

Allergen Immunotherapy for the Prevention of Allergic Asthma

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Abbreviations AD Atopic dermatitis/eczema · AIT Allergen immunotherapy · AR Allergic rhinitis/Allergic rhinoconjunctivitis · SLIT Sublingual immunotherapy · SR Systematic Review

Abstract

Purpose of review: Children with allergic rhinitis (AR) have a high risk of developing asthma. An effect beyond end of allergen immunotherapy (AIT) has been demonstrated, and moreover a preventive effect on the development of asthma in children with AR is suggested. The aim of this review is to discuss the evidence for the asthma preventive capacity of AIT.

Recent findings: According to the recently published systematic review and clinical practice AIT guideline from The European Academy of Allergy and Clinical Immunology (EAACI), there is sufficient evidence to recommend a 3-year course of AIT for children and adolescents with moderate to severe AR and grass/birch pollen allergy, for the prevention of asthma for up to 2 years post-AIT. Further, a recent high-quality trial demonstrated a preventive effect of a 3-year course of AIT with a sublingual grass tablet on asthma symptoms and medication 2 years post-AIT in children with AR and grass pollen allergy.

Summary: AIT has a disease-modifying and asthma preventive effect, which may influence the indication for AIT in the future.

Introduction

Allergic respiratory diseases are among the commonest chronic diseases [1–4] and cause a considerable burden to individuals leading to impaired quality of life [5] and an economic burden to the patients and to the society. They encompass allergic rhinitis (AR)/rhinoconjunctivitis (ARC) and asthma, which frequently start in early childhood and continue throughout adulthood.

Many factors such as atopic heredity play a role in the risk of development of allergic disease, but also sensitization in early life and/or early manifestations of atopic diseases, e.g., atopic dermatitis (AD) and food allergy, or later manifestation such as AR is associated with a higher risk for development of other allergic manifestations such as asthma [6, 7]. AR frequently precedes the onset of asthma and is a major risk factor for later development of asthma [1, 2]. AR and asthma often co-exist and up to 50% of patients with AR have bronchial hyperreactivity (BHR) [1, 8, 9]. It has been shown that children with AR have a 3-fold increased risk of developing asthma later in life, when compared to those without AR [6, 10], especially those with BHR [11]. Further, childhood atopic eczema and AR are found strongly associated with

the incidence and persistence of adult atopic asthma and with allergic asthma persisting into adulthood [12].

Allergen immunotherapy (AIT) is a specific therapeutic approach having been used for more than 100 years, and that has been proven effective for the treatment of the allergic airway diseases AR and allergic asthma leading to a sustained reduction in symptoms and need for symptomatic treatment. AIT is regarded a disease-modifying intervention in IgE-mediated allergic disease, with a therapeutic effect, even beyond end of AIT [13–15], and with the potential for a preventive effect [16–19]. Studies assessing the long-term effectiveness of AIT in children with AR have indicated that AIT also might reduce the risk of developing asthma [20–23] and bronchial hyperreactivity.

During the last decades, some studies and recent Systematic Reviews and meta-analyses addressing the possible preventive capacity of AIT have been performed.

The aim of this review is to discuss the present evidence for the preventive capacity of AIT as regards development of asthma and its implications in clinical practice.

Methods of the review

This review is mainly based on the most recently published systematic review and meta-analysis from EAACI Allergen Immunotherapy Guidelines, “Allergen Immunotherapy for the prevention of allergy: A systematic review and meta-analysis” [24] and “EAACI Guidelines on Allergen Immunotherapy: Prevention of allergy” [25••], and supplemented with studies published hereafter.

The search strategy for the EAACI Systematic Review and meta-analysis is described in detail in the preceding developed and published protocol [26•]. The systematic review aimed to identify, describe, and evaluate studies of the preventive effect of AIT on development new allergic disease or new sensitizations in any population, including the development of asthma in healthy individuals and in individuals with already developed sensitization and/or atopic manifestation, e.g., atopic dermatitis or AR. Two methodologists independently screened nine international biomedical databases, extracted data, and performed a quality assessment using generally accepted and described tools. All populations at all ages, all routes of AIT, and all allergens were included. The systematic review identified 15 randomized controlled trials (RCTs) of varying quality and 15 controlled before and after studies (CBA) of lower quality. The systematic review and following guidelines also included data available on EudraCT from an unpublished RCT on prevention of asthma in children with AR [24, 27]. The EAACI guidelines was prepared using the

Appraisal of Guidelines for Research & Evaluation (AGREEII) approach including representation of all relevant stakeholders, evaluation of lack of evidence and of facilitators, and barriers for the implementation.

