

REVIEW ARTICLE

Immunotherapy in allergic rhinitis and lower airway outcomes

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Abstract

Allergic rhinitis and asthma constitute two clinical expressions of a single-condition, respiratory allergy. Allergen immunotherapy (AIT) is a form of treatment specifically aimed at modifying the response to sensitizing allergens. The inherent potential benefit of AIT is the simultaneous treatment of all clinical expressions of respiratory allergy. Current data support the effectiveness of subcutaneous and sublingual immunotherapy in rhinitis. Studies also provide proof for a beneficial effect in allergic asthma. Even more, substantial evidence points to the preventive effect on the progression from rhinitis to asthma. Despite the current knowledge on the basic mechanisms underlying the immunological effect of AIT is vast, the specific mechanisms for the preventive effect of primary sensitization or new sensitizations are poorly understood. This review aimed to provide a critical overview of the current knowledge on the effectiveness of AIT and its potential role in secondary prevention of respiratory allergy progression.

Respiratory allergy is nowadays considered a single condition which affects both upper and lower airways, integrated in the 'one-airway' concept. The association of allergic rhinitis (AR) and asthma has been extensively established, and the common mechanistic pathways leading to inflammation also share multiple characteristics. Also, it is well known that rhinitis frequently precedes the onset of asthma, allowing a window of opportunity for intervention (1). Initially, allergen immunotherapy (AIT) was empirically developed to treat AR in 1911, mirroring the emergence of the first vaccines in infectious diseases. Nowadays, we understand that one of the inherent potential benefits of AIT is the simultaneous treatment of all clinical expressions of respiratory allergy, that is from rhinoconjunctivitis to asthma (2). This is a major advantage, compared to some of the other pharmacological therapies which selectively treat one of the target organs. Also, data indicate that AIT has a carry-over effect beyond the period during which it is administered, somehow reverting the clinical expression of the disease. Furthermore, it may also be able to exert a preventive effect in two modes: decreasing the risk of developing asthma in patients who only suffer AR and diminishing the tendency of the allergic patients to become sensitized to further allergens (3). This

review aimed to provide a critical overview of the current knowledge on the effectiveness of AIT and its potential role in secondary prevention of respiratory allergy progression.

Does immunotherapy for AR treat associated asthma?

Subcutaneous allergen immunotherapy (SCIT) has extensively been evaluated in AR, as this has been the primary indication of AIT. Data provided by different meta-analysis of published trials have shown that it is an effective treatment, decreasing both symptom and medication scores (4, 5). In the last decades, sublingual immunotherapy (SLIT) has become a widely used form of AIT. Again, meta-analysis of studies has assessed its efficacy, indicating a reduction in symptoms and the need of medication (6–8). Nevertheless, and despite meta-analyses are nowadays considered to hold the highest degree of evidence, critical appraisals have been published and should also be carefully considered (9, 10).

But initial evidence on the effect of AIT in asthma came from small studies, with the primary objective to assess the efficacy for AR; therefore, they were underpowered to correctly evaluate the effect on asthma (11). Nevertheless, results were good enough for further research and trials in which

the primary objective was to assess AIT impact on asthma followed. Assessment of AIT in asthma has only been adequately reported in studies designed to address this aim. In trials where the primary indication of AIT was rhinitis, it is difficult to infer the effect on asthma symptoms, either because they have not been examined, because patients with asthma symptoms were excluded, or because the low number of patients with asthma or the mildness of the disease renders underpowered results to draw conclusions (12, 13). Therefore, the effect of AIT on asthma has to be evaluated from specifically designed trials. A summary of the most relevant meta-analysis on the efficacy of AIT in asthma is shown in Table 1.

A recent Cochrane review on SLIT for asthma was unable to reach conclusions on the efficacy, due to the lack of data for important outcomes such as exacerbations and quality of life and use of different nonvalidated symptom and medication scores according to the authors (18). On the contrary, other systematic reviews have been able to show a beneficial effect on symptoms and medication scores (7, 8, 15). These discrepancies may have been due to the different design of the studies and the choice of outcomes. As an example, in the mentioned meta-analysis on SLIT for asthma (18), the selected primary outcome for efficacy was exacerbation requiring emergency department visit or hospitalization, but this is an unlikely event to happen in well-conducted trials where patients are monitored and provided rescue medications precisely to avoid severe adverse events.

