

Review

Does allergen immunotherapy for allergic rhinitis prevent asthma?

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Key Messages

- Allergic rhinitis and asthma are closely associated conditions, and children with allergic rhinitis often develop asthma over time.
- Allergen immunotherapy is the only known treatment that modifies the natural progression of allergic disease and induces long-term remission.
- Allergen immunotherapy to house dust mite and grass pollen might reduce the development of new sensitization to additional allergens, although robust evidence is lacking.
- Grass pollen allergen immunotherapy in children with seasonal allergic rhinitis prevents asthma symptoms.
- Further studies are required to investigate underlying mechanisms, study immunotherapy to other allergens such as house dust mite, and assess cost-effectiveness of this approach.

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ABSTRACT

Asthma and allergic rhinitis (AR) have overlapping clinical and pathologic features, sustained by an underlying T helper 2 bias, resulting in airway inflammation that extends from the nose to the lung. Children who are mono-sensitized often develop polysensitization over time, and they are at high risk of developing asthma. The effect of allergen immunotherapy (AIT) is allergen specific, resulting in symptom improvement and reduction in medication requirement. It is the only known treatment that alters the natural history of allergic disease and induces long-term remission. A bystander or allergen-nonspecific effect of AIT has also been proposed—that AIT to 1 allergen might reduce the risk of development of sensitization to other allergens. Furthermore, several observational studies and clinical trials, in seasonal (pollen) and perennial (house dust mite) AR, have investigated a protective effect of AIT to prevent asthma. The overall evidence favors an asthma preventive effect of AIT in AR to grass and birch tree pollen. Fewer studies have investigated the use of AIT in children with perennial AR due to house dust mite allergy to prevent asthma, and the results are less convincing. The use of AIT to reduce the risk of progression to asthma, in children with AR, potentially has high impact, and it will make AIT more attractive and cost-effective. However, most studies have been of small sample size or of poor design, using different allergens and AIT methodology, making it challenging to draw firm conclusions. There is a need to do adequately powered studies with optimal design and assess cost-effectiveness of this strategy.

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Introduction

Asthma and rhinitis are 2 common chronic conditions that often coexist.¹ These 2 respiratory syndromes can be linked into a united

airway disease.² The united airway disease hypothesis proposes that upper and lower airway diseases can be manifestations of a single inflammatory process within the respiratory tract. Up to 80% of people with asthma report rhinitis symptoms, and asthma risk is increased by 8-fold in children with rhinitis.¹ Many teenagers have both asthma and rhinitis, although clinical asthma may appear first in some children, whereas rhinitis symptoms are apparent before asthma in others. Many children with rhinitis may have features of asthma even when lacking typical asthma symptoms and not

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clinically diagnosed with having asthma. In the Isle of Wight cohort, 22.4% of 10-year-old children with rhinitis had bronchial hyperactivity even when they had no asthma symptoms.³ The progression from rhinitis and bronchial hyperresponsiveness (BHR) to asthma has been found in several studies.⁴ This is not surprising as the common underlying mechanisms, being the T helper 2 (T_H2) immune responses in these individuals, based on their atopic predisposition and airway epithelium, act in a similar way from the nose to the lung.⁵ This theoretically provides an opportunity where, if T_H2 immune responses can be suppressed, it might be possible to halt the progression of rhinitis to asthma in these children with atopy.

The potential use of allergen immunotherapy (AIT) for the prevention of asthma could be aimed at preventing asthma in otherwise healthy but high-risk children or to reduce the risk of progression to asthma in children with other allergic diseases, such as allergic rhinitis (AR) and atopic dermatitis (AD).^{6–8} The latter is an attractive proposition, given the concept of the atopic march, which alludes to the progression of allergic diseases, from one to the other in the same individual as the child grows.⁵ Typically, it implies that a child would first have eczema, and then food allergy during early childhood, followed by asthma and rhinitis in later childhood. The concept of “typical atopic march” has recently been challenged in favor of “allergic comorbidity.” This implies that many children (and adults) have more than one disease or even that the diseases can follow each other, but not all children with atopy are on the same trajectory referred to as the atopic march.⁹ Nonetheless, the common underlying pathophysiology means that selecting children with AD or AR is attractive because intervention is targeted at those with a high risk of asthma development.

