SIAIP

Italian Journal of Pediatric Allergy and Immunology number 03 | 2025 | 17-21

Mini Review

Allergen Immunotherapy in Allergic Rhinitis and Asthma

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SUMMARY

Many publications have clearly demonstrated positive immunological effects and clinical efficacy of allergen immunotherapy (AIT) in allergic rhinitis (AR)/rhinoconjunctivitis and asthma due to many allergens. Other demonstrated effects of AIT in allergic respiratory diseases include long-lasting efficacy and the prevention of progression of AR to asthma. AIT is currently restricted to carefully selected patients with AR who are unresponsive to appropriate pharmacotherapy and HDM-driven allergic asthma. Due to its preventive and long-term effects, AIT should be probably considered early in patients with AR and asthma, following proper diagnosis and cost-benefit evaluation, in order to inhibit the progression of the allergic inflammation to airway remodeling and to reduce the amount of drugs needed.

KEYWORDS: allergen immunotherapy, rhinitis, asthma

INTRODUCTION

Many epidemiological studies indicate that up to 40% of the global population suffers from respiratory allergic diseases, such as allergic rhinitis (AR)/rhinoconjunctivitis and asthma [1,2].

After the first studies of Curtis and Noon [3,4], allergen immunotherapy (AIT) has been empirically used [5] for the treatment of allergic respiratory diseases. Starting in 1980, many position papers, practice parameters and guidelines on AIT have been published and have clearly demonstrated positive immunological effects [6] and clinical efficacy of AIT in allergic rhinitis (AR)/rhinoconjunctivitis [7] and asthma due to many allergens [8].

Both sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT) have been shown to be effective in adults as well as in children in treating AR [9] and asthma [10,11].

Moreover, international documents [2,12,13] suggest the use of AIT in allergic respiratory diseases.

Other reported effects of AIT in allergic respiratory diseases include long-lasting efficacy, a potential preventive effect on the onset of new allergic sensitizations, and the prevention of AR progression to asthma.

Long-lasting efficacy was first reported in the Preventive Allergy Treatment study (PAT) study, in which a 3-year course of SCIT with standardized allergen extracts showed long-term clinical effects in children with allergic rhinoconjunctivitis for up to 7 years after treatment [14].

Other long-term randomized controlled trials (RCTs) in patients with AR treated with SQ grass SLIT tablet [15] and Japanese cedar SLIT tableT [16] demonstrated efficacy over 3 years of treatment, with sustained effects for at least 2 years post-treatment.

Moreover, a real-world study demonstrated the long-term effectiveness of AIT in AR, showing reductions in AR prescriptions compared with controls [17].

The preventive effect on the onset of new allergic sensitizations has been reported [18-20], but a recent review and a meta-analysis do not confirm this effect [21,22].

Received: September 8, 2025
Published: October 23, 2025

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How to cite this article: Novembre E. Allergen Immunotherapy in Allergic Rhinitis and Asthma. Italian Journal of Pediatric Allergy and Immunology 2025;39(03):17-21. https://doi.org/10.53151/2531-3916/2025-1500

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THE LINK BETWEEN THE UPPER AND LOWER AIRWAYS

There is a link between the upper and lower airways, and the concept of united airways disease (UAD) has been proposed [23]. The lung and nose inter-reactions are based on numerous evidence [24]. In particular, the epidemiologic evidence shows that AR is frequently associated with asthma, and most asthmatics have rhinitis [25].

In a 20-year follow-up study, approximately 75% of children with pollen-AR at 4 or 8 years of age had persistent disease for up to 24 years, and 30% developed asthma [26].

However, the underlying mechanism of the relationship between typical diseases of the united airway, such as AR and asthma, needs to be further explored [27].

In the progression of rhinitis to asthma, the role of polysensitization has been underlined. In fact, the asthma-rhinitis multimorbidity is associated with IgE polysensitization in adolescents and adults [28], and the risk of adult-onset asthma increases with the number of allergic multimorbidities [29].

Recently, the "one-airway-one-disease"concept was reassessed in the MeDALL hypothesis: rhinitis alone (local disease) and rhinitis with asthma multimorbidity (systemic disease) should be considered as two distinct diseases, possibly modulated by the microbiome, and may be a model for understanding the epidemics of chronic and autoimmune disease [30].

