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# House Dust Mite Allergy and Associated Allergen-Specific Immunotherapy in Allergic Asthma

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## Abstract

Allergic asthma, an important subtype of asthma endotypes, is characterized by allergen-specific and Th2 cell-mediated airway inflammation. Except for pharmacologic treatment, Allergen-specific immunotherapy (ASIT) has also been considered as a potential therapy for allergic asthma. House dust mite (HDM) is a common airborne allergen among patients with allergic asthma. This review is focused on the relationship between HDM allergy and allergic asthma, underlying mechanism of ASIT, and current evidence of HDM-specific immunotherapy for allergic asthma. It was demonstrated that HDM allergy is a risk factor associated with disease development of allergic asthma. The induction of immune tolerance by regulatory T cells was proved to play a pivotal role in the immunological mechanisms of ASIT. Experimental studies in murine models of allergic asthma reveal that HDM-specific immunotherapy has not only therapeutic efficacy but also preventive potential for disease development. The clinical trials also demonstrated the efficacy of HDM-specific immunotherapy in reducing asthma symptoms and medication use. Today, the clinical application of ASIT in allergic asthma has limitation when considering the extent of benefit and systemic adverse reactions. Although sublingual immunotherapy with HDM extract was demonstrated to have better safety profile when comparing with subcutaneous immunotherapy. To make HDM-specific immunotherapy more practicable in clinical application, further advances in the development of immunotherapy and clinical trials are needed.

**Keywords:** House dust mite; Allergy; Allergic asthma; Allergen-specific immunotherapy; Subcutaneous immunotherapy; Sublingual immunotherapy

## Introduction

There is an increasing trend in the global prevalence, morbidity, and economic burden associated with asthma in recent decades [1]. The Global Strategy for Asthma Management and Prevention Report [2] defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements are involved. Both host factors (primarily genetic) and environmental factors (primarily allergen exposure) are considered to contribute to the development and expression of asthma [3]. Pharmacologic treatment to achieve and maintain asthma control is the main treatment for the management of most asthmatic patients today. However, some measures that identify risk factors and further reduce exposure to these risk factors are also crucial to improve asthma control and reduce medication use. Recent research revealed that asthma is more likely a heterogenous disease in view of clinical manifestations or pathophysiologic mechanisms, and asthma phenotypes or endotypes are evolving to classify subgroups of asthmatic patients [4,5]. The biologically-targeted treatment could benefit specific groups of asthmatic patients on the basis of asthmatic classifications and understanding of pathophysiological mechanisms. Allergic asthma, one important subtype of asthma endotypes, is characterized by a hypersensitivity to airborne allergen and Th2 cell-mediated airway inflammation [4]. The house dust mite (HDM) is considered an important airborne allergen associated with asthma attack in the domestic environment [2]. Further, although allergen-specific immunotherapy (ASIT) has been developed to treat patients with allergic disease for many decades, the role of ASIT in allergic asthma has not been clearly identified. The aim of this review is thus to discuss the risk factor of HDM allergy on allergic asthma, potential strategy of HDM-specific immunotherapy and underlying mechanism, and both experimental and clinical studies of HDM-specific immunotherapy for allergic asthma.

## Data source and study selections

Through Pubmed, Medline, and Google Scholar databases, a broad literature review was performed in the following areas of HDM allergy, allergic asthma, immune tolerance, and allergen-specific immunotherapy. Studies of animal models were selected based on the immune tolerance induction of allergic airway inflammation. Clinical trials of allergen-specific immunotherapy with HDM extracts for allergic asthma were reviewed from Cochrane and Pubmed databases which were published before Oct, 2014.

## Risk factor of dust mite allergy on allergic asthma

The HDM, a cosmopolitan guest in human habitats, feed on organic detritus such as flakes of human skin and flourish in the environment of dwellings. The allergy to HDM has become a common health problem in many people [6]. The HDM in domestic environments is also considered a common risk factor of asthma attacks in asthmatic patients [2]. Recent advances in purification of allergens, immunological studies of allergic diseases, and epidemiological studies have furthered our understanding about the relationship between HDM allergy and allergic asthma [7-9]. The predominant species of dust mite in Taiwan,

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Australia, and Western Europe is *Dermatophagoides pteronyssinus* (Der p), whereas *Dermatophagoides farinae* (Der f) is predominant in many areas of the United States, Japan, and Europe. The current use of allergen nomenclature is approved and maintained by a systematic nomenclature of the Allergen Nomenclature Sub-Committee of the World Health Organization and International Union of Immunological Societies (WHO/IUIS) [10]. Today, there are 17 groups of allergens which have been molecularly characterized from *Dermatophagoides pteronyssinus*. The group 1 and 2 allergens from *Dermatophagoides pteronyssinus* (Der p1 and Der p2) are the most important among patients with allergic diseases. The Der p1 and Der p2 allergens was reported to react with about 80% of sera from allergic patients [9].

