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Immunotherapy for House Dust Mite Sensitivity: Where are the Knowledge Gaps?

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Abstract

House dust mites (HDM) are found in the environments where human habitation exists. Their density is dependent on environmental relative humidity; therefore higher populations are present in areas of the world with higher humidity levels e.g. coastal areas, tropics. To date 24 HDM allergens have been identified. Many of these represent digestive enzymes since HDM feces are the major source of allergen exposure. IgE- medicated sensitization to HDM allergens is an important factor in the pathogenesis of allergic diseases since it is the most common aeroallergen detected by skin testing or in vitro IgE assays.

Sensitization to HDM allergens often occurs early in life and appears to play an important role in the progression from allergic rhinitis to asthma (the so-called “Allergic March”) in children. HDM sensitization is also associated with asthma across all age groups. Efforts to control environmental exposure to HDM allergens have often proven to be unsuccessful. While medications can improve symptoms, only immunotherapy currently provides disease modifying effects in allergic rhinitis and asthma. Several systemic reviews and meta-analysis indicate that both SCIT and SLIT are effective in the treatment of allergic rhinitis and asthma for HDM sensitivity. In this report we review recent studies and the evidence for the use of HDM SCIT and SLIT. Fundamental gaps in knowledge are identified which could lead to improved approaches to HDM allergy.

Keywords

House dust mites; Allergen immunotherapy; Allergic rhinitis; Asthma; *Dermatophagoides pteronyssinus*; *Dermatophagoides farinae*

Introduction

House dust mites (HDM) are eight-legged arachnids within the Acari order. There are a number of Acari mites, but only dust and storage mites within the Astigmata suborder are allergenic, commonly called “domestic mites.” House dust mites are in the family Pyroglyphidae, primarily consisting of *Dermatophagoides pteronyssinus*, *Dermatophagoides*

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farinae and *Eroglyphus maynei* are the most common (80-90% of all HDM) [1, 2]. Storage mites *Blomia tropicalis* are present in tropical regions, and *Gylcyphagus* and *Lepidoglyphus* may be present in rural homes [3].

HDM are approximately 75% water by weight. They, however, are unable to drink water on their own, so they are dependent on absorbing water through their legs from humidity in the environment. They absorb water at a relative humidity of at least 65%, lose water by evaporation at approximately 55%, and survival decreases once humidity is below 50%. HDM are also poikilothermic (cannot control their own body temperature). Their proliferation is optimal at 75-80% relative humidity and 25-30 degrees Celsius [1,3]. They are able to survive large fluctuations in humidity and temperature by burrowing themselves into areas where moisture can be better retained, such as in mattresses, carpets, or sofas. Therefore, it may take months of low humidity for HDM to die, and longer for their allergens to dissipate [4].

HDM feed off of desquamated human or pet skin. Their digestive system produces fecal particles surrounded by a peritrophic membrane, approximately 20 pellets per day and around the size of a pollen grain (10-35 mcg diameter) [1,4]. The fecal pellets contain the allergenic material, are easily airborne, and inhaled when disturbed.

HDM are ubiquitous, found on all continents including the Antarctic research station [3]. An estimated 84% of homes in the United States have detectable dust mite allergen [1]. Regions with the highest dust mite population densities tended to be coastal cities with moderate-to-warm outdoor temperatures and high rainfall; inland cities with dry climates were low in density. In addition, cities at high altitude such as Caracas, Bogota, and Nairobi have high HDM densities due to seasonally high rainfall and outdoor humidity. *D. farinae* tend to dominate in dryer environments due to its lower critical equilibrium activity, whereas D. *pteronyssinus* are found in more humid regions [3].

House-dust was first identified as an allergen around 1920, with extracts from vacuum cleaner bags used for both diagnosis and immunotherapy [4]. HDM as the allergenic source within was unknown until Voorhorst et al.'s identification of *Dermatophagoides pteronyssinus* in 1967 [5].

The first mite allergen identified was the cysteine protease D. pteronyssinus allergen I, or Der p 1 in 1980, followed by Der p 2, and homologous D. farinae 1 and 2 [4]. Up to 97% of HDM-allergic patients are sensitized to Der p 1. More recently, Der p 23 has been identified as an allergen in greater than 70% of HDM-allergic patients [6]. While not highly involved in respiratory allergic disease, Der p 11 appears to be a major allergen in atopic dermatitis [7]. Der p 10 is a tropomyosin and cross reacts with shrimp tropomyosins, but immediate hypersensitivity reaction risk to crustacean ingestion is unclear [1,8]. There are currently 24 different types of dust mite allergens [1,2].

