>
</tr>
<tr>
<td>AIT for prevention of asthma in children with AR due to HDM</td>
<td>Further evaluation of GAP trial</td>
<td></td>
</tr>
<tr>
<td>Optimal age of introduction for AIT for prevention</td>
<td>RCT</td>
<td>High</td>
</tr>
<tr>
<td>Optimal duration of AIT for prevention</td>
<td>RCT</td>
<td>High</td>
</tr>
<tr>
<td>Evaluation of health economics of AIT for prevention</td>
<td>Cost-effectiveness analysis of RCT</td>
<td>Medium</td>
</tr>
<tr>
<td>Evaluation of influence of AIT for prevention on Qol in different age groups</td>
<td>Qol as outcome in RCTs</td>
<td>High</td>
</tr>
<tr>
<td>Evaluation of adherence in AIT for prevention in different age groups</td>
<td>Adherence measured in RCTs and real life studies</td>
<td>Medium</td>
</tr>
<tr>
<td>Evaluation of acceptability of AIT for prevention in different age groups</td>
<td>RCTs</td>
<td>Medium</td>
</tr>
</tbody>
</table>
Box 4. Summary

- AIT is not recommended for the prevention of new sensitizations
  - in healthy individuals
  - in individuals with established allergic disease
- AIT is not recommended for prevention of new allergic manifestations in
  - Children with atopic dermatitis / food allergy
- A three year course of AIT (SCIT or SLIT) can be considered in children with moderate – severe AR and grass/birch pollen allergy, not sufficiently controlled with optimal pharmacotherapy, for short-term (i.e. < 2 years post-treatment) prevention of the onset of asthma in addition to improving the control of AR. It is uncertain, whether this asthma preventive effect is maintained over a longer period
  - Before initiating AIT the possible benefits including the beneficial effects on controlling AR symptoms, disadvantages and potential harms and costs should be discussed with the patient / family on an individual basis
- AIT (SCIT or SLIT) cannot be recommended for prevention of the onset of asthma in children with AR and allergy to HDM or other allergens than birch/grass pollen – neither for short-term or long-term prevention

Dietary interventions in infants aimed at the prevention of food allergy are not covered in these Guidelines: they form part of the ‘EAACI food allergy and anaphylaxis guidelines’
Box 5 Key messages for primary care about referral to allergy services

- **AIT to prevent allergy is not recommended for:**
  - Parents who are planning a family
  - Healthy infants/children
  - Infants/children with AD and/or food allergy

- **AIT may have a role in delaying/preventing progression from seasonal AR/ARC to asthma**
  - Primary care teams should consider referring children with troublesome AR/ARC not responding sufficiently to optimal pharmacotherapy for a specialist assessment with a view to considering AIT to improve control of AR/ARC and also simultaneously delay/prevent asthma
  - In such families, there will need to be an assessment made of the potential benefits, risks and costs of AIT

- **AIT may be indicated in those with perennial AR/ARC on clinical grounds but not only for delaying/preventing progression to asthma**

**Acknowledgements**

We would like to acknowledge the support of EAACI and the EAACI Allergen Immunotherapy Guidelines Group in developing these guidelines. We would like to thank xxxxxxx for their assistance in preparing the guidelines. We would also like to thank our expert panel and everyone who provided comments on the draft guidelines (xxxxxxxxxxx) and the EAACI Executive Committee for their helpful comments and suggestions.

**Authors’ contribution**

xxxxxxxxxx

**Conflicts of interest**

xxxxxxxxxx
Recommendations for individuals with allergic rhinitis: barriers and facilitators to implementation, audit criteria and resource implications of recommendations

<table>
<thead>
<tr>
<th>Prevention of development of asthma in patients with AR</th>
<th>Evidence level</th>
<th>Grade</th>
<th>Key references</th>
<th>Barriers to implementation</th>
<th>Facilitators to implementation</th>
<th>Audit criteria</th>
<th>Resource implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>In children with AR and grass/birch pollen allergy a 3 year course of AIT (SCIT or SLIT) can be recommended for short-term (i.e. &lt; 2 years post treatment) prevention of the onset of asthma in children with daily symptoms and need for medication</td>
<td>I</td>
<td>A</td>
<td></td>
<td>Failure to recognize manifestations, Lack of knowledge amongst patients, caregivers and professionals about the benefits of AIT, Lack of access to AIT, Unavailability of AIT, Concerns about side-effects, Economic aspects</td>
<td>Information amongst patients, caregivers and professionals about the benefits of AIT, Reimbursement of AIT</td>
<td>Proportion of potentially eligible patients referred from primary care for a specialist assessment, Proportion of potentially eligible patients formally considered for AIT</td>
<td>Thorough investigation of the patient including proper assessment of relevant allergies. AIT need to be prescribed, made available and administered to patients</td>
</tr>
</tbody>
</table>
References


37. Song W, Lin X, Chai R. [Efficacy evaluation of standardized dust mite allergen specific immunotherapy to patients of allergic rhinitis]. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2014; 28:300-2.


Ref Type: Online Source


47. Asero R. Injection immunotherapy with different airborne allergens did not prevent de novo sensitization to ragweed and birch pollen north of Milan. Int Arch Allergy Immunol 2004; 133:49-54.