The development and pathogenesis of allergic asthma is complex, and the specific role of allergens in the development of asthma remains incompletely understood even today. In a comparing study of children in different regions of Australia, more children were sensitized to Der p1 and had significantly more active asthma in regions where Der p1 exposure levels were higher [11]. In addition, a positive correlation between airway hyperresponsiveness and Der p1 exposure in Australian children suggested that HDM allergen could be an important cause of childhood asthma [12]. In a cohort study of children in New Zealand, both airway hyperresponsiveness and diagnosed asthma were demonstrated to be related strongly with serum IgE levels [13]. In another study, the positive skin prick tests and elevated serum IgE were also demonstrated to be associated with asthma development in children [14]. It was also established in a longitudinal study of a birth cohort of children that the development of asthma is associated with sensitization to common allergens such as dust mite and cat dander [15]. These studies suggest that atopy is a potential risk factor for developing asthma in children. From a review of available epidemiological studies of asthma, the percentage of asthma cases attributable to atopy ranged from 10% to 80% in different population-based studies and according to different definitions of atopy (defined as a positive skin prick test or elevated serum IgE level), [16] although the authors concluded that the percentage of asthma cases attributable to atopy is usually less than one half, the current study also illustrated that allergic asthma plays a large proportion in total asthma cases.

The above-mentioned studies suggest that HDM allergy could not only be a risk factor for symptom exacerbations but also be related to disease development of allergic asthma.

## A practicable strategy in managing allergic asthma: Allergen-specific immunotherapy

In theory, a strategy to reduce allergen exposure could have the benefit of symptom control in asthmatic patients who were atopic to this allergen. Because dust mites live anywhere in the domestic environment, many measures such as chemical or physical methods have been developed to reduce the load of HDM allergens in the indoor environment. A meta-analysis of HDM control measures for asthma had enrolled 55 trials involving 3,121 mite-sensitive patients with asthma [17]. The author concluded that chemical and physical methods of HDM exposure reduction cannot be recommended because no statistically significant improvement was demonstrated in the intervention group either in asthma symptoms scores or in medication use. However, other studies showed that environmental intervention to reduce HDM exposure can have some efficacy of symptom reduction in children with asthma [18,19]. Since there are conflicting results for HDM control methods in atopic patients with asthma, a recommendation for widespread use of HDM control methods cannot be made for the lack of strong evidence in reducing asthma symptoms in these patients [20,21].

The characteristic pattern of inflammation found in allergic diseases is also seen in allergic asthma, with activated mast cells, increased numbers of activated eosinophils, and increased numbers of Th2 cells which release mediators that contribute to the airway inflammation [22]. By secreting the cytokines IL-4 and IL-13 that drive IgE production by B cells, IL-5 that is solely responsible for eosinophil differentiation in the bone marrow, and IL-9 that attracts and drives the differentiation of mast cells, Th2 cells play a central role in allergen-specific airway inflammation of allergic asthma [22]. Immunotherapy is defined as the treatment of disease by inducing, enhancing, or suppressing an immune response. While medications such as antihistamines or corticosteroids only relieve or control symptoms of allergic disease, immunotherapy has the potential to rebuild the immune response and modify the natural course of allergic diseases. Allergen-specific immunotherapy (ASIT, also called desensitization or specific immunotherapy) requires the identification and administration of specifically relevant allergens to induce immune tolerance in allergic patients. In 1911, Leonhard Noon and John Freeman demonstrated their pioneer work in ASIT using grass pollen extract on human hay fever [23]. In the past one hundred years, many modalities of ASIT have been developed with the purpose to cure allergic diseases [23,24]. Today, the ASIT is also thought as a therapeutic option for allergic diseases such as allergic rhinitis and asthma [25,26]. Among these developments of ASIT, the administration of allergens via the sublingual intake or by subcutaneous injection has become the major modality with high practicability and efficacy [27,28]. While the efficacy of both subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) have been demonstrated, the safety profile of SLIT has been demonstrated to be more favorable in contrast to SCIT, which has been found to have more systemic adverse reactions [28-31]. New ways of allergen administration, including oral, epicutaneous, and intralymphatic routes are also being investigated to improve the efficacy and safety of immunotherapy [24,29]. Allergen extract may also contain bioactive substances that have Th2-promoting capacities, thereby reducing the efficacy of tolerance induction [31,32]. New developments of immunotherapy in allergen preparations include recombinant wild-type allergens, recombinant hypoallergenic allergen derivatives, and CpG-adjuvanted allergens [23,24,33]. These advances in ASIT could make HDM-specific immunotherapy a practicable strategy in managing patients with allergic asthma.

