



House-Dust Mite Immunotherapy in Asthma: Uncertainties and Therapeutic Strategies

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Abstract

Purpose of review The prevalence of house dust mites (HDM)-sensitization is high in allergic asthma (AA), especially in tropical/subtropical countries in Asia and South America. As HDM-sensitization can contribute to the subsequent development of HDM-driven asthma, poor asthma control and exacerbations, allergen immunotherapy (AIT) might reduce the growing global burden of allergic asthma.

Recent findings AIT builds immunotolerance via upregulation of T-regulatory (reg) cells, leading to increase secretion of IL-10 and TGF- β which suppress the Th2 response to allergens. IL-10 also induces the class-switch to plasma cells that produce IgG4 that competes with Ig E's binding on mast cell. Encouragingly, 2 recent multicentre trials showed that HDM AIT could lead to improvements in clinically relevant health outcomes: reduction in asthma exacerbations and inhaled corticosteroid usage.

The uptake of AIT remains low due to difficulties with long-term adherence and lack of robust cost-effectiveness studies. There is limited standardization of techniques to compare the efficacy between different AIT administration routes and formulation. In clinical

practice, it is challenging to differentiate “asthma with HDM sensitization” from “HDM-driven asthma”. Additionally, *Blomia tropicalis* (Blo.t) play an important allergenic role especially in tropics, in addition to the *Dermatophagoides* species but is not found in many AIT formulations. It is uncertain if Blo.t sensitised patients will respond equally to these HDM AIT.

Summary We will summarise (a) global differences in HDM sensitization, (b) disease-modifying mechanisms behind HDM AIT (c) differences between the subcutaneous and sublingual route (d) therapeutic strategies in HDM-driven asthma to maximise cost-effectiveness.

Introduction

House dust mites (HDM) sensitisation is reported in 50–85% of patients with allergic asthma (AA) and allergic rhinitis (AR) and plays a major role in driving airway disease development [1, 2•]. Its presence in patients with AR is a risk factor for the future development of allergic asthma (AA) and poor asthma control [3]. Asthma is a major chronic respiratory disease that affects more than 350 million people worldwide; the associated healthcare burden is significant and projected to increase [4, 5]. It is a heterogeneous disease with many clinical phenotypes of which AA is the most common [1]. Targeting modifiable risk factors such as HDM sensitization might mitigate the growing burden of asthma. Nonetheless, though HDM allergen immunotherapy (AIT) may be effective in reducing asthma exacerbations [6••], the treatment is costly and requires long-term adherence. Hence, to maximise cost-effectiveness of HDM AIT, doctors must first select patients with HDM-driven asthma and not merely HDM sensitization. [7••,

8]. To reduce the risk of anaphylaxis and severe bronchospasm, severe allergic asthma with low lung-forced expiratory volume in first second (FEV1) are excluded.

The efficacy of HDM AIT might also be affected by ethnic and geographical heterogeneity in HDM prevalence. Despite the variation in geography and detection techniques [1, 2•], the burden of HDM sensitization might be greater in Asian countries which have reported a high prevalence of 70–95%, compared with 50–70% in Western populations [9–13]. Additionally, though *Dermatophagoides pteronyssinus* (*D.p*) and *D. farina* (*D.f*) are the most ubiquitous HDM species in Europe and North America, *Blomia tropicalis* (*Blo.t*) plays a prominent aeroallergenic role in the tropics and subtropics [14].

In this review, we will summarise the global differences in HDM sensitisation, the differences in commonly used HDM AIT formulations and the therapeutic strategies in clinical practice.

Prevalence of HDM sensitisation

HDM flourish worldwide except in the arctic regions and high-altitude areas [15]. The prevalence of each aeroallergen varies widely among different regions due to variations in geography, climate and urbanization. In the subtropical and temperate regions, *D.p* and *D.f* are the most prevalent species [16, 17•], whereas a third HDM, *Blo.t*, is noted to be highly prevalent in Asia and South America [9, 17•, 18–20]. HDM is the main aeroallergen in tropical urban countries with approximately 90% of subjects sensitised to both *Dermatophagoides* and *Blo. t*, unlike temperate countries [10, 17]. In Asia, *Blo.t* sensitisation prevalence rate ranges from 23% in Vietnam to 85% in Taiwan [17]. *Blo.t* is the predominant mite in Singaporean homes [9]. For other Asian

countries except Singapore and Vietnam, it was found that the sensitisation rate is higher to *Dermatophagoides* compared to *Blo.t* [17]. Hence in the diagnosis of HDM sensitisation in the tropics, all 3 HDM must be included in the diagnostic tests.

Large studies such as the National Health and Nutrition Examination Survey in USA and the European Community Respiratory Health Study I reported the overall prevalence of HDM to be approximately 20% [21, 22]. Compared with the general population, the proportion of asthmatics with HDM sensitization is reported to be even higher at 50–85%. [23]. With the high prevalence of HDM sensitization, it is not surprising that HDM allergy is the most common cause of allergy in AA worldwide if we use the calculation of population-attributable risk. Despite geographical differences in HDM allergy, as high as 45 to 85% of asthmatics in Europe, North and South America, Australasia and South-east Asia have HDM allergy [24].

Migration and long term habitation in a tropical urban climate with a high HDM prevalence is a major risk factor for the new development of HDM sensitization, as demonstrated in subjects who moved from China to Singapore [10•]. It is interesting to note that Asian studies consistently report a significantly higher prevalence of HDM sensitisation, ranging from 70 to 90% [9–13]. Among the Asian countries, the highest HDM sensitization rates were reported in Singapore (70 to > 90%), followed by Taiwan (85–90%) and South India (89.7%) [9, 10•, 11, 13]. Hence, geographical variation of HDM and genetic predisposition might play a critical role in HDM sensitisation.

Pathophysiology of HDM driven AA and the “allergic march”

HDM faecal pellets contain a high concentration of aeroallergens [25], which consists of body proteins and digestive enzymes within detached cells and gut wall [26, 27]. These pellets measure only 10–40 µm in diameter and are able to enter the upper and lower respiratory tract via the inhalation route. These allergenic proteins are powerful inducers of TH2 pathway, leading to activation of eosinophils and mast cells, resulting in the hallmark features of AA, e.g. airway inflammation, mucous hypersecretion and airway hyperresponsiveness (Fig. 1).

Innate immune response to allergen in the development of allergic asthma (AA)

There are 24 groups of mite allergens, classified according to their molecular profile and immunogenicity. The World Health Organization and the International Union of Immunological Societies (WHO/IUIS) currently classified