The present review include data from RCTs as described in EAACI AIT systematic review and meta-analysis [24] and guidelines [25••] on the AIT asthma preventive effect in different populations, as described in Tables 1, 2, and 3. In addition, it includes further data from the only RCT on this topic published afterwards. Thus, this review includes RCTs on the AIT asthma preventive effect in healthy infants and young children with sensitization and/or AD [28, 29] as described in Table 1, the asthma preventive effect of subcutaneous immunotherapy (SCIT) [11, 30–34] and sublingual immunotherapy (SLIT) [35–37, 38••] in children with AR as described in Tables 2 and 3. The results are supported by two large real-life studies [39, 40]. Also, the AIT preventive effect on the development of new sensitization is discussed, based on the EAACI systematic review and meta-analysis since no new RCTs on this topic have been published.

The evidence

AIT for prevention of development of new asthma

Strategies to prevent asthma by AIT may address different populations, e.g., healthy infants and young children with sensitization and/or early manifestations such as AD or older children/adolescents with manifest allergic disease such as AR. Currently we have data for AIT in healthy infants/young children with sensitization and/or AD and children/adolescents with AR.

AIT in healthy infants and young children with sensitization and/or AD

Two RCTs investigated the potential preventive effect of AIT in infants with a family history of atopy and/or sensitization and/or AD focusing on the effect of SLIT drops on asthma [28] and oral AIT on eczema, wheeze, and food allergy [29], respectively. One RCT investigated the possible preventive effect of asthma and new sensitizations in children with AD and sensitization to one or more food allergens [28] of 1 year SLIT with a mixture of house dust mite (HDM), cat, and Timothy grass allergens. Meanwhile, due to a predefined stop-rule with immunological changes, indicating that the treatment was not delivering sufficient allergen transmucosally to trigger an immunological response, recruitment was interrupted before planned and the trial reduced to a pilot study status. There were no differences in asthma prevalence between the two groups after 4 years follow-up [28]. One recent large high-quality RCT [29] of oral HDM AIT to infants with a family history of allergic diseases showed no preventive effect on AD, wheeze, and food allergy at 1 year of age. Based on these studies, there is currently no good evidence for the prevention of asthma in healthy individuals or children with atopic eczema by AIT, but further good studies are needed. The characteristics and results from these studies are summarized in Table 1.

Table 1. RCTs investigating the preventive effect of AIT in infants/children with family history of atopy, early sensitization, and/or atopic dermatitis (AD)

Study	Subjects included (n)/age	Participants	Outcomes	Intervention	Allergens for AIT	Risk of bias	Main results	Comments
Holt, 2013, USA and Australia	N 50/age: 18–30 months 25 active/25 placebo	Infants with a family history of atopy, AD, and sensitization to ≥ 1 food allergen	Development of asthma and sensitizations at 48 months	SLIT (drops) with a mixture of soluble allergens vs. placebo for 12 months	House dust mite, cat, Timothy grass	Moderate	No difference in asthma prevalence (4/25 in SLIT group; 4/25 in placebo group). No significant differences in rates of sensitization	There was no difference between active/placebo groups in early immunological changes, as an indication that the treatment was not delivering sufficient allergen transmucosally to trigger immunological recognition by the infant mucosal system at 6 month. Therefore recruitment was terminated and study status changed to pilot study
Zolkipli, 2015, UK	n = 111 < 1 year 57 active, 54 placebo	Infants at high risk of atopy (≥ 2 first-degree family members with allergic diseases) but negative skin prick test to common allergens	Development of eczema, wheeze, food allergy, and sensitizations after 12 months	House dust mite oral AIT (drops) vs. placebo for 12 months	House dust mite	Low	No effect on eczema, wheeze, and food allergy or on house dust mite sensitization. Significant reduction ($P = 0.03$) in sensitization to any common allergen (16%; 95% CI 1.7–30.4%) in the active group (5 [9.4%]) vs. the placebo group (13 [25.5%])	