Data from recent large studies on SLIT have provided promising and more robust results both for rhinitis and asthma. Regarding pollen AIT, different grass and ragweed tablet formulations have demonstrated efficacy in rhinoconjunctivitis (21–27), some studies reporting absence of asthma worsening during treatment (28, 29), or even an improvement of asthma despite the study was not adequately powered for this assessment (30).

House dust mite (HDM) tablets are also under development. A trial by Bergmann et al. (31) in a group of 509 participants demonstrated a significant improvement in rhinitis symptoms during 1-year treatment with HDM tablets (300 and 500 IR vs placebo), continuing in a 1-year follow-up. The study by Mosbech et al. on the effect of a HDM tablet (1, 3 or 6 SQ vs placebo) on AR and asthma included 604

patients. In the rhinitis patients, there was a 28.8% decrease in the total combined rhinitis score when comparing the six SQ-HDM-treated group and placebo ($P < 0.0357$), and an improvement in quality of life (32). In the asthma study, a small reduction ($-81 \mu\text{g}$) in the daily dose of inhaled corticosteroids necessary to control asthma was shown (33), which resulted larger ($327 \mu\text{g}$) in a more severe subgroup of patients (34). Based on these results, an inhaled corticosteroid reduction study was performed on 834 not-well controlled mild-moderate asthma patients. This large trial has clearly shown a positive effect of the SQ-HDM-tablet on asthma exacerbations (35). A trial by Wang et al. (36), enrolling 484 patients, was unable to prove a better outcome for the active group on HDM drop AIT, on the primary efficacy criterion which was well-controlled asthma during a period of inhaled steroid reduction. But also in this study, a *post hoc* analysis showed significant efficacy in the more severe subgroup (patients with moderate, but not mild, persistent asthma).

Mechanisms of benefit of AIT

Currently, the two main routes of AIT delivery are SCIT and SLIT; both can be considered a systemic administration in contrast to other organ-targeted forms which were experimented previously, such as intranasal or bronchial immunotherapy, and were abandoned mainly due to adverse effects. So, it is assumed that both SCIT and SLIT exert a systemic modulation of the allergic response. Among others, it has been shown that there is a shift from a 'classical' type 2 immune response (characterized by cytokines such as IL-4, IL-13, and IL-5) inducing allergen-specific IgE production (37), to a 'modified' type 2 response characterized by the synthesis or specific IgG antibodies (mainly IgG4), which is related to a 'blocking' effect. This occurs as a result of an underlying induction of regulatory responses (mainly Treg, but also Breg), characterized by IL-10 and TGF-beta (38). These modifications have been shown mainly in *ex vivo/in vitro* assays performed on peripheral mononucleated cells, demonstrating a 'systemic' modification. Secondly, a reduction in the allergic inflammation has been demonstrated in target organs. In the human nasal mucosa, AIT is associated with elevated numbers of IL-10+ and TGF-beta+ T cells and FoxP3+ CD4+ and FoxP3+ CD25+ phenotypic

Table 1 Meta-analysis and systematic reviews on AIT for asthma

AIT	Study	Patients	Population	Allergen/s	Symptom scores	Medication scores
					SMD (95% CI)	SMD (95% CI)
SLIT	Olaguibel et al. (2005) (14)	193	Pediatric	Multiple	-1.42 (-2.51, -0.34)*	Not reported
	Calamita et al. (2006) (15)	1706	Pediatric and adult	Multiple	-0.38 (-0.79, 0.03)	-0.91 (-1.94, 0.12)
	Penagos et al. (2008) (16)	441	Pediatric	Multiple	-1.14 (-2.10, -0.18)*	-1.63 (-2.83, -0.44)*
	Compalati et al. (2009) (17)	476	Pediatric and adult	HDM	-0.95 (-1.74, -0.15)*	-1.48 (-2.70, -0.26)*
	Normansell et al. (2014) (18)	5077	Pediatric and adult	Multiple	Not reported†	Not reported†
	Liao et al. (2015) (19)	454	Pediatric	HDM	-1.20 (-2.07, -0.33)*	-0.52 (-1.75, 0.71)
SCIT	Abramson et al. (2010) (20)	3459	Pediatric and adult	Multiple	-0.59 (-0.83, -0.35)*	-0.53 (-0.80, -0.27)*

AIT, allergen immunotherapy; HDM, house dust mite; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual immunotherapy.

