



The role of allergy immunotherapy in the treatment of asthma

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Purpose of review

Asthma and allergic rhinitis are two of the most widespread chronic medical conditions. Asthma, a condition which encompasses chronic inflammation of the lower airway resulting in expiratory obstruction, may represent an end phase along the allergic disease spectrum ultimately stemming initially from nasal allergic rhinitis and bronchial hyper-reactivity. The purpose of this review was to evaluate the available published literature over the past 12 months regarding the role of allergy immunotherapy in the treatment of asthma.

Recent findings

Recent clinical trials, systematic reviews, and meta-analyses have demonstrated that allergen-specific immunotherapy (ASI), especially sublingual immunotherapy for as short as 12 months, may help improve asthma symptoms and reduce medication usage. However, studies have not demonstrated overall improvement in pulmonary function tests despite improvement in symptoms. Barriers to asthmatic patients initiating and maintaining ASI include lack of payment by health insurer, inconvenience, and potentially worsening asthma exacerbations/symptoms for patients with severe disease.

Summary

ASI may change the natural course of allergic asthma by reducing the risk of acute respiratory exacerbations and symptoms. Additional studies are necessary to examine whether early treatment of allergy sensitivities with ASI may ultimately prevent the progression to asthma.

Keywords

allergen-specific immunotherapy, asthma, house dust mite, subcutaneous immunotherapy, sublingual immunotherapy

INTRODUCTION

Asthma and allergic rhinitis are two of the most widespread chronic medical conditions affecting approximately 300 million people throughout the world and 9% of the US population [1,2]. Allergic rhinitis has been conservatively estimated to cost more than 2 billion dollars annually in the United States [3] and approximately 80% of patients with classic asthma symptoms simultaneously report nasal symptoms; not surprisingly, nearly 40% of patients with allergic rhinitis also report coexistent asthma [4].

Allergic rhinitis includes ocular-nasal symptoms consistent with an allergic cause, such as clear rhinorrhea, nasal congestion, pale nasal mucosa, and red and watery eyes in response to inhaled allergens [5]. Asthma, a condition which encompasses chronic inflammation of the lower airway resulting in expiratory obstruction, may represent an end phase along the allergic disease spectrum ultimately

stemming initially from nasal allergic rhinitis and bronchial hyper-reactivity [6]. Both asthma and allergic rhinitis affect the mucosa of the respiratory tract, and thereby may share a shift from T-helper cell type 1 (TH1) to T-helper cell type 2 (TH2) immunologic mediated imbalance [7].

Allergic rhinitis has been shown in multiple studies to increase the risk for future development of asthma/airway reactive disease [8,9]. Both conditions may cause worsening symptoms through re-exposure of airborne allergens, thereby propagating frequent mast cell sensitization, release of inflammatory

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KEY POINTS

- ASI is an effective mode of therapy for the treatment of allergic asthma.
- Immunotherapy to house dust mite, with the major strains consisting of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, has been demonstrated to improve asthma symptoms and reduce medication usage such as inhaled corticosteroids.
- ASI has not consistently demonstrated improvement in pulmonary function tests, despite improvement in overall asthma symptoms.

mediators, cytokines (IL-4, IL-5, and IL-6), and cysteinyl leukotrienes, ultimately leading to chronic mucosal inflammation [7,10], vascular permeability, vasodilation, and rhinorrhea [11]. This thereby results in long-acting inflammation by antigen-mediated activation of mast cells, basophils, and eosinophils [12]. During a late-phase response occurring several hours after the initial IgE-mediated reaction to the initial allergen exposure, symptoms of nasal congestion and lower airway obstruction ensue with increased bronchial hyper-responsiveness to subsequent airborne allergens and irritants [13]. As a result, suboptimally controlled allergic rhinitis may lead to worsening asthma symptoms [14].

The progression from allergic rhinitis to asthma has been hypothesized to occur via the following: elicitation of the nasal-bronchial reflex, preferential increase in oral vs. nasal inhalation because of nasal obstruction, reduction in filtration/humidification of the nose, and postnasal rhinorrhea of inflammatory mucus into the lower airways [15]. Prevention of nasal congestion and rhinorrhea resulting from the early allergic response may, thereby, help mitigate this progression of allergic rhinitis to asthma. Standard pharmacotherapy for allergic rhinitis consists of antihistamines, topical intranasal steroids, and immunotherapy.