Table 2. RCTs investigating the preventive effect of SCIT in patients with allergic rhinitis (AR)

Study	Subjects included (n)/age	Participants	Outcomes	Intervention	Allergens for AIT	Risk of bias	Main results	Comments
Crimi, 2004, Italy	N 30 (15 active, 15 placebo) Age 20–54 years	Patients with seasonal AR, but no asthma and monosensitized to <i>Parietaria judaica</i>	Development of asthma and bronchial hyperresponsiveness (BHR) after end of 3 years SCIT	SCIT vs. placebo Rapid up dosing cluster regimen	Parietaria pollen	Moderate	A total of 9/29 developed asthma symptoms at the end of the study: 7 (47%) in the placebo group, 2 (14%) in the SCIT group ($P = 0.056$) No changes in BHR	Authors conclude that Parietaria SCIT appears to prevent natural progression of AR to asthma; but the results were not statistically significant
Grembiale, 2000, Italy	N 44 (22 active, 22 placebo). Age: 10–38 years	Subjects with a documented history of AR, no reported asthma symptoms	Development of asthma and BHR after end of 2 years SCIT	SCIT vs. placebo	House dust mite	Low	None in the SCIT group developed asthma vs. 9% in the placebo group ($P = 0.49$) All had normal lung function test at inclusion PD ₂₀ FEV ₁ within normal range of 50% of SCIT subjects ($P < 0.0001$) and significantly higher than in placebo group ($P < 0.0001$) No changes in PD ₂₀ FEV ₁ in placebo group	Positive correlation between PD ₂₀ FEV ₁ before SCIT and magnitude of improvement in BHR suggest that early intervention is likely to be of greater benefit
Jacobsen, 2007, European multicenter study Niggemann, 2006 Möller, 2002	N 205 (103 SCIT, 102 controls) Age at baseline: 6–14 years Follow-up at 10 years: 147 (79 active, 68 controls) Follow-up at 5 years (2 years after end of treatment): 183 (95 active, 88 controls) Follow-up at 3 years (end of treatment): 191 (97 active, 94 controls)	Children with birch and/or grass pollen-induced AR	Development of asthma and BHR after 3 years (end of SCIT) vs. only symptomatic treatment and after 5 and 10 years	SCIT for 3 years vs. pharmacotherapy only	Grass and/or birch	High	OR for no-asthma 4.6 (95% CI: 1.5–13.7) in favor of SCIT group after 10 years At 5 years follow-up, significantly less in the SCIT group had asthma compared to controls (OR 2.68, 95% CI: 1.3–5.7) i.e., at end of SCIT significantly fewer in the SCIT group had asthma compared to controls (OR 2.52, $P < 0.05$).	Randomized controlled, but not blinded study. All in both groups received symptomatic pharmacotherapy as needed

Table 2. (Continued)

Study	Subjects included (n)/age	Participants	Outcomes	Intervention	Allergens for AIT	Risk of bias	Main results	Comments
Song, 2014, China	N 102 (51 active, 51 symptomatic pharmacotherapy only) Age: > 5 years	Patients with AR allergic to house dust mites	Onset of asthma and development of new sensitizations 2 years after end of SCIT	SCIT vs. pharmacotherapy for 3 years	House dust mite	High	No significant differences between SCIT and control group in BHR in change from baseline of PC ₂₀ after 10 years None in the SCIT group developed asthma vs. (22%) in the control group developed asthma ($P < 0.01$) Few new sensitizations (2/43, [4.7%]) in the SCIT group vs. 17/41 (41.5%) in the control group ($P < 0.01$)	Authors conclude that early application of SCIT can prevent the development of asthma

Table 3. Studies investigating the preventive effect of OIT or SLIT in patients with allergic rhinitis (AR)