AIT is the only treatment of allergic disease, specifically AR and venom allergy, with a disease-modifying effect. It therefore lends itself as an ideal intervention to “correct” the underlying defect in immune responses, potentially averting progression to asthma in many children.^{10–12} Although there are variations in methodology, primarily AIT is carried out through the subcutaneous route (subcutaneous immunotherapy or SCIT) or the sublingual route (sublingual immunotherapy or SLIT). AIT is generally well-tolerated, although systemic reactions do occasionally occur during SCIT and rare fatalities are reported.^{8,13} SLIT is

safer and more convenient to administer. Oral symptoms are common, especially in the first few weeks, but systemic reactions are extremely rare. However, there is a small risk of development of eosinophilic esophagitis in patients undergoing SLIT.¹⁴

AIT to common aeroallergens is effective in the treatment of AR, reducing symptoms and medication requirement and improving quality of life.¹⁵ However, the risks, discomfort, and cost associated with AIT often prevent AIT being used as the first-line therapy. Practices vary widely in different countries. If (and when) AIT should be used for AR is still debated. In most western countries, it is most often used as an adjuvant to pharmacotherapy. If AIT can prevent asthma development in children with AR, the risk versus benefit ratio would clearly tilt in favor of AIT, with substantial beneficial effect on clinical outcomes for the individual. It can be argued that those children with milder disease, who could otherwise be controlled with simple pharmacotherapy, such as nasal steroids and antihistamine, should be offered AIT not only for its long-term disease-modifying effect on AR but also if it was convincingly found to have a protective effect on the development of asthma.

Bystander Effect

AIT is directed toward the allergen in question and hence sometimes referred to as “allergen specific” immunotherapy. In AIT, the allergen, whether administered by the subcutaneous or oral route, is taken by the dendritic cells, which in turn influence T helper (T_H) cells, with consequent suppression of allergy favoring T_H2 responses. This is considered allergen specific, resulting in inhibition of T and B memory cells and production of immunoglobulin (Ig)E antibodies to that allergen. The enhancement of T regulatory cells with resulting production of interleukin 10 and transforming growth factor beta supports this switch from T_H2 to T_H1 immune response and further results in the production of blocking IgG1 and IgG4 antibodies.^{10,16} Could there be a bystander or global effect such that T and B regulatory cells suppress effector cell responses to other allergens and thereby prevent development of new allergic sensitization? This could theoretically be a pathway to prevent progression of AR to