AIT IN THE PREVENTION OF THE PROGRESSION OF AR TO ASTHMA

Many studies have investigated the preventive role of AIT in the treatment of allergic respiratory diseases [8,21,31-33]. The most rigorous study was a meta-analysis of Kristiansen et al. [32] in which 6 RCTs (3 with SCIT and 3 with oral-sublingual) in the prevention of the onset of asthma in those with established AR were selected. Random-effects meta-analysis of these RCTs demonstrated a significant reduction in the risk of developing asthma in subjects with established AR.

Subgroup analyses showed that AIT was beneficial in those aged < 18 years but not in those aged ≥ 18 years, receiving SLIT as well SCIT, receiving pollen AIT, but not receiving HDM AIT.

Few RCTs where the primary outcome was the onset of asthma in subjects with AR have been published. Moller et al. [34] evaluated 208 grass and/or birch-sensitized children aged 6 to 14 years from 6 European pediatric centers and an open control group. All had moderate to severe hay fever symptoms, and 40 had mild asthma. A 3-year SCIT with standardized allergen extracts of grass pollen (*Phleum pratense*) and/or birch pollen was given. One hundred fifty-one children without asthma before the start of SCIT were evaluated for asthma onset, and the actively treated children had significantly fewer asthma symptoms after 3 years, as evaluated by clinical diagnosis (OR 2.52).

In another open randomized study [35] involving 6 Italian pediatric allergy centers on 113 children aged 5 to 14 years with hay fever (without asthma) and monosensitization to grass pollen received SLIT for 3 years or standard symptomatic therapy. Development of asthma after 3 years was 3.8 times more frequent in control subjects.

Later, the largest double-blind placebo controlled RCT on prevention of asthma development was conducted in 812 children with grass pollen-induced rhinoconjunctivitis, who were treated with SLIT for 3 years and then followed for 2 years [36]. Even if this trial did not meet as its primary endpoint ~~of~~ the difference in time to onset of asthma between the AIT and placebo groups, it did show that AIT significantly reduced the risk of developing asthma symptoms or using pharmacotherapy for asthma, whether during the 2-year follow- up period or the entire 5-year study period.

A recent review [21] presented a descriptive summary of the available evidence on the preventive aspects of AIT with respiratory allergens. From randomized and non-randomized studies on grass and/or tree pollen-based AIT for preventing asthma development in children with AR/conjunctivitis, favorable evidence was available, but studies on the preventive effects of AIT with other allergens, such as HDM, resulted in inconclusive findings.

Not only do systematic reviews and meta-analyses demonstrate the preventive effect of AIT in asthma, but the value of retrospective data has also been underlined. In fact, retrospective claims database studies [37,38] have confirmed the sustained benefits of grass and birch pollen AIT in terms of significantly reduced progression of AR and asthma, and a significantly decreased risk of new-onset asthma. In the study of Devillier [37], 2851 patients treated with grass pollen tablets and 71,275 control patients were studied. Reduction in the risk of asthma onset was seen in the SLIT tablet group in all three analytical time periods. The relative risk reduction was around 30% during treatment and around 40% during follow-up.

In another recent systematic review and meta-analysis of RCTs for asthma prevention [38], a possible preventive effect of AIT in asthma onset was found, with a larger effect in children when completing 3 years of therapy, and in mono-sensitized patients after at least 3 years of therapy. Risk of bias and heterogeneity of studies were also reported.

AIT IN OFFICIAL DOCUMENTS

AIT in allergic rhinoconjunctivitis

In the ARIA documents, AIT should be restricted to carefully selected patients who are unresponsive to appropriate pharmacotherapy according to guidelines (antihistamines + inhaled corticosteroids) and for whom effective and cost-effective AIT is available [21]. In the EAACI document [13], it is stated that AIT should be considered in patients with AR, with or without conjunctivitis, evidence of IgE-sensitization to 1 or more clinically relevant allergens, and moderate to severe symptoms despite regular and/or avoidance strategies. In clinical practice, the combination of corticosteroids and antihistamines is considered the most effective combined strategy for the management of AR [39].

AIT in allergic asthma

The EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma [40] state that to date only AIT with HDM SLIT-tablet has demonstrated a robust effect in adults for critical end points (exacerbations, asthma control, and safety). Thus, it is recommended as an add-on to regular asthma therapy for adults with controlled or partially controlled HDM-driven allergic asthma (conditional recommendation, moderate-quality evidence). HDM SCIT is recommended for adults and children, and SLIT drops are recommended for children with controlled HDM-driven allergic asthma as an add-on to regular asthma therapy to decrease symptoms and medication needs (conditional recommendation, low-quality evidence).