Study	Subjects included (n)/age	Participants	Outcomes	Intervention	Allergens for AIT	Risk of bias	Main results	Comments
Möller, 1986, Sweden	<i>n</i> = 30 (14 active, 16 placebo) Age: 8–16 years	Children with AR due to birch pollen allergy	Development of asthma and safety after end of 10 months oral AIT	Oral (capsules) vs. placebo for 10 months	Birch	Moderate	No development of asthma in oral IT group vs. 5 in the placebo group	Similar adverse effects in both groups. No systemic reactions
Novembre, 2004, Italy	<i>n</i> = 113 (54 active, 59 controls = standard symptomatic therapy) Age: 5–14 years	Children with hay fever limited to grass pollen	Development of asthma after end of 3 years SLIT	SLIT (drops) 4 months co-seasonal each year vs. pharmacotherapy for 3 years	Extract of mixed grass pollens	Moderate	After first year of SLIT, 6 in the SLIT group had asthma vs. 6 in the control group. After the second year, 7 in the SLIT group and 16 controls had asthma (<i>P</i> 0.058). After the third year, 8 in the SLIT group and 18 controls had asthma (<i>P</i> 0.0412). Relative risk of development of asthma after 3 years was 3.8 (95% CI: 1.5–10.0) in control group compared to intervention group	At entry into the study, no subject reported seasonal “asthma” with more than 3 episodes per season “Asthma” was not well defined, only as “cough and wheezing—breathing difficulty”
Marogna, 2008, Italy	<i>n</i> = 216 (144 active, 72 treated with drugs only) Age: 5–17 years	Children with AR ± intermittent asthma	Development of asthma, new sensitizations and BHR after end of 3 years SLIT Safety	SLIT drops vs. pharmacotherapy for 3 years	House dust mite (<i>n</i> 98), grass (<i>n</i> 41), birch (<i>n</i> 4), Parietaria (<i>n</i> 1)	High	Higher prevalence of intermittent and persistent asthma in control group (30/66, 45.4%) compared to the SLIT group (17/130, 13.1%) Less new sensitizations in SLIT group (4/130) vs. controls (23/66) (OR 0.06; 95% CI, 0.02–0.17) Increased rate of polysensitizations in control group compared to SLIT group (OR SLIT vs. control at year 3: 0.33; 95% CI, 0.17–0.61) In SLIT group 34 vs. 39 in control group developed asthma as defined by strict diagnostic criteria incl. reversibility test. No difference between groups <i>P</i> = 0.67 In the SLIT group, the number with asthma	Reduced onset of intermittent or mild persistent asthma, and decreased bronchial hyperreactivity and new sensitizations
Valovirta, 2017 European multicenter study (11 countries)	<i>N</i> 812 (398 active, 414 controls) Age: 5–12 years at inclusion	Children with grass pollen-induced AR, without asthma, and no overlapping allergies	Time to onset of asthma, asthma symptoms and medication after 5 years	SLIT tablet vs. placebo once daily for 3 years, followed by a blinded follow-up period of 2 years	Grass	Low		

Table 3. (Continued)

Study	Subjects included (n)/age	Participants	Outcomes	Intervention	Allergens for AIT	Risk of bias	Main results	Comments
							symptoms or asthma medication usage was significantly less than in the placebo group (OR 0.66; <i>P</i> 0.036; 95% CI [0.45; 0.97]) at the end of the trial, during the post-treatment follow-up period and during the entire 5-year trial period	

AIT in children/adolescents with AR

As summarized in Tables 2 and 3, and EAACI AIT Systematic Review and Guidelines [24, 25••], four RCTs addressed the effect of SCIT (Table 2) and another four the effect of SLIT (Table 3) in patients with AR on the prevention of development of asthma. Of these, one study reported asthma preventive effects at the end of 3 years SCIT and further, 2 and 5 years post-SCIT [11, 32, 33]. Three of these RCTs investigated the longer-term asthma preventive effect 2 years after the end of AIT [11, 32, 34]. Three [30, 31, 35] were small studies with a trend towards less development of asthma in the AIT group, but without significant differences. Three studies [33, 36, 37] showed a significant reduction of the development of asthma in the AIT groups as compared to the control groups up to 2 years post-AIT. The EAACI Systematic Review (SR) and meta-analysis [24] demonstrated a significant preventive effect of AIT on the development of asthma up to 2 years post-AIT in patients with AR and predefined subgroup analyses showed that AIT with either SLIT or SCIT was beneficial for those aged < 18 years and for pollen AIT. For HDM AIT, there was an OR of 0.20 in favor for AIT, which was not statistically significant, but it cannot be excluded that this can be ascribed to the very small groups in the HDM study. There was a high degree of heterogeneity, and therefore the meta-analysis should be interpreted with caution. Furthermore, the results were supported by two large-scale, real-life, retrospective, non-randomized CBAs [39, 40], based on German longitudinal prescription databases; both reporting a preventive effect of AIT on the progression from AR to asthma.