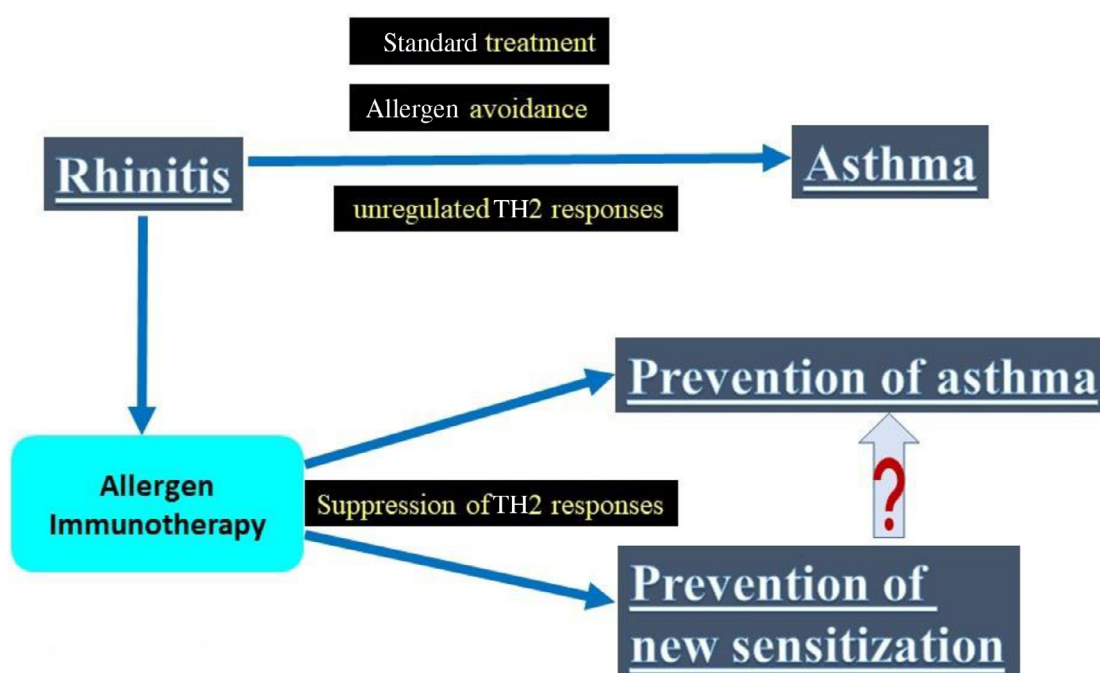


Figure 1. A proposed pathway for allergen immunotherapy to prevent asthma in those with allergic rhinitis. Allergic rhinitis carries a high risk of future asthma development, if managed with standard therapy. Allergen immunotherapy, by suppressing T_H2 responses, may induce global immune tolerance, preventing new allergen sensitization and asthma.

asthma (Fig 1). We know that monosensitized individuals, over time, develop polysensitization and associated allergic diseases. For instance, children with AR to pollen may develop sensitization to other common allergens. If AIT, directed against pollen, has a wider effect on the immune responses, we might see protection against the development of new allergic sensitization in these children. There have been a number of observational studies and clinical trials investigating this hypothesis.

Observational Studies

In a prospective, observational study of 134 children with asthma and monosensitization to house dust mite (HDM), 75 children were treated with SCIT for 3 years and followed up for 6 years.¹⁷ Of 69 children, 52 (75.4%) in the SCIT group had no new sensitization, compared with 18 of 54 children (33.3%) in the control group ($P < .001$). Purolo et al,¹⁸ in a large retrospective survey of 8396 patients, noted that monosensitized patients with asthma or rhinitis are less likely to develop further allergic sensitization, if given immunotherapy (23.75%), compared with those who continued on standard treatment (68.0%; $P < .001$). Patients were assessed over a 7-year period (4 years of AIT and 3 years follow-up). However, in another long-term follow-up study, 10 years after completion of SCIT for childhood asthma, no difference in the acquisition of new allergen sensitization was observed between the treated and control groups.¹⁹

Clinical Trials

Several small randomized controlled trials (RCTs) without longer term follow-up have a protective effect of AIT. In 1997, in a small randomized prospective study, Roches et al²⁰ found that HDM SCIT prevents new sensitization in patients monosensitized to HDM. Of 22 patients in the AIT group, compared with all 22 in the non-AIT group, 10 developed new sensitization over a 3-year period.²⁰ In a small open RCT, 15 children receiving HDM SCIT for asthma for 3 years and 14 controls on standard treatment were studied. During the treatment period, 3 of 10 (4 dropouts) in the control group developed new sensitization, whereas none did so while on SCIT.²¹ In another RCT of 3 years of grass pollen SCIT, a reduction in acquisition of new sensitization was observed.²² There were 20 (77%) subjects in the SCIT group, compared with 3 (23%) in the control group, who had no new sensitizations against a defined allergen panel.

Furthermore, 2 large trials assessed the effect of SLIT. In an open RCT of 511 patients with AR, randomized to SLIT or standard treatment for 3 years, new skin sensitizations appeared in 38% of the controls and in 5.9% of the patients with SLIT ($P = .01$).²³ In another open RCT, 216 children with AR were randomized to receive standard treatment and SLIT for 3 years.²⁴ New sensitizations appeared in 34.8% of controls and in only 3.1% of patients with SLIT (odds ratio [OR], 16.85; 95% confidence interval [CI], 5.73–49.13).

RCTs that followed subjects after completion of the trial have conflicting results. There were 2 small RCTs, one in patients with birch pollen allergy and the other in children with HDM or grass pollen allergy, both followed for 2 years, which failed to reveal a preventive effect of AIT on new sensitization.^{18,25} However, Eng et al^{26,27} reported 6- and 12-year follow-up of a study of 13 patients who underwent SCIT to grass pollen and compared them with 10 control group subjects. In addition to the usual AIT beneficial effects, new sensitization was reduced (60% in SCIT) compared with 100% of the control subjects ($P < .05$).