*Statistically significant ($P < 0.05$).

†Authors felt unable to perform meta-analysis due to high variability of reporting and use of nonvalidated scores.

regulatory T cells (39, 40), as well as a reduction in mast cells, basophils and eosinophils, and inflammatory mediators (41–44). Effects of AIT in the lung have mainly been assessed in murine models (45–48), while there are limited experimental data on the decreased inflammation in humans (49, 50).

Due to the systemic effect of AIT, it is difficult to ascertain whether local modifications exerted in the inflammatory response in the upper airway may secondarily impact in the lower airway, or vice versa. Despite some data suggest a positive impact on asthma control by treating rhinitis (51, 52), others have not been able to show such effect (53, 54).

Safety outcomes of AIT

One of the major drawbacks of AIT is the potential induction of severe adverse events, especially asthma exacerbation or anaphylaxis. Data from meta-analysis and large trials show that, taken together, SLIT shows a better safety profile than SCIT. In SCIT induction phases, the rate of systemic reactions is approximately 0.1–0.2% of injections and 2–5% of patients (55), while for SLIT, according to a review, the rate was 0.056% of doses (56). Uncontrolled asthma has been identified as an independent risk factor for serious adverse effects (57, 58); therefore, it is of major importance to assess asthma status initially upon prescription of AIT, and thereafter, before administration, as recommended by national and international guidelines (55).

Does immunotherapy for AR prevent progression to asthma?

There are several potential pathways by which AIT may prevent the onset of asthma (Fig. 1): by halting the progression from rhinitis, by preventing new sensitizations or by avoiding the primary development of allergy.

Although previous reports from uncontrolled studies had suggested the possible preventive effect of AIT in asthma development, the first study specifically addressed to evaluate the preventive effect of SCIT was a randomized placebo-controlled study with 44 patients monosensitized to HDM with AR and bronchial hyper-reactivity (59). After 2 years of SCIT, the provocative dose of methacholine increased by fourfold in the active group, and within the normal range in

half of the patients; while 9% of patients in the placebo group developed asthma, none of the SCIT-treated patients did. The Preventive Allergy Treatment study (60) was the first large prospective randomized controlled long-term follow-up study specifically designed to show whether SCIT could prevent the development of asthma in 183 children suffering birch and/or grass pollen seasonal AR. After 3 years, the SCIT group showed a significant reduction in risk of developing asthma (odds ratio 2.52; $P < 0.001$). This preventive effect proved to be persistent in time over a 10-year follow-up period (61).

As mentioned before, other studies have reported a positive effect of SCIT in preventing the progression from AR to asthma, but they lack the power to draw conclusions as they are either not specifically designed for this purpose or retrospective small clinical studies (62, 63). In an uncontrolled study with 41 patients with AR receiving grass pollen SCIT for 3 years, the authors reported a significant decrease in bronchial responsiveness. The results were, however, influenced by fluctuations in pollination intensity during the period of study (64).