HDM allergens play a major part of allergic disease. In one cross-sectional study of 628 allergic rhinitis patients, 56% of patients were sensitized to HDM [9]. In studies within different countries, 45-85% of asthmatics were sensitized to mites [10]. Exposure in early childhood to HDM allergens has been found to be a significant determinant of the

subsequent development of asthma (The ‘Allergic March’) [11,12]. Asthmatics sensitized to HDM have been found to have a lower FEV1 and FEV1/FVC ratio than asthmatics without sensitization [13]. In the Copenhagen Allergy Trial, 50% of subjects with HDM-induced rhinitis had HDM-induced asthma, while 95% of HDM-induced asthma also had HDM-induced rhinitis [14,15]. In Kim et al.'s study, 46.3% of patients with atopic dermatitis were sensitized to HD, with a higher level of Der f 1 concentrations correlating with more severe symptoms[16].

While the main tenet for primary through tertiary treatment of allergic disease is avoidance, it is challenging to effectively do so [1]. Suggested physical interventions include impermeable HDM bedding, regular vacuuming with a high efficiency appliance, and heating, freezing, or desiccation [9]. However, no study has found significant clinical benefit with these interventions [17,18]. Acaricide chemicals are effective in killing mites, but unfortunately the effect is short-lived and there is concern about the safety of use in homes [1]. Clearly, currently available medications can provide symptom relief of allergic rhinitis and asthma control, yet they do not alter the underlying immunologic mechanisms in the long term. Immunotherapy, however, has been found to provide an effective and sustained disease-modifying effect in HDM-associated allergic rhinitis and asthma. In this review we will examine the evidence for the use of subcutaneous and sublingual immunotherapy (SCIT and SLIT, respectively) in the treatment of allergic respiratory diseases and identify gaps in our knowledge.

HDM SCIT for Allergic Rhinitis and Asthma

Subcutaneous immunotherapy (SCIT) involves the administration of allergenic extracts in incrementally increasing quantities to an effected individual via an injection route. HDM-SCIT involves the usage of commercial extracts that are made from whole-mite culture or from isolated mite bodies (USA) and thereby creating a variable ration of group 1 (Der p1 and Der f 1) to group 2 (Der p 2 and Der f 2) allergens depending upon the type of preparation. The therapeutic dose range for dust mites appears to be between 500 and 2000 AU (activity units) for a targeted maintenance dose of 7 ug of Der p 1 and 10 ug of Der f 1. SCIT-HDM typically involves an 8 to 24-week build-up phase followed by 3 to 5 years of a monthly maintenance phase. The build-up phase can vary in length and the dosing protocol whereby an allergist can employ a regular, cluster, or rush protocol to achieve maintenance. Ultimately, SCIT appears to improve clinical symptoms (nasal, ocular, and respiratory), reduce rescue medication usage, improve lung function indices, and more importantly has the potential to bring about intrinsic disease-modifying effects such that the allergic inception of asthma and acquisition of new sensitizations can be completely or partially abrogated. The mechanisms of actions by which SCIT induces “allergenic tolerance” involves the induction of FOXP3+ CD25+ regulatory T cells (Tregs) specific to such allergens, induction of “blocking antibodies such as IgG4 and IgA2 [19], as well induction of regulatory cytokines such TGF-beta and IL-10 [20] that skew the response from a TH2 to a Treg or TH1 pattern [21].

Many studies and meta-analyses have been conducted to document the efficacy and safety and SCIT. A study by Pifferi et al [22] in asthmatic children found that HDM-SCIT reduced