Zolkipli et al,⁶ using HDM SLIT in healthy nonsensitized infants ($n = 111$), revealed that the risk of development of any allergic sensitization was reduced in infants given prophylactic HDM SLIT for 1 year compared with placebo ($P = .03$). However, further follow-up at

3 years and 6 years of age revealed that the difference was no longer significant (at 3 years: $P = .12$ and at 6 years: $P = .06$).^{28,29}

Thus, there is currently only low-level evidence in support of a preventing effect of AIT on new sensitization.³⁰ Small RCTs favor an overall preventive effect on new sensitization during AIT, but longer term effects after cessation of IT are not supported by studies, with conflicting results from both observational studies and clinical trials. Thus, robust evidence is lacking. However, the concept of a bystander effect may extend beyond the specific allergen it is targeting, and it can induce a global immune tolerance with a potential to correct the T_H2 bias present in these individuals. However, this is yet unproven, and large, randomized trials are needed with at least 2 years post-AIT follow-up. If confirmed, it could provide 1 plausible explanation (among others) of how AIT could prevent the development of clinical allergic diseases.

Asthma Preventive Effect

Longitudinal Observational Studies

Large-scale, real-life, retrospective analysis of health care data supports an asthma protective effect of AIT in those with AR. In a retrospective analysis of routine health care data, Schmitt et al³¹ identified a consecutive cohort of 118,754 patients with AR, of which 2431 (2.0%) started SCIT. The risk of incident asthma was significantly lower in patients treated with AIT (risk ratio, 0.60; 95% CI, 0.42–0.84; $P = .003$) over the next 5 years.³¹ The same group of researchers, in a further retrospective analysis of health care data, revealed that AIT for asthma prevents disease progression of asthma in terms of severity (from Global Strategy for Asthma Management and Prevention [GINA] step 1 to GINA step 3 and GINA step 3 to step 4).³² Recently, 2 retrospective analyses of German databases and 1 of French health care data were reported. In an analysis of 2851 patients with AR treated with grass pollen SLIT tablet, compared with 71,275 non-AIT control patients, asthma was less frequent in the SLIT tablet group (OR, 0.7; $P = .002$).³³ In another analysis, the outcome of various AIT regimens (both SCIT and SLIT), used for birch pollen-associated AR, was assessed 6 years after cessation of AIT. New-onset asthma risk was significantly reduced in the AIT vs non-AIT group (OR, 0.83; $P = .001$).³⁴ In the database analysis of the French cohort of 1099 patients with AR treated with grass pollen SLIT tablets and 27,475 control subjects, 11 (1.8%) and 782 (5.3%) patients initiated asthma treatment (indicating incident asthma) in the SLIT and control groups, respectively. The relative risk of medication dispensing for new asthma was significantly lower in the SLIT group (62.5% [29.1%–80.1%; $P = .003$]).³⁵ However, such data analyses carry a high risk of bias as those who opted to, or were selected for, AIT, are different in many relevant aspects from those who do not undergo this treatment. Hence, RCTs are required to get higher quality evidence.

Clinical Trials

A number of clinical trials have reported an asthma prevention effect of SCIT to pollen in seasonal AR. However, most are of relatively small size and often not of high quality design. In 1986, Möller et al³⁶ reported the outcome of a small RCT of 3 months of AIT to birch pollen in 16 children vs 14 with placebo. Apart from improving symptoms of AR (the primary outcome), an asthma preventive effect was noted at 10 months after SCIT as none of the treated children developed asthma, compared with 5 of the untreated children.

Grembiale et al³⁷ in 2000 reported results of a study with an a priori aim to assess whether AIT can prevent development of asthma and associated BHR in those with AR. There were 40 subjects, sensitized to HDM and perennial AR with BHR, randomized to HDM AIT and placebo. After 2 years of treatment, a 4-fold improvement in

methacholine PD₂₀ was found with no change in the placebo group ($P < .001$). During this period, no one in the AIT group developed asthma whereas 9% in the placebo did. They concluded that AIT to HDM may be an appropriate prophylactic treatment for patients with rhinitis and airway hyperresponsiveness. More recently, a nonrandomized Chinese trial reported 2 years assessment, after completion of a 3-year course of SCIT, in 106 patients with HDM AR with 40 controls using standard treatment.³⁸ The controls had more asthma (OR, 3.57; 95% CI, 1.05–12.91; $P < .05$) compared with the SCIT-treated group.