The evidence for an asthma-preventive effect of SLIT is weaker than for SCIT, and there are no long-term data. In an open randomized study with grass pollen SLIT over 3 years in children with AR, the control group had a 3.8 times greater likelihood of developing asthma compared to SLIT-treated subjects (65). Another open randomized study of 3-year treatment with SLIT (HDM or pollen extracts) in children with AR and intermittent asthma showed a lower occurrence of persistent asthma in SLIT patients (odds ratio 0.04) and a significant decrease in the number of children with a positive methacholine challenge (66). However, a previous double-blind placebo-controlled (DBPC) study on the effect of Parietaria pollen SLIT treatment for 2 years in children with AR did not find any difference in the number of patients with asthma in the SLIT vs placebo group at 8 years of follow-up (67). A retrospective survey (68) and an observational study (69) in both adults and children have also reported less frequency of asthma symptoms in patients receiving SLIT. Altogether, these studies lack enough robustness and therefore do not allow to draw definitive conclusions on the capacity of SLIT treatment to prevent secondary asthma in patients with AR. Preliminary results of a high-quality DBPC trial on SLIT, the GRAZAX Asthma Prevention study (<http://clinicaltrials.gov/ct2/show/NCT01061203>), suggest a positive preventive effect of SLIT.

Besides its role in secondary asthma prevention, AIT may prevent the development of new allergic sensitizations and subsequently impact the natural history of the disease. However, the evidence is weak and based on either retrospective or nonrandomized studies. Two studies have shown the reduction in new sensitizations in monosensitized children treated with HDM SCIT. In one prospective nonrandomized study, 22 asthmatic children were treated for 3 years with HDM SCIT and compared to matched nontreated controls. The authors reported a significant reduction in the number of new sensitizations between the active and the control group (54% vs 100%; $P = 0.001$) (70). In a more robust long-term follow-up study evaluating 134 children with intermittent asthma monosensitized to mites, 75 were treated with

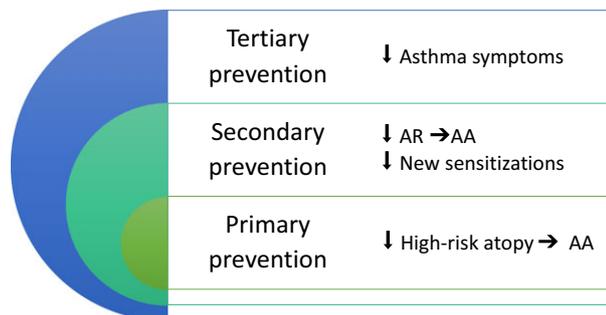


Figure 1 Effect of allergen immunotherapy in the prevention of allergic asthma. AA, allergic asthma; AR, allergic rhinitis.

SCIT for 3 years and 63 controls treated with symptomatic medication. After 6 years, two-thirds of the control group had developed one or more new sensitizations compared to only a quarter the SCIT group (71). These observations were confirmed in an open-labeled study on 147 children with AR monosensitized to HDM. After 5-year treatment with SCIT, 75% of the treated children had no new sensitizations compared to 47% in the control group (72).

For pollen SCIT, a very large retrospective study evaluated 7182 monosensitized patients with different allergies, treated with SCIT for 4 years, compared to 1214 open controls treated only with symptomatic drugs. After a follow-up period of three further years, 76% of controls had developed new sensitizations compared to 27% in the active group (73). In a small prospective open study, 13 patients monosensitized to grass pollen were treated with a preseasonal course of SCIT for 3 years and compared to 10 matched controls. Six years after the discontinuation of the immunotherapy, the percentage of new sensitizations was significantly lower in the patients with previous SCIT (61%) compared with controls (100%) (74). This effect was again confirmed after twelve years of discontinuation of the immunotherapy (75).

Marogna et al. have performed two open randomized studies in which among other outcomes, they evaluated the effect of SLIT on the development of new sensitizations. In the first study, 511 patients with AR were randomized to receive drugs alone or drugs plus SLIT openly for 3 years. New sensitizations to respiratory allergens appeared in 38% of the controls vs 5.9% of the SLIT patients (76). Very similar results were reported in a second study performed in 216 children with AR allergic to HDM, grass, Parietaria, or birch pollen, randomized to receive either SLIT with the relevant sensitizing allergen plus drugs during 3 years or drugs

alone (control group). The rate of new sensitizations was significantly reduced in the SLIT group (3.1%) compared to the control group (34.8%) (66). In a further study, the same authors prospectively evaluated the long-term effect of SLIT in 59 patients, compared with 12 control subjects. The total duration of the follow-up was 15 years. All the control subjects developed positive tests to allergens previously negative, while this occurred in less than a quarter of the patients receiving SLIT (77). However, no evidence for a reduced sensitization rate was seen in a recent randomized DBPC pilot study with children mono-/oligosensitized to HDM or grass, yet not symptomatic, after receiving active SLIT ($n = 15$) vs placebo ($n = 16$) for a period of 2 years (78).