For the longer-term preventive effect, at least 2 years post-AIT, two high risk of bias SCIT RCTs [11, 32, 34] in patients with AR showed a significantly lower risk for developing asthma in the SCIT groups as compared to the controls, up to 7 years post-AIT [11, 32, 33], and 2 years post-AIT [34]. A large recently published low risk of bias RCT (Grazax Asthma Prevention = GAP trial) [27, 38••] explored the effect of a 3-year course of SLIT tablets on the prevention of asthma in 812 children with AR and grass pollen allergy. This study [38••] failed to demonstrate the preventive effect of AIT on the development of asthma as defined by very strict *a priori* criteria, including spirometric reversibility after the administration of inhaled beta-2-agonists (OR = 0.91; 95% CI [0.58 to 1.41]) [27, 38] 2 years post-AIT. However, this study did demonstrate that the number of subjects with asthma symptoms or with use of asthma medication was significantly lower in the SLIT group compared to the placebo group at the end of the 5-years' trial period (OR 0.66; 95% CI 0.45 to 0.97; $P < 0.036$), during the 2-year post-AIT follow-up, and during the entire 5-year trial period. In addition, the AR symptoms were significantly reduced during the entire 5-years' trial period. Further, it appeared that this preventive effect was strongest for the youngest children [38]. Also two high risk of bias non-randomized studies including one with grass pollen SCIT [22, 23] and one with HDM SCIT [41] in children with AR suggested a long-term effect. As published in the EAACI SR [24], the meta-analysis on the longer-term asthma preventive effect showed no overall evidence of reduction in the risk of developing asthma, but there was a high degree of heterogeneity so the results should be interpreted with caution. Furthermore, the negative result was due to one RCT with very strict diagnostic criteria, for the primary outcome (GAP, as already discussed above), whereas in the same study there was a significant effect on asthma symptoms and/or

medication use, but these variables were not included in the meta-analysis as they were secondary outcomes [38].

Thus, it is a question which asthma outcome parameter(s) is most relevant—a diagnosis based on demonstrated reversibility or on symptoms and medication use or a score combining symptoms and medication use, as suggested as the optimal outcome measure for AIT for allergic AR [42]. There is an urgent need to define and standardize the optimal clinical asthma outcomes that should be used in future clinical trials for preventive effect of AIT. Furthermore, none of the studies reported specifically on the prevention of allergic asthma.

AIT for the prevention of the development of new allergic sensitization

Besides the asthma preventive effect AIT may prevent the development of new allergic sensitizations, and thus possibly have an impact on the natural course of allergic diseases. This hypothesis was primarily based on previous retrospective, non-randomized studies indicating a preventive effect of AIT as regards development of new sensitizations, though the evidence was weak.

Nine RCTs [29, 34, 37, 43–48] of varying quality with varying allergens and formulations investigating the AIT preventive effect on new allergic sensitization showed inconsistent results. The inconsistent evidence, found in RCTs, is also reflected in a number of high risk of bias CBA studies [22, 49–60].

Recent SRs and meta-analyses concluded that, though some studies indicated an effect, there is currently either very weak and uncertain [61] or no good overall evidence for a preventive effect of AIT on the development of new sensitizations [24, 62]. Heterogeneity among the trials is considerable and there is a lack of good long-term studies to evaluate a possible preventive effect on the development of new allergic sensitizations sufficiently.

Meanwhile, one low risk of bias RCT [29] on oral HDM AIT for healthy infants at high risk of developing allergic disease found a significant reduction in sensitization to any common allergen (HDM, grass pollen, cat, peanut, milk, and egg) in the active group as compared with the placebo group at the end of the trial, but no difference in HDM sensitization [29].