Concomitant improvement and prevention of asthma with treatment of allergic rhinitis utilizing allergen-specific therapy (e.g., immunotherapy) have been previously observed [16]. This may be because of a reduction in nasal inflammation, suppression of histamine dominated immunologic changes, and immunomodulation leading to a more TH1 vs. TH2 dominated response [17]. Current pharmacotherapy for asthma is effective and may temporarily relieve symptoms; however, medications alone cannot cure or modify the disease course. Sublingual (SLIT) and subcutaneous (SCIT) immunotherapy provide an opportunity to modify the immune system, and thereby potentially

improve clinical symptoms of both allergic rhinitis and asthma, and when initiated early enough, may prevent the development of new sensitivities to allergens and asthma in children and adults with allergic predisposition [18].

REVIEW

Allergen-specific immunotherapy (ASI) should be considered an option in patients with allergic diseases who have had inadequate reduction in symptoms with environmental avoidance measures, standard pharmacotherapy, or patients who seek to potentially avoid long-term pharmacotherapy according to current practice guidelines [19]. Therapy should be initiated in conjunction with a desire to alter immunological tolerance with the ultimate goal of improving asthma symptoms, decreasing bronchial hyper-responsiveness, and improving overall pulmonary function. The mechanism of action of ASI is likely the result of a switch from TH2 to TH1 mediated immunity. This subsequently results in a reduction in the production of IL-4, IL-5, and IL-13 cytokines, which may be important in reducing upper and lower airway inflammation [20].

ASI is administered by giving small controlled doses of allergens to patients over a period of time (usually at least several years) and titrated to promote immune tolerance, while ameliorating allergic symptoms [21]. The development of SLIT in the 1980s was an important advancement, with reduction in systemic side-effects from SCIT and improved tolerance especially in pediatric patients. ASI remains underutilized and is likely used in only a small fraction of patients with allergic rhinitis or asthma as primary therapy.

The Joint Task Force of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology immunotherapy practice parameters justify the use of using a representative allergen for immunotherapy treatment within a subgroup of allergens as adequate efficacy against an entire similar group of allergens [22]. ASI is the only treatment that may change the natural course of allergy sensitivities into allergic asthma, and thereby reduce the risk of acute respiratory exacerbations. With a significant increase in the prevalence of asthma and allergies, the goal of reducing asthma symptoms and medication usage is of prime public health importance. Adverse reactions are rarely reported, but may be categorized into two realms: local reactions, such as erythema, pruritus, and edema at the administration site, and systemic reactions which may clinically appear as urticarial, gastrointestinal

symptoms, wheezing, headache, or as anaphylaxis. An apprehension for the use of ASI in patients with severe asthma is the concern of increasing the likelihood of systemic adverse respiratory exacerbations in those with severe asthma symptoms at baseline.

HOUSE DUST MITE IMMUNOTHERAPY CLINICAL TRIALS AND IMPROVEMENT IN ASTHMA

The safety of SLIT compared with SCIT is one of the many reasons for renewed interest in the sublingual route of administration. ASI, specifically SLIT, has

been studied extensively, with many recent clinical trials evaluating efficacy (Table 1). A systematic review evaluating 34 randomized controlled trials of children aged 4–18 with allergic asthma or rhinoconjunctivitis treated with SCIT (920 children) or sublingual therapy (1583 children) found high strength of evidence and low bias that SLIT improves asthma symptoms, and moderate strength of evidence that SLIT improves rhinitis and conjunctivitis symptoms [23]. The house dust mite is one of the most common allergens in patients with asthma, with the major strains consisting of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