## Immunological mechanisms of allergen-specific immunotherapy

In the past two decades, a new subtype of T cells with immunosuppressive function and associated cytokine profiles, termed regulatory T (Treg) cells, has been discovered [34,35]. There are two major subsets of Treg cells. Natural Treg cells (also called NTreg cells) are $CD4^+CD25^+$ T cells formed in the thymus, whereas inducible Treg cells (also called iTreg or Tr1 cells) can be induced from naive $CD4^+CD25^-$ T cells in the periphery [36]. Through the production of interleukin-10 (IL-10) and transforming growth factor-β, Treg cells suppress the development and functions of other effector T cells such as Th1 and Th2 cells [36]. It has been found that the different profile of allergen-specific T cell populations (Th1, Th2, and Treg) determines the development of a healthy or allergic immune response to allergen exposure. Thus, low Treg cells numbers and high Th2 cell numbers were found to result in an allergic response, whereas a mixed Th1/Th2 cell response and high Treg cell response were observed in nonallergic individuals [37,38]. The balance between allergen-specific Treg and

Th2 cells influences the development of allergic or healthy immune responses against allergens.

There have been several hypotheses proposed to explain the immunological mechanisms of ASIT [23]. These hypotheses include tachyphylaxis, induction of T-cell anergy, switching from Th2 to Th1 response, and Treg cells. Both the advances in allergological research and the understanding of Treg cells indicate that Treg cells play a key role in the tolerance induction of ASIT [33,39-41]. It was demonstrated that the functional insufficiency of Treg cells observed in patients with allergic asthma can be reversed by ASIT [42]. The allergen-specific Treg cells, especially Tr1 cells have been shown to correlate with allergen tolerance and can be induced by ASIT in humans [43-45]. The suppression of allergen-specific Th2 cells and decreased IL-4, IL-5, and IL-13 production caused by Treg cells is the essential step in ASIT. Treg cells are also involved directly or indirectly with the following mechanisms of suppression of different inflammatory cells, such as eosinophils, mast cells, and basophils. Furthermore, IL-10 mediated by Treg cells not only affects tolerance in effector T cells, but also regulates the allergen-specific antibody isotype formation from IgE toward a non-inflammatory antibody of IgG4 [46]. These findings reveal that induction of immune tolerance by regulatory T cells play a pivotal role in the immunological mechanisms of allergen-specific immunotherapy.

## Experimental evidence of HDM-specific immunotherapy in allergic asthma

In recent decades, experimental studies of allergic asthma on murine models have been widely used to investigate disease pathogenesis and develop new therapeutics [47-49]. The exposure of sensitized mice to inhaled allergen challenge can elicit Th2 cell-mediated airway inflammation, airway hyperresponsiveness, and airway remodeling that mimic the responses observed in human allergic asthma. These responses are allergen-specific and can be successfully induced by not only ovalbumin, but also dust mite allergens and other peptides. Although some limitations of results observed in experimental studies are present [50-52], these murine models of allergic asthma are still considered a crucial surrogate for studying asthma *in vivo*. The experimental evidence of HDM-specific immunotherapy efficacy in allergic asthma are discussed below and summarized in Table 1.

In a Der p2-sensitized murine model of asthma, it was demonstrated that mice treated by local nasal immunotherapy with recombinant Der p2 peptide and a fungal immunomodulatory peptide had reduced airway inflammation [53]. In a study by Hsu et al. mice ingested with plant extract containing recombinant Der p5 peptide were also demonstrated to have attenuated allergic airway inflammation [54]. Two studies of immunotherapy with Der f extract via sublingual or local nasal administration both highlighted the therapeutic efficacy in murine models of allergic asthma [55,56]. In another study by Ou-Yang et al., the intra-peritoneal vaccine administration before sensitization with a recombinant bacille Calmette-Guerin (rBCG) that expressed Der p2 peptide was shown to have preventive effect on the subsequent development of allergic airway inflammation [57]. Our previous study also demonstrated that oral ingestion of recombinant Der p2-containing milk before sensitization could prevent the development of airway inflammation and airway hyperresponsiveness in a murine model of allergic asthma [58]. These results from experimental studies suggest that HDM-specific immunotherapy, by administration with recombinant dust mite peptide, and by different administration routes, can serve as a potential therapy for allergic asthma or as a strategy to prevent the development of allergic asthma.