rescue medication use, improved allergen-specific airway hyper-responsiveness, and substantially reduced asthma exacerbations (8 to 2 per year). Similarly for adults with poorly-controlled allergic rhinitis, Varney et al [23] showed that one year of SCIT produced substantial reduction in symptom scores, recue medication usage, and skin prick test sensitivity to dust mite extracts. Perhaps, the best evidence comes from two recent Cochrane reviews with on focusing on asthma and the other on allergic rhinitis. In the former meta-analysis by Abramson et al [24], 88 studies on 3459 asthma subjects (pediatric and adult) were included of which 42 trials were for dust mites. For the 42 included trials on dust mites, the combined SMD (standardized mean difference) for symptom scores was −0.48 (95% CI −0.96 to 0) effectively indicating a borderline improvement in asthma symptoms when compared to placebo. The number needed to treat in order to have one patient from deteriorating was calculated to be 6 for HDM immunotherapy. Asthma medication scores also showed improvement with an SMD of −0.61 (95% CI −1.04 to −0.18) compared to placebo. With regard to allergen-specific bronchial hyper-reactivity (BHR), a modest reduction was noted for all immunotherapy, in general, and was markedly pronounced for dust mite immunotherapy with an SMD of −0.98 (95% CI −1.39 to −0.58). Symptomatic deterioration, in terms of risk ration, was assessed for each type of immunotherapy and compared with placebo. For mite immunotherapy, the RR was found to be 0.62 when compared to placebo. Specific safety data with regard to house dust mite SCIT was not elaborated in this meta-analysis, though the NNT to elicit a local reaction or a systemic reaction were 16 and 9 respectively for all forms of immunotherapy including house dust mites. It should be noted that considerable heterogeneity was observed between the studies included in this meta-analysis in terms of dosage/duration of therapy and outcomes measured. Yet another Cochrane review of immunotherapy in allergic rhinitis also had similar conclusions with regard to efficacy and safety of injection immunotherapy, though specific subgroup analyses data specific to HDM were not available [25].

More recently, Calderon et al [26] performed an evidence-based analysis of house dust mite allergen immunotherapy. Their analysis included 44 total studies with 19 trials for allergic asthma and 7 trails for allergic rhinitis specific to SCIT. The included trials encompassed 20 SCIT treatment arms for allergic asthma and 7 SCIT treatment arms for allergic rhinitis. Specifically for allergic asthma, the maintenance dose of Der p 1 ranged from 7 to 17.5 ug with the cumulative dose ranging from 68 to 250 ug. There was wide variability with regard to duration and frequency of injections. For efficacy, nine of the nineteen studies reported a statistically significant response compared to placebo with regard to symptoms. With regard to safety, very few studies had reported numeric data to ascertain this to any meaningful extent. The overall conclusion from this analysis was that safety reporting was poor and not readily quantifiable. For allergic rhinitis, the dose of major allergen ranged from 7 to 30 ug with cumulative dose ranging from 60 to 1420 ug and duration ranging from 11.5 to 24 months. For efficacy, 3 studies reported a statistically significant response compared to placebo with regard to symptoms. Safety reporting was yet again poor in this subgroup analysis with systemic and local reactions reported in a number of studies.

In terms of disease modification, HDM-SCIT appears to prevent the onset of new sensitizations in asthmatic children who are mono sensitized to HDM.[27.28] With regard to schedule, a recent study by Nieto Garcia et al [29] showed that a cluster protocol employing

high-dose hypoallergenic HDM-SCIT in adults and children was safe and well-tolerated, and could conceivably reduce health care cost and time required to achieve maintenance and augment compliance.

More recently, there have been attempts to create recombinant HDM allergens that would retain immunogenicity, but mitigate allergic reactivity [30]. A recent study by Asturias et al [31] demonstrated this concept by producing a recombinant hybrid from Der p 1 and Der p 2 sequences. These approaches, while still in relative infancy, are quite promising novel approaches to improve efficacy of immunotherapy while simultaneously minimizing safety concerns, thereby promoting a more favorable benefit-to-risk ration. Vitamin D has garnered some attention in the atopic world in the past decade, and a small trial of using Vitamin D as an adjunct to HDM-SCIT demonstrated some favorable outcomes for this group compared to SCIT alone of pharmacotherapy [32].

SLIT for HDM-Induced Asthma and Allergic Rhinitis

In addition to traditional subcutaneous allergen immunotherapy (SCIT), sublingual immunotherapy (SLIT) for allergic rhinitis and allergic asthma has undergone a number of clinical trials. Most of these studies have been conducted in Europe and Asia. Currently in the United States, only grass and ragweed pollen tablets are approved by the US Food and Drug Administration (FDA) for sublingual immunotherapy. Large-scale multicenter US trials of house dust mite (HDM) sublingual tablets are underway.