A summary of relevant studies assessing prevention of asthma onset and new sensitizations is provided in Table 2.

In a nonclinical research design, a recent very large retrospective study of routine healthcare databases from German National Health Insurance beneficiaries identified a cohort of 118 754 patients with AR but without asthma who had not received AIT in 2005 (80). Patients were stratified into one group starting AIT in 2006 and one group receiving no AIT in 2006. Both groups were observed regarding the risk of incident asthma in 2007–2012. The risk of incident asthma was significantly lower in patients exposed to AIT (RR, 0.60; 95% CI, 0.42–0.84) compared with patients receiving no AIT in 2006.

Previous data from epidemiologic studies have shown that allergen sensitization in early life is the most important risk factor for the development of asthma later in childhood (81), and the Isle of Wight primary prevention study suggests that prevention of early sensitization in the first 2 years of life can also prevent the development of atopic asthma at 10 and 18 years (82). To date, two studies have

Table 2 Immunotherapy for the secondary prevention of asthma onset and new sensitizations

Outcome	AIT	Study	Population	Allergen	Result	Evidence*
Asthma onset	SCIT	Grembiale et al. (2000) (59)	Adults	HDM	Positive	Ib
		Möller et al. (2002) (60)	Children	Birch/grass	Positive	
		Jacobsen et al. (2007) (61)	Children	Birch/grass	Positive	
	SLIT	La Rosa et al. (1999) (67)	Children	Parietaria	Negative	IIb
		Madonini et al. (2003) (68)	Adults and children	Multiple	Positive	
		Novembre et al. (2004) (65)	Children	Grass	Positive	
		Milani et al. (2008) (69)	Adults and children	Multiple	Positive	
New sensitizations	SCIT	Marogna et al. (2008) (66)	Children	Multiple	Positive	III
		Des Roches et al. (1997) (70)	Children	HDM	Positive	
		Pajno et al. (2001) (71)	Children	HDM	Positive	
		Purello-D'Ambrosio et al. (2001) (73)	Adults (>14 years)	Multiple	Positive	
		Eng et al. (2002) (74)	Children	Grass	Positive	
		Inal et al. (2007) (72)	Children	HDM	Positive	
		Eng et al. (2006) (75)	Children	Grass	Positive	
	SLIT	Marogna et al. (2004) (76)	Adults	Multiple	Positive	IIb
		Marogna et al. (2008) (66)	Children	Multiple	Positive	
		Marogna et al. (2010) (77)	Adults	HDM	Positive	
		Szépfolusi et al. (2014) (78)	Children	HDM	Negative	

AIT, allergen immunotherapy; HDM, house dust mite; SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual immunotherapy.

*Evidence according to Shekelle et al. (79).

addressed the possible role of SLIT for primary prevention of respiratory allergy in children at high risk. In 2013, Holt et al. published the results of a pilot study assessing the prophylactic use of SLIT in high-risk children, with a positive family history of atopy and personal history of atopic dermatitis and food allergen sensitization. Fifty infants aged 18–30 months were randomized to receive a HDM, cat, and timothy grass pollen mixture or placebo administered sublingually daily for a year. This study failed to demonstrate significant differences in sensitization or asthma onset between the groups at 4 years of follow-up (83). Unlike this previous study, Zolkipli et al. (84) could recently demonstrate a significant reduction in sensitization to new allergens in children prophylactically treated with SLIT. This was a prospective, randomized DBPC, proof-of-concept study involving 111 infants <1 year of age at high risk of atopy (positive atopic family history) with no sensitization to common allergens at randomization. After a year of treatment with a high-dose house dust mite (HDM) SLIT, there was a 50% reduction in sensitization to any allergen in the active group. Although no significant effect in reduction in clinical manifestations of atopy could be demonstrated at the first-year evaluation, this may later become apparent, so the authors plan a follow-up at 3 and 6 years of age. This will also help to clarify the endotypes of asthma that could be influenced by SLIT.