## Clinical evidence on the efficacy of HDM-specific immunotherapy in allergic asthma

A systematic review and meta-analysis of subcutaneous immunotherapy (SCIT) for treatment of asthma enrolled 88 trials published before 2005 [59]. Most of these enrolled studies reported SCIT with HDM extract (42 studies), which was followed by immunotherapy with pollen (27 studies) and animal dander (10 studies). Although the heterogeneity in the medication and symptom scores were significant among these trials, this meta-analysis confirmed the efficacy of injection ASIT in reducing symptom scores, reducing asthma medication requirements, and alleviating airway hyperresponsiveness [59]. The stratifying analysis of HDM-specific immunotherapy in this review also exhibited the benefits such as reducing symptom scores [60-71], medication use [60,62,63,66-73], and allergen-specific airway hyperresponsiveness [63,65,69,74-76]. However, adverse reactions accompanied by SCIT were also discussed in this review [59]. It was reported that 1 in 16 treated patients could be expected to have a local adverse reaction; about 1 in 9 treated patients could be expected to develop a systemic adverse reaction; and an occurrence of 1 fatal reaction per 2.5 million subcutaneous injections has been estimated [59]. After 2005, several randomized double-blind, placebo-controlled studies of allergic asthma patients also demonstrated that SCIT with HDM extract could be efficacious and safe in symptoms score, medication use, or airway hyperresponsiveness [77-80]. Though most adverse reactions can be adequately and safely managed, patients should be informed that SCIT still has risk of adverse reactions [59]. The size of benefits and consideration of adverse reactions make clinical

| Trials | Therapeutic modalities | Outcome | References |
|---|---|---|---|
| **Experimental studies (murine models)** | Treatment | The reduced allergen-specific airway inflammation was demonstrated by administration with recombinant Derp2 peptide+fungal immunomodulatory peptide (local nasal route), recombinant Derp5 peptide (oral ingestion), and Der f extract (sublingual or local nasal route). | [53-56] |
| | Prevention | The reduced induction of allergen-specific airway inflammation was shown by vaccination with recombinant BCG containing Derp2 peptide (intraperitoneal injection), and recombinant milk containing Der p2 peptide (oral ingestion). | [57,58] |
| **Clinical studies** | Treatment | A meta-analysis and four RCTs demonstrated the efficacy of SCIT with HDM extracts in reducing symptom scores, reducing medication use, and improving allergen-specific airway hyperresponsiveness. About 1 in 9 treated patients were expected to develop a systemic adverse reaction.<br>A meta-analysis and three RCTs showed the efficacy of SLIT in reducing symptom scores and medication use. Another article of systemic review indicated that no severe systemic reactions was observed in asthmatic patients treated with SLIT. | [59,77-80]<br>[81-85] |
| | Prevention | An RCT revealed that SCIT with HDM extract may be a prophylactic treatment for subsequent development of asthma in monosensitized patients with allergic rhinitis. | [88] |
| SCIT: Subcutaneous Immunotherapy ; SLIT: Sublingual Immunotherapy | | | |

**Table 1:** Summary of the experimental and clinical evidence of HDM-specific immunotherapy in allergic asthma.

application of SCIT difficult when most asthmatic patients can be controlled well by anti-asthmatic medications.