Calderon et al [26] also performed an evidence-based review of commercially available SLIT HDM formulations in patients with allergic rhinitis and asthma. In their review, the authors identified SLIT studies of randomized, double-blind, placebo controlled trials for HDM-induced asthma and for HDM-induced allergic rhinitis. Fourteen studies of HDM-induced asthma met the inclusion criteria. Studies were conducted on subjects with mild to moderate-severe asthma. All studies excluded severe asthmatics wide heterogeneity in the cumulative dosage of major HDM allergen administered (60 mg of Der p 1 to 23, 695 of Der f 1), duration of treatment and month of initiation was observed. Only two studies found a statistically significant difference in symptom scores or symptom-related efficacy outcomes. No clear relationship between dose and efficacy was detected. Interestingly, most (10 of 14) studies were on children less than or equal to 16 years old, 3 studies in adults only (18-50 years old), and one in both age groups. Safety issues were not generally reported in detail, but stated that no or few adverse effects were noted. In a study by Bush et al [33], treatment associated adverse events were not different between active (55%) and placebo (60%) treatment groups. While SLIT is felt to confer a better safety profile than SCIT, a reported case of anaphylaxis in an 8 year-old child receiving maintenance SLIT with HDM-allergen gives pause [34]. Fortunately, the child recovered an injection of epinephrine. The patient was noted to have small oral mucosal lacerations which may have led to increased systemic absorption of the allergen. Bush et al [33], in their report, also noted that preexisting oral mucosal lesions and gastrointestinal issues (e.g. gastro-esophageal reflex) appeared to increase the risk of adverse effects to HDM-SLIT. The overall risk for an anaphylactic episode due to SLIT has been estimated at 1 per 100 million does [35]. Fifteen SLIT studies for HDM-induced allergic rhinitis were reviewed by Calderon et al [26]. Only two of these

studies utilized tablet formulations of HDM allergens; the others utilized liquid preparations. Again dosages, treatment initiation dates, and duration of therapy varied widely across studies. Only two studies reported a statistically significant difference between active treatment versus placebo in symptom scores or symptom-related efficacy criteria. Four studies administered QoL questionnaires with only one study in adults showing an improvement in the active treatment group. Seven studies were conducted in children, but no differences in outcomes were noted between active versus placebo treatment groups. No significant treatment related adverse events were reported, although one study found 96% of both active and placebo groups experienced adverse events (many were “non-local”).

Since the publication of the Calderon [26] review, five additional randomized placebo-controlled, double-blind articles of SLIT for HDM-induced allergic rhinitis and/or asthma have been published.

In an interesting study of 95 elderly (60-75 y.o.) adults conducted in Poland [36], three years of HDM SLIT led to significant improvement in total nasal symptoms and a reduction in mean medication scores in the actively treated group compared to those receiving placebo. Active treatment also significantly decreased nasal airway resistance following nasal provocation compared to placebo. No systemic reactions were reported and only three subjects in the active treatment group experienced local adverse events.

A study of 120 adults and children from China examined the onset of action of HDM-SLIT in controlling nasal symptoms [37]. By 14 weeks of active treatment, nasal symptoms were significantly lower compared to placebo. Unfortunately, there was a high drop-out rate in both treatment groups (20% active SLIT, 38% placebo, respectively). No serious adverse events were reported.

A report on 102 Brazilian children (5-15 y.o.) with allergic rhinitis compared HDM-SLIT alone or in combination with a mixed bacterial vaccine to placebo [38]. After 18 months of treatment, symptoms were decreased in the groups receiving active HDM-SLIT. Again a high drop-out rate (31.4% overall) limited the study. Three subjects in the active treatment group withdrew due to non-serious adverse events.

In another study from China, [39] 60 children (4-18 y.o.) with mild-moderate HDM-induced asthma received either placebo or active HDM-SLIT for 48 weeks. At 12 weeks, asthma symptoms scores significantly decreased in the active treatment group. In addition, the percentage of peripheral blood Th17T cells declined after 24 weeks, and the percentage of CD 4+ CD 25+ Treg cells increased at 24 weeks in the active treatment group.

A multicenter European trail of 2 doses of HDM-SLIT in a tablet formulation was recently reported [40]. The study was conducted on 509 adults with allergic rhinitis treated for one year and 427 were re-evaluated after an immunotherapy-free year. The onset of action was apparent at 4 months in the active treatment groups. Symptom scores were significantly decreased in both active treatment groups compared to placebo. Efficacy continued in active treatment groups during the treatment-free follow-up year. No serious adverse events occurred, but local application reactions were noted.

Published studies of HDM-SLIT from the United States are limited. In the first peer-reviewed published report on HDM-SLIT from the US, Bush et al [33] randomized 31 adults (18-50 y.o.) with allergic rhinitis +/− mild intermittent asthma to high dose, low dose HDM-SLIT, or placebo. Twenty-one subjects completed the study (9 high dose, low dose 7, placebo 5) over a 12-18 month period. No significant differences were found in symptom-medication scores among the groups. High-dose HDM-SLIT decreased the bronchial threshold to HDM bronchoprovocation which was accompanied by increased serum specific Ig64 levels. No serious symptom reactions were noted. Mild-moderate local adverse effects were reported in all groups.