The differences between both studies would suggest that the window of opportunity is in the first year of life, before allergic sensitization has developed.

Potential mechanisms by which AIT may exert preventive effects

The onset of the allergic respiratory disease is influenced by different factors, such as the patterns of allergic sensitization (85), or in the case of allergic asthma, the presence of previous rhinitis. Allergic rhinitis rather than a risk factor may represent an early stage of the disease (86); in this scenario, AIT may intercept such progression.

Current data indicate that allergic asthmatic patients may be characterized by an expanded IgE repertoire regarding the numbers or type of recognized allergen components (87–90). One could speculate that limiting the number of sensitizing epitopes, AIT could reduce the risk of asthma onset. Potential mechanisms by which AIT may decrease the risk of new sensitizations are, among other, modifications in the cytokine microenvironment (less Th2-prone) (91) or a bystander effect by which regulatory responses after AIT may downregulate established inflammatory responses driven by different T-cell epitopes (92, 93). The induction of specific IgG (mainly IgG4) antibodies with blocking activity may have a protective role not only through the inhibition of IgE-mediated effector function of mast cells and basophils, but also through the inhibition of IgE-facilitated antigen presentation (IgE-FAP) to T cells by dendritic cells (94, 95). The IgE repertoire in allergic patients develops gradually in terms of clonality and affinity. Early intervention with AIT to counteract a less developed IgE repertoire contributes to the

inhibitory effect of specific IgG blocking antibodies in FAP-mediated T-cell activation. This effect is beneficial or even essential for preventing further development of new allergic sensitizations (96).

Final considerations

Allergic diseases are not confined to one organ; they are systemic conditions which should be managed as such. In the case of respiratory allergy, it is well known that rhinitis and asthma often coexist. On the whole, current published data indicate that both SCIT and SLIT are effective for AR and asthma. Substantial evidence indicates a preventive effect in the progression from AR to asthma. But we must be aware that these conclusions cannot be generalized: not all patients are the same and not all products are equivalent. In this era of precision medicine, there is a need to phenotype the most adequate patients who will benefit from AIT, taking into account among other characteristics, severity and specific sensitization profiles (97, 98). Also AIT products vary in quality, potency, and molecular allergen content (99), so the clinical effect is not homogeneous.

In the context of the ‘one-airway’ concept, when evaluating the effect of AIT, it is appropriate to consider results affecting both the upper and the lower airways. Indeed, in trials addressing AR, adverse effects, including asthma exacerbations are usually reported. But most rhinitis studies specifically exclude patients with asthma, unless it is mild. Therefore, any therapeutic effect of AIT on asthma in these patients is intrinsically limited. On the other hand, some studies are designed to assess asthma as the primary indication. Nevertheless, many asthma trials also suffer of several limitations. One is disease severity of patients enrolled in trials, which usually is mild and requiring low dose of inhaled corticosteroids and rescue bronchodilators, allowing for little improvement. As has been mentioned, probably slightly more severe patients may benefit more from AIT (34, 36), just like more severe rhinitis. Another limitation is that there is no consensus on which are the most adequate study designs and outcomes to assess AIT efficacy in asthma. There is a lack of validated symptom and medication scores, or a unanimous definition of asthma exacerbations. The consequence is a great variability of results, difficult to compare or to pool for meta-analyses; this should prompt scientific societies to develop guidelines on the most appropriate designs to further evaluate AIT in asthma.

Author contributions

VC, OL, and ML contributed to the conception and drafting of the manuscript, and all approved the final version.

Conflicts of interest

VC has received fees as speaker for ALK, Allergy Therapeutics, Leti and Stallergenes, and as advisor for Circassia. OL declares no conflict of interests. ML has received fees as speaker for Allergy Therapeutics, HAL Allergy, Leti and Stallergenes.

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