A modified ASIT with allergen administration via the sublingual route (SLIT) has also been investigated for many years. A meta-analysis of SLIT for treatment of allergic asthma in pediatric patients enrolled 9 trials published before 2006 [81], with six of these trials reporting immunotherapy with HDM extract. Although a heterogeneity in scoring systems was also present among different trials, this meta-analysis confirmed the efficacy of SLIT in reducing both symptom scores and rescue medication use in children with allergic asthma. After 2006, there were also several randomized double-blind, placebo-controlled studies that demonstrated efficacy of SLIT with HDM extract in patients with allergic asthma [82-84]. Most of the adverse reactions occurred in pediatric patients receiving SLIT included oral itching, nasal-ocular, and gastrointestinal (GI) symptoms. There was no lethal or severe systemic reactions reported in above studies. Most adverse reactions were mild and were well managed. A systemic review of ASIT for pediatric asthma and rhinoconjunctivitis [25], three RCTs of HDM-specific immunotherapy reported a head-to-head comparison of safety and efficacy between SCIT and SLIT [84-86]. The comparison indicated no systemic reaction observed in SLIT group versus 4 systemic reactions (including 1 anaphylaxis event) observed in SCIT group. These clinical findings indicated the efficacy and safety of SLIT for patients with allergic asthma, thereby suggesting that SLIT can be a more favorable choice than SCIT due to its fewer occurrences of systemic adverse reactions [28-30]. These clinical evidence of HDM-specific immunotherapy via sublingual or subcutaneous routes both demonstrates their efficacy for reducing asthma symptoms and use of medications (Table 1).

In addition to scientifically accepted modalities of SCIT and SLIT, other routes of allergen administration, such as oral ingestion, epicutaenous or intralymphatic injection, are being investigated to improve the efficacy and safety profile [23]. However, more well-controlled clinical trials are needed to illustrate the comparison between these novel modalities and SCIT or SLIT.

The PAT-study, a randomized controlled study of 205 children, showed that ASIT with pollen extract could reduce the subsequent development of asthma in children with seasonal rhino conjunctivitis after 3 years of follow-up [87]. In another randomized controlled study of 44 monosensitized subjects with allergic rhinitis, SCIT with HDM extract was demonstrated to be a potential prophylactic treatment in reducing airway hyper responsiveness and subsequent development of asthma [88]. Despite the fact that this study exhibited HDM-specific immunotherapy being able to protect atopic patients from the development of asthma, more large randomized controlled studies are needed to confirm the preventive efficacy of HDM-specific immunotherapy.

## Future Directions

When considering the extent of the benefits and adverse reactions of ASIT, it is always considered as an alternative therapy in selected groups of allergic asthma patients. The clinical guidelines for asthma management provide limited suggestion of ASIT for allergic asthma [2]. Further research focusing on the clinical application of HDM-specific immunotherapy in allergic asthma is still needed. For example, experimental studies commonly test HDM-specific immunotherapy in young, healthy mice with limited pharmacologic treatment. Also, while most clinical studies enrolled children or young individuals for ASIT, in the real world, most patients with allergic asthma may not be young.

| |
|---|
| ➢ Which group of patients can respond well? Young? Old? Or both? |
| ➢ Can HDM-specific immunotherapy replace the role of anti-asthmatic medications? |
| ➢ Which route of allergen administration has the best efficacy and lowest adverse reaction? |
| ➢ What is the best allergen preparation? |
| ➢ Can HDM-specific immunotherapy be used as a vaccine to prevent the development of allergic asthma? |

**Table 2:** Future directions of HDM-specific immunotherapy in allergic asthma.

Therefore, further trials are needed to evaluate the benefit of ASIT in older individuals. In addition, there are no studies that directly compare ASIT with anti-asthmatic medications such as inhaled corticosteroids for allergic asthma. However, some properties of ASIT, such as its long-lasting effects [89], better safety profile in patients receiving SLIT [25], and potential to prevent the development of asthma in atopic patients [87,88], make this therapeutic strategy worthy of further investigation. New strategies with better experimental models, clinical trials that incorporate better design, subgroup patient selection, as well as allergen delivery routes with improved safety, preparation regimen, and outcome measurement are still needed (Table 2).

## Conclusion

Much accumulating evidence is demonstrating that HDM allergy play important roles not only in asthma exacerbations but also in allergic asthma development. Based on mechanism of immune tolerance induction by Treg cell, ASIT with HDM extract is a potential strategy in managing allergic asthma. Evidence from experimental and clinical studies both show that HDM-specific immunotherapy effectively reduces allergic airway inflammation and asthma symptoms. Evidence from experimental models and a clinical study also suggest that HDM-specific immunotherapy could be a potential strategy in preventing disease development of allergic asthma. The concern of fatal systemic adverse reactions occurring in SCIT has limited the application of ASIT in clinical practice, especially in children. SLIT indicates a new milestone of ASIT for its better safety profile. However, to make HDM-specific immunotherapy more practicable in clinical application, newer approaches both in experimental and clinical studies of allergic asthma are still needed.

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