SCIT vs. SLIT for HDM Sensitivity

Recent systemic reviews suggest that both SCIT [41] and SLIT [42] are effective in the treatment of allergic rhinoconjunctivitis and asthma. However, due to dosing issues and duration of treatment, it is difficult to compare SCIT and SLIT for HDM-associated rhinitis and asthma. Further relatively few HDM SCIT studies have been conducted in children. Nevertheless, a statistically significant beneficial effect of active versus placebo has been observed more often with SCIT than for SLIT [26].

Alternative Routes for HDM-Allergen Immunotherapy

Oral, bronchial, and nasal administration of allergen immunotherapy have been attempted, but largely abandoned due to adverse events or lack of ease of administration. Epicutaneous administration of allergen immunotherapy has been used for a grass-pollen sensitivity but reports of HDM-epicutaneous administration are lacking [43]. Intra-lymphatic administration of pollen allergen immunotherapy has been reported, but studies with HDM allergens are also not available [43]. In the one reported study of HDM-SLIT for atopic dermatitis in children, Panjo et al [44] demonstrated effectiveness in reducing AD scores and rescue medication use. Intense itching occurred in 2 subjects leading to discontinuation of the therapy. Further studies will be needed to clarify the role of HDM-SLIT in atopic dermatitis.

Conclusions

IgE-mediated sensitivity to HDM allergens plays a major role in allergic rhinitis and allergic asthma in adults and children. Sensitization to HDM allergens may be the initial event in the so-called “Allergic March” in children. Allergen immunotherapy offers a potential to be disease-modifying by inducing beneficial immunological changes and by completely or partially abrogating the inception of asthma and new allergen sensitizations.

While systemic reviews [41,42] suggest that SCIT and SLIT are beneficial in the treatment of allergic rhinitis and asthma, the review by Calderon et al [26] raises important concerns about the role of SCIT and Slit in the management of HDM-induced allergic diseases. Among the issues are: 1) Appropriate doses of HDM allergens and duration of treatment, 2) Lack of large, multicenter adequately powered studies, 3) Poorly defined disease severity and entry criteria, 4) Timing of initiation of treatment, 5) Few pediatric studies, 6) Standardized efficacy outcome criteria, and 7) Lack of adequate evaluation of HDM allergen

exposure levels. Many of these concerns remain unanswered at present, but efforts to address them are underway. For example, current studies being conducted with HDM SLIT tablets may answer some of the questions [14,40]. Nevertheless, the authors of this review agree that while SCIT and SLIT offer benefits to patients with HDM-induced allergic rhinitis and asthma and concur with the call for more rigorous long-term double-blind, placebo-controlled randomized trials [26].

Abbreviations

CI	Confidence Interval
Der p 1	House dust mite *Dermatophagoides pteronyssinus* allergens
Der p 2	House dust mite *Dermatophagoides pteronyssinus* allergens
Der p 23	House dust mite *Dermatophagoides pteronyssinus* allergens
Der f 1	House dust mite *Dermatophagoides farinae* allergens
Der f 2	House dust mite *Dermatophagoides farinae* allergens
HDM	House Dust Mites
IgA2	Immunoglobulin, A2 and G4
IgG4	Immunoglobulin, A2 and G4
IL-10	Interleukin-10
NNT	Number Needed to Treat
RR	Relative Risk Ratio
SCIT	Subcutaneous Immunotherapy
SLIT	Sublingual Immunotherapy
SMD	Standardized Mean Difference
TGF-beta	Transforming Growth Factor Beta
TH1	T-helper cells, type 1 and 2
TH2	T-helper cells, type 1 and 2
Tregs	T-regulatory Cells

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Key Points

- Sensitization to HDM allergens plays an important role in allergic respiratory disease across all age groups.
- Early life HDM sensitization may progress to asthma in children.
- SCIT and SLIT with HDM allergens can improve allergic respiratory disease (allergic rhinitis and asthma) symptoms and may prevent the development of asthma in children.
- Significant knowledge gaps exist in terms of dosage, duration, and outcome measures for HDM immunotherapy. Large scale, multicenter studies are needed especially in children. Ongoing studies of HDM allergen SLIT trials may address some of these issues.