The preventive allergy treatment study provided the most convincing evidence for a long-term effect of AIT to AR on asthma prevention. In 2002, Möller et al³⁹ reported the results of an open RCT of 205 children, with grass or birch pollen seasonal AR, given SCIT or standard treatment. At the end of 3 years of treatment, actively treated children had significantly fewer asthma diagnosis (OR, 2.52; $P < .05$) and significantly improved BHR ($P < .05$). Furthermore, there was a continued effect of less asthma at 5 years (2 years after completion of AIT; OR, 2.68; CI, 1.3–5.7) and 10 years (7 years after completion of AIT; OR, 2.5; CI, 1.1–5.9) observed as evaluated by clinical symptoms.^{40,41} However, the study findings were subject to considerable bias given that it was an open randomized trial with the controls following standard treatment rather than treated with placebo.

Crimi et al⁴² reported in 2004 results of a small, double-blind, placebo-controlled (DBPC) RCT of 30 subjects with AR, without asthma, who were monosensitized to *Parietaria* and given SCIT for 3 years. By the end of 3 years, a nonsignificant ($P = .06$) reduction in progression to asthma was observed in the SCIT treatment group (SCIT: 2 of 15 vs placebo: 7 of 15).⁴² However, there was no difference in BHR between the groups. Thus, the only DBPC RCT using SCIT to pollen did not find a difference in either asthma or BHR between the 2 groups.

Sublingual Immunotherapy

As SLIT started to become more popular in late 1990s and early 2000, several studies reported the preventive effect of SLIT on the development of asthma. An open RCT reported the outcome of 3 years of SLIT, compared with standard treatment, in 113 children with grass pollen AR without asthma.⁴³ SLIT not only improved hay fever symptoms, but there was a nearly 4-fold reduction in the development of asthma over this period. Subsequently, the preventive effect of SLIT on asthma and BHR in children was evaluated in a larger open RCT of 216 children (SLIT = 144; standard therapy = 72).²⁴ After 3 years, SLIT-treated children had less mild persistent asthma (OR, 0.04; 95% CI, 0.01–0.17) and the number of children with a positive methacholine challenge result decreased after 3 years, only in the SLIT group.

To date, the largest RCT with optimal design is the Grazax Asthma Prevention trial that recruited 812 children (aged 5–12 years) with grass pollen AR and without a history of concomitant asthma. The stated objective was to investigate the preventive effect of grass pollen SLIT for 3 years on the risk of developing asthma.⁴⁴ Asthma was defined as a combination of wheezing episodes plus “on asthma treatment with response” or “reversible bronchoconstriction.” There was no significant protective effect of SLIT on asthma as defined previously. However, there was improvement in several clinically meaningful parameters, such as a reduction in the risk of experiencing asthma symptoms and the use of asthma medications, throughout the 3 years of trial and 2 years of follow-up period.

House Dust Mite Allergen Immunotherapy and Asthma Prevention

An observational study failed to reveal the preventive effect of HDM SLIT treatment on the development of new sensitization or on BHR.⁴⁵ Although, few clinical trials have focused on HDM AIT in AR

and asthma prevention and none with the rigor of a DBPC design, the result seems encouraging. In 2014, Song et al⁴⁶ reported the results of an open RCT, where 102 patients with mite AR were randomized to SCIT for 3 years ($n = 51$) and control ($n = 51$) using standard therapy alone. Although the study was aimed at assessing the therapeutic effect of HDM AIT on rhinitis, they also intended to observe the effect on the development of asthma and new allergen sensitization. In the SCIT group, 17.4% of those treated with standard therapy, compared with no one in the AIT group, developed asthma over this period. The effect persisted for 2 years after completion of treatment.⁴⁷ The authors concluded that mite AIT improves rhinitis and prevents new allergen sensitization and development of asthma. In 2 open RCTs published by Marogna et al^{23,24} in 2004 and 2008, 3 years of SLIT to HDM or grass pollen, in those with AR, resulted in improvement in BHR, and mild persistent asthma was less frequent in the SLIT group.