The development of new sensitizations may impose a higher risk for the development of further symptomatic allergies, suggesting that attempts to prevent the development of new sensitizations might be relevant. However, this has not been investigated sufficiently. A subgroup analysis in the EAACI SR [24] showed a tendency towards an effect in children and adolescents after 3 years of AIT, supporting the rationale of the clinical effect.

Thus, there is currently no good evidence for a preventive effect of AIT for the development of new sensitizations, but some positive data suggest this topic as a relevant focus for future high-quality trials.

Safety

The AIT safety issues are recently described in the EAACI SR [13] and guideline for AR [63]. As has been described thoroughly in other publications, SCIT may be associated with allergic side effects. That is why it is recommended that SCIT should be administered in a specialist setting. Fatalities are very rare and have not been reported with the use of SLIT. In a recent meta-analysis on the efficacy

of the grass pollen SLIT tablet [64], no episodes of anaphylaxis were reported, despite the description of seven treatment-related adverse events, treated with adrenalin in the SLIT RCTs. In recent real-life clinical studies of AIT, the overall rate of adverse reactions is similar for SCIT and SLIT [65, 66], but less severe systemic reactions were reported with SLIT than with SCIT. The safety profile of AIT for prevention is not regarded as being different from AIT for the treatment of AR.

Using AIT for the prevention of the development of new allergic diseases or sensitizations requires the use of products with a high level of safety, especially if the AIT products are meant to be used in healthy individuals for the primary prevention of allergic diseases. However, if AIT is indicated as part of the treatment of an already existing allergic disease, and the preventive effect is regarded as an additional effect, then the safety profile should be considered in that context.

Summary and perspectives

Problems in evaluation of the evidence

The heterogeneity in the populations under study, in the methods employed, and in the outcomes studied makes it challenging to interpret the evidence. The results of individual studies are difficult to compare because of, e.g., different populations, methods, outcome measures, diagnostic criteria and severity, and cutoff values for measuring sensitization. Besides, the mode of administration and the products used for AIT differ as regards allergens, formulation and strength [67, 68] schedules, dose, route of administration, and duration of the intervention [67, 69]. Additionally, many studies are small without sufficient power and adjustment for confounders.

The significant heterogeneity seen in meta-analysis can be explained by the study design, study population, products, and schedules evaluated. Therefore, an individual product-based evaluation of the evidence for efficacy is strongly recommended before treatment with a specific product is initiated [19, 70]. The author recommends the treating physicians to be aware that not all AIT products used currently provide sufficient data to support their efficacy in clinical practice.

AIT for the treatment and prevention in patients with AR

As previously described [13, 63], patients with AR and pollen allergy often benefit from AIT in reducing AR symptoms and need for medication. Therefore, AIT is recommended for treatment of patients with moderate-to-severe pollen-induced AR if not optimally controlled on antihistamines and nasal corticosteroids [63].

The RCTs included in the above evaluation of asthma prevention in subjects with AR [11, 27, 32, 33, 36–38] included patients with a history of AR and the need for medication combined with documented pollen allergy for at least one previous season. Meanwhile, it appears that children and adolescents included in the prevention studies did not necessarily fulfill the criteria for recommendation of AIT for the treatment of AR, just as they did not necessarily meet the “Allergic Rhinitis and its Impact of Asthma” (ARIA) [71] criteria for moderate/severe AR. So far, there has not been any description of AR severity

Some gaps in the evidence

- AIT for the prevention of asthma in children with AR due to grass pollen - long term effects
- AIT for the prevention of asthma in children with AR due to HDM
- Optimal age for initiating AIT for prevention
- Optimal product, administration form, dose, schedule and duration of AIT for prevention
- Define standardized relevant outcomes, including asthma-related outcomes and quality of life (QoL) for future studies on AIT prevention
- Evaluation of influence of AIT for prevention on QoL in different age groups
- Evaluation of health economics of AIT for prevention
- AIT for the prevention of new allergic sensitizations
 - at allergen level
 - at molecular level
- AIT for the prevention of the first allergic disease

Fig. 1. Some gaps in the evidence.