According to the Global Initiative for Asthma (GINA) 2024 document[2], in the case of allergic asthma, SLIT/SCIT utilization for adults, adolescents, and children is possible as an add-on therapy in the intermittent as well as persistent, well or partially controlled asthma. The advice was to use professional judgment for all patients, checking cost/benefit, local eligibility, and payer criteria.

AIT IN ASTHMA PROGRESSION

In a population-based cohort study, the role of allergy immunotherapy in asthma progression was evaluated. Individuals aged 14 years or older were classified as having incident asthma during the observation period. The severity of asthma was classified according to the treatment steps recommended by the GINA [2]. In all, 4111 patients (10.5%) received AIT. AIT exposure was associated with a significantly decreased likelihood of asthma progression from GINA step 1 to GINA step 3 [41]. This is particularly important since AIT has been regarded as contraindicated in unstable and/or severe asthma [2,42], but with the availability of biologics [43] severe and unstable asthma may be kept under control to a degree where this approach can be reconsidered. Moreover, trials of AIT added to biologics showed additional benefit of these combinations, not only enhancing safety and tolerability, but possibly efficacy as well [44].

WHEN TO START AIT

Many studies have clearly demonstrated the clinical efficacy of AIT in AR/rhinoconjunctivitis[7] and asthma[8]. Other studies indicate that the AIT has long-term effects [14-16], is effective in preventing the onset of asthma in subjects with allergic rhinitis [31-33], and prevents progression from mild to more severe asthma [41]. According to official guidance, AIT should be considered in patients with AR and moderate to severe symptoms despite regular and avoidance strategies [12,13] and allergic asthma [2,40].

In a recent randomized, double-blind, placebo-controlled, phase III trial [45] the efficacy and safety of house dust mite sublingual immunotherapy-tablet in children with allergic rhinitis/rhinoconjunctivitis was demonstrated in patients (90.6%; n = 1321/1458) using antihistamines plus inhaled corticosteroids as symptom-relieving medication.

However, in a prospective, non-randomized, open study in HDM AR in adult patients in whom resistance to previous standard pharmacotherapy was not an inclusion criterion, early intervention with AIT similarly helped to improve the efficacy of AR treatment [46].

In another single-center, randomized, controlled, open-label, prospective clinical study in very young children (1-4 years) with HDM AR and in whom the presence or absence of symptomatic medication at the start of the study was not limited, SLIT tablets demonstrated efficacy, safety, and immunomodulatory effects [47].

Therefore, AIT may have beneficial effects not only in moderate, but also in mild AR and in very young patients. AIT should thus be considered early in the treatment of patients with persistent AR and allergic asthma, following proper diagnosis and cost- benefit evaluation, in order to inhibit the progression of the allergic inflammation to airway remodeling and to reduce the amount of drugs.

In fact, there is strong evidence from literature that AIT is cost-effective compared to standard drug therapy alone [48], and the real cost-effectiveness of allergen immunotherapy could be even higher, as most studies consider only during-treatment costs and do not consider long-term benefits or preventive effects [49].

Probably the best time to start AIT could be at the moment that continuous pharmacological therapy is needed. In case of allergic asthma, the early use of AIT, decreasing the likelihood of asthma progression, could reduce the number of patients of severe asthma who require biologics and, therefore, reduce the high costs of this therapy [41].

In conclusion, there are many reasons to consider early use of AIT (Tab. I) in AR and allergic asthma. Patients should be informed of the advantages of this type of therapy, and became an active part in the decision. At the same time, all efforts should be made to remove barriers to the use of AIT [50].

TABELLA I. Reasons for an early start of AIT.

1. AIT has numerous positive immunologic effects with the potential capacity to modify the course of the disease
2. AIT significantly reduces clinical symptoms and drug consumption in subjects with allergic respiratory diseases
3. AIT has long-term clinical effects
4. AIT is effective in preventing the onset of asthma in subjects with allergic rhinitis. This effect appears to be linked to sensitization to pollens rather than to dust mites
5. AIT may prevent progression from mild to more severe asthma
6. AIT is safe
7. AIT is cost-effective compared to standard therapy alone, and the cost of AIT is very low compared to other immunologic therapies (biologics).

FUNDING
The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

ETHICAL CONSIDERATION
No ethical consideration should be provided because it is a revision.

CONFLICTS OF INTEREST STATEMENT
The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR'S CONTRIBUTION
EN: writing-original draft, and editing;

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