It also seems that children and adolescents do better than adults. In a recent meta-analysis, the overall evidence for an asthma preventive effect of AIT, in those with perennial AR due to HDM allergy, was not seen, despite a 5-fold reduction (OR of 0.20), which is likely due to small sample size of the clinical trials.⁸

Discussion

For the asthma preventive effect, most studies have been done in children with seasonal AR and the evidence favors a preventive effect of AIT (SCIT or SLIT) to pollen. There seems to be a preventive effect of AIT to grass and birch pollen, lasting for at least 2 years, on the development of new asthma.⁸ This is consistent with interrupting the atopic march. However, most studies were small or of suboptimal design, and hence the quality of evidence is weak. One large high-quality study unfortunately did not meet its primary goal of preventive asthma as defined a priori. Evidence in adults is primarily from observational studies, but where both age groups are included, there is some indication that the effect is stronger in children.⁸ Furthermore, it remains uncertain whether asthma is prevented or delayed as longer term follow-up is limited to few studies with inadequate study design. There are only a few studies using HDM, and the preventive effect on asthma is not evident. In contrast, for the prevention of new sensitization, HDM AIT had a stronger effect than pollen AIT.

The heterogeneity of the studies is a major problem in drawing a firm conclusion whether AIT treatment is effective in preventing asthma. This is at least partly due to the number of relevant factors that might influence the eventual outcome (Fig 2). Although AD and food allergy also increase the risk of subsequent asthma development, most AIT studies have focused on AR, given the close association between AR and asthma as 2 respiratory allergies that often coexist, or follow one another in the later part of the atopic march. The main question is, which allergen to target? As revealed in the review, for new sensitization, the evidence favors a preventive effect of AIT, especially to HDM. For asthma, most evidence is for grass pollen, but some studies have also looked at tree or birch pollen and others have investigated AIT to HDM. To some extent, this is contrary to the causation of allergic disease. Asthma, and associated lower airway inflammation, is more often driven by HDM rather than pollen, and hence HDM AIT should be more protective. However, as children with AR over time develop asthma, the idea is that suppression of T_H2 bias at this stage with pollen AIT would prevent acquisition of HDM sensitization, and subsequently asthma. Overall, though, studies have revealed conflicting results, few have looked at both new sensitization and asthma prevention in the same study and none have found a chronological sequence, where a longer-term follow-up, after completion of AIT, results in reduction in HDM sensitization and subsequent prevention of asthma. Age is a major determinant. The original idea of interrupting the atopic march applies primarily to children and adolescents. However, many studies have included

- **At-risk population:** Children with other allergic conditions; atopic dermatitis, food allergy or allergic rhinitis or and/or other risk factors.
- **Allergen:** Pollen, house dust mite, others
- **Age:** Children, adolescents, adult
- **AIT regimens**
- **Duration of AIT:** 3 years or less
- **Severity of allergic rhinitis**
- **Presence of other characteristics such as BHR at recruitment**

Figure 2. Factors to consider in asthma prevention studies. AIT, allergen immunotherapy; BHR, bronchial hyperresponsiveness.

adults and seems to reveal a protective effect over time, although this seems to be less marked than in children.

The third major issue is the AIT regimens—SCIT or SLIT, pre- or co-seasonal vs perennial AIT, SLIT drops vs tablets, and 3 years vs shorter duration. No studies have directly compared product, route, dose, duration, and AIT schedules used in the AIT prevention trials. However, a subgroup analysis in a recent meta-analysis suggested that pollen AIT, using both SCIT and SLIT routes, is effective in preventing asthma and a 3 years of AIT duration is more effective than when given for a shorter period.⁸ Thus, although the studies share the overall concept, that is, halting the atopic march and possibly underlying mechanisms, the effectiveness found in one study cannot be easily translated into another using a different product, AIT schedule, or tested in a different age group. There is thus a need to do adequately powered studies with optimal design using a standard product, targeting an appropriate allergen and age group, and ensuring a longer-term follow-up. Finally, the cost-effectiveness of this approach needs to be factored in when investigating the health economic ramifications of AIT.

Conclusion

The balance of evidence favors an asthma preventive effect of AIT in those with pollen AR given AIT for at least 3 years, using either SCIT or SLIT. There is weak evidence supporting an asthma preventing effect in perennial rhinitis due to HDM allergy. There is little doubt that AIT is effective in AR, inducing long-term disease remission, and it is generally well tolerated without substantial adverse effects. Yet, currently, it is used mostly as a second-line therapy when standard pharmacotherapy fails to control the disease effectively. It can be argued that with the additional benefit of preventing asthma, AIT could be recommended as a first-line therapy. However, there are considerable knowledge gaps that require further studies, including optimal age groups, allergen preparation, mode of delivery of AIT, and duration of treatment. Large, well-designed, long-term, placebo-controlled trials

are needed before AIT can be recommended in children with AR from isolated pollen or HDM allergy to prevent asthma.

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