(mild/moderate/severe) or stratification (intermittent/persistent) in the prevention trials, and thus these subjects may have had a milder disease, than those included in the studies on the efficacy of AIT.

However, based on baseline descriptions of the populations in these studies [11, 27, 32, 33, 36–38], it is reasonable to assume that most of the patients

Key Points

- In children / adolescents with moderate to severe AR and grass/birch pollen allergy, not sufficiently controlled with antihistamines / nasal corticosteroids a three year course of AIT SCIT or SLIT has demonstrated to deliver:
 - a sustained effect on AR symptoms and the use of medication beyond the end of AIT
 - a preventive effect on the development of new asthma.
 - a sustained preventive effect on asthma symptoms and medication use, for at least two years after the end of AIT (demonstrated by some studies)
- AIT may be indicated in individuals with perennial AR on clinical grounds, but not only for preventing the progression to asthma
- Only AIT products with a documented effect for the relevant allergen should be used
- Before initiating AIT the possible benefits and harms, the patients' preferences, adherence and costs should be discussed with the patient / family on an individual basis
- There is an urgent need for more high-quality evidence and clinical trials on AIT for prevention

Fig. 2. Key points.

included had persistent symptoms.

None of the studies on the prevention of the development of asthma in AR included preschool children, and at present, no evidence for AIT for the prevention in this age group exists.

The AIT administration form, schedules, products, and doses used in the AIT prevention trials vary. According to the subgroup analysis in the EAACI SR [24], it appears that SCIT and SLIT are both effective, and that a 3-year AIT course is preferable to a shorter course. The studies demonstrating a longer-term preventive effect used 3-year courses of continuous AIT.

The different AIT prevention trials and SRs [24] did not compare different AIT products, SLIT drops versus tablets, or pre/co-seasonal versus perennial AIT. However, the results from two lower quality, real-life non-randomized, CBA treatment studies, based on large German longitudinal prescription databases [39, 40], supported that SCIT [39] and grass pollen SLIT tablets [40] with natural allergen extracts have a preventive effect on the progression from AR to asthma, and that a treatment course for at least 3 years tends to have a stronger preventive effect than AIT for less than 3 years. Further high-quality RCTs and real-life studies are necessary to confirm this.

Gaps in the evidence

For many areas there is currently no evidence or only low quality evidence, thus representing gaps in the current evidence (Fig. 1), which need to be addressed by reanalyzing data from existing studies and in future studies.

Conclusion

There is good evidence indicating that AIT administered as SCIT or SLIT can prevent the development of asthma in children/adolescents with moderate/severe AR and pollen allergy, who are sub-optimally controlled despite appropriate pharmacotherapy, up to 2 years post-AIT, and maybe even longer as regards asthma symptoms and medication use. Even in patients with milder AR, AIT might modify the natural disease history, with a preventive effect regarding the development of asthma (Fig. 2).

The initiation of AIT should always be preceded by a discussion with the patient/family considering the possible benefits, harms, disadvantages, costs, preferential route of AIT (SCIT vs. SLIT) based on an individual evaluation, personal preferences, and considerations for AIT adherence. Using AIT for preventive purposes should take into consideration all normal safety recommendations that are in place for AIT used in the treatment of AR, as indicated in the EAACI Guideline on AIT for AR [63].

Since the indication for AIT for the prevention of asthma is related to the indication for the treatment of AR, the products, schedules, and doses used should be proven effective for AR with the relevant allergen product. Therefore, only those products registered and with the indication for AR should be used for allergy prevention purposes.

Some patients with less severe AR may prefer AIT in an attempt to reduce medication use and avoid side effects of other treatments, to obtain long-term efficacy and/or to obtain the asthma preventive effect.

The asthma preventive effect may in the future downgrade the level of severity of AR required before initiation of AIT in children and adolescents with AR and pollen allergy, especially grass pollen allergy.

Therefore, AIT as a relevant treatment option for children and adolescents with less severe AR due to pollen allergy should be further investigated, as well as high-quality studies are warranted to investigate AIT for prevention in HDM allergic patients with AR.

Compliance with ethical standards

Conflict of interest

S. Halken reports personal fees from different companies, e.g., MEDA, Stallergenes, Allergopharma, and ALK-Abelló, outside the submitted work.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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