Table 1. Recent trials evaluating immunotherapy in the treatment of asthma

Study	Study characteristics	Number (age, years)	Conclusions
Dust mite SLIT			
Wang <i>et al.</i> , 2014 [27 ^{***}]	Randomized double-blind controlled trial (12 months) comparing house dust mite SLIT and placebo in achieving well controlled asthma and reduction in inhaled corticosteroid use	465 (14–50)	In patients with moderate asthma: Well controlled asthma success rate was greater in SLIT group than in placebo group (80.5 vs. 66.1%). No significant difference with mild asthma A higher percentage of patients with an asthma control questionnaire score <0.75 was achieved (56.6 vs. 40.0%) Greater mean reduction in inhaled corticosteroid use (218 vs. 126.2 µg)
Mosebech <i>et al.</i> , 2014 [28 ^{***}]	Randomized double blind controlled trial (12 months) comparing standardized quality house dust mite SLIT tablet and placebo in reducing inhaled corticosteroid use	604 (~14–55)	Mean reduction of 81 µg daily of inhaled corticosteroid between patients with mild-to-moderate asthma in the six standardized-quality house-dust mite treatment group
De Blay <i>et al.</i> , 2014 [29]			Posthoc analysis revealed: a reduction of 327 µg daily was observed in the six standardized-quality house-dust mite treatment group subgroup of mild-to-moderate asthma patients with baseline daily inhaled corticosteroid use of 400–800 µg
Li <i>et al.</i> , 2014 [30]	Retrospective cohort study evaluating predictive factors for clinical response in mild asthmatic children undergoing 3 years of SCIT to house dust mite	185 (4–14)	Clinical response to SCIT was 69.7%. Factors associated with clinical response to SCIT in children with asthma were: tobacco smoke exposure, family history of atopy, serum total IgE level >965 Ku/l, and a serum IgE/total IgE ratio >6%.

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

The causal role of house dust mites in allergic asthma has been previously demonstrated [24]. Nearly half of patients with asthma have house dust mite sensitization and it may be the most clinically problematic allergen for acute exacerbations [25]. ASI in individuals sensitized to house dust mite may concomitantly improve asthma symptoms, which has been recently studied extensively and will be the primary focus of this review.

According to the WHO, the only currently available causal treatment for respiratory allergic disease such as asthma is ASI [26]. A double blind placebo controlled randomized clinical trial in China evaluating SLIT to *D. pteronyssinus* and *D. farinae* demonstrated that in patients with baseline moderate persistent asthma, a significantly higher proportion of asthma symptoms were well controlled after 12 months of ASI with a concomitant reduction in inhaled corticosteroid use compared with those receiving placebo [27[■]].

The later findings, notably a reduction in inhaled corticosteroid use in patients with asthma, have been similarly reported using a standardized quality house dust mite SLIT tablet. This multisite randomized double blind parallel group placebo controlled trial in Europe demonstrated an 81 µg daily reduction in inhaled corticosteroid use after 1 year of SLIT in individuals with mild-to-moderate asthma and sensitivity to house dust mite [28[■]]. A posthoc analysis of the same clinical trial showed that participants who required 400–800 µg daily of inhaled corticosteroid and partly controlled asthma at baseline had a 327 µg daily reduction in inhaled corticosteroid use, improvement in asthma control, and increase in asthma-related quality of life [29].

In children with at least mild asthma undergoing 3 years of SCIT to *D. pteronyssinus* and *D. farinae*, nearly 70% may have a clinically significant response. Factors associated with an effective clinical response include history of tobacco smoke exposure, family history of atopy, total IgE level greater than or equal to 965 KU/L, and an allergen-specific IgE level/total serum IgE level greater than or equal to 6% [30]. The clinical evidence suggests that definite treatment of house dust mite allergy with ASI appears to play an important role in the treatment of asthma and mitigating symptoms.

IMMUNOTHERAPY AND IMPROVEMENT IN ASTHMA SYSTEMATIC REVIEWS AND META-ANALYSES

Several systematic reviews and meta-analyses have been published recently further elucidating the association with improvement in asthma and initiation of SCIT and SLIT (Table 2). In a systematic

review of 61 studies with participants ranging from 7 to 72 years of age evaluating single-allergen immunotherapy regimens, there was high-grade evidence that SCIT improved asthma symptom scores and decreased asthma medication usage. However, there was low strength of evidence that SCIT improved asthma symptom-medication scores and inconsistent findings on pulmonary function, despite the majority of the studies showing improvement in bronchial hyper-reactivity compared with participants using placebo [31[■]].

A recent retrospective meta-analysis of 16 randomized double-blind placebo controlled trials evaluating the clinical efficacy and safety of SLIT for allergic asthma found that after 12 months of therapy, SLIT reduced asthma symptoms, medication scores, and improved clinical response in house dust mite sensitive asthma patients compared to placebo. Interestingly, duration of therapy for more than 12 months did not confer additional clinical benefits. There was no consistent effect on pulmonary function tests (forced expiratory volume in 1 s) or serum levels of antigen-specific IgG4 and IgE in participants undergoing immunotherapy compared with controls [32[■]]. In support of these findings, a meta-analysis evaluating the efficacy and safety of house dust mite SLIT in children with asthma over a period of 4–18 months demonstrated that SLIT significantly decreased asthma symptoms scores. Although overall serum IgG4 levels increased in SLIT participants, there was no difference in serum antigen-specific IgE levels or medication scores [33[■]].

A recent position paper by the International consensus on allergy immunotherapy summarized a thorough evaluation of the literature, systematic reviews, and meta-analyses in regards to SCIT and SLIT for the treatment of allergic asthma. The position paper stated that SCIT and SLIT should be conditionally recommended in patients with allergic asthma with moderate-to-high evidence showing efficacy after at least 3 years of therapy [34]. Immunomodulation after ASI is observed in many patients to remain after the end of active treatment, which thereby results in retained clinical benefit by potentially preventing worsening of asthma symptoms over time despite treatment cessation [35].

The potential benefits must be balanced against the risk, side-effects, inconvenience, and cost incurred, especially since the efficacy on pulmonary function tests has not been found to be consistent [34]. One of the challenges highlighted in the manuscript in evaluating the literature to date is that there is no unified consensus on optimal clinical end points with use of ASI in asthmatic patients; thus,

Table 2. Summary of systematic reviews and meta-analysis

Study	Study characteristics	Number studies (age)	Conclusions	Years studied
Erekosima <i>et al.</i> , 2014 [31 [■]]	Randomized controlled trials evaluating single allergen immunotherapy in children and adults with asthma.	61 (7–72)	High strength of evidence: SCIT improves asthma symptom scores, reduces asthma medication usage Moderate strength of evidence: SCIT improves combined asthma and rhinoconjunctivitis symptom scores Moderate strength of evidence: SLIT improves rhinitis and conjunctivitis symptoms Inconsistent evidence: SLIT improves pulmonary function testing	1967–2012
Tao <i>et al.</i> , 2014 [32 [■]]	Retrospective meta-analysis of randomized double-blind placebo controlled trials evaluating the clinical efficacy and safety of SLIT for mild-to-moderate allergic asthma	16 (4–65)	SLIT significantly reduces asthma symptoms and medications scores compared to placebo after 12 months of therapy No consistent effect on pulmonary function tests or antigen-specific IgG4/IgE serum levels.	1990–2010
Liao <i>et al.</i> , 2015 [33 [■]]	Meta-analysis evaluating the efficacy and safety of dust mite SLIT in children with asthma	11 (mean age 6.5–15)	SLIT significantly decreased asthma symptom score and increased serum IgG4 levels than control participants. No change in dust mite-specific IgE levels or medication score	1990–2012

SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

designing optimal clinical trials has become challenging.

CONCLUSION

There is a very strong anatomic, functional, and immunologic relationship between the nasal upper airway and bronchial lower airway. Nasal stimulation by airborne allergens, especially the house dust mite, is challenging to avoid despite strict environmental measures in patients with allergic asthma. Exposure to house dust mite and other allergens may induce nasal obstruction and edema, thereby reducing nasal breathing and filtration and leading to bronchial inflammation and lower airway obstruction. Recent clinical trials, systematic reviews, and meta-analyses have demonstrated that ASI, especially SLIT, may help improve asthma symptoms and reduce medication usage. Despite the clinical evidence, there are no sublingual aqueous forms of immunotherapy approved for use by the Food and Drug Administration.

Although traditional pharmacotherapy with inhalant corticosteroids may help mitigate the symptoms associated with allergic asthma, only ASI for as short as 12 months, especially against house dust mite, may change the natural course of allergic asthma by reducing the risk of acute respiratory exacerbations and symptoms. The mechanism of action of ASI is likely the result of a switch from TH2 to TH1 mediated immunity with a subsequent reduction in inflammatory cytokines, such as IL-4, IL-5, and IL-13, resulting in reduced upper and lower airway inflammation. Barriers to asthmatic patients initiating and maintaining ASI include lack of payment by health insurer, inconvenience, and potentially worsening asthma exacerbations/symptoms for patients with severe obstructive disease. Additional studies are necessary to examine whether early treatment of allergy sensitivities with ASI may ultimately prevent the progression to asthma.

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Conflicts of interest

D.J.M. and S.Y.L. conceptualized and designed the study, assisted in selecting the articles to be in the manuscript, drafted the initial manuscript, and approved the final manuscript as submitted. All authors had full access to the manuscripts selected for this review, and take responsibility for drafting the final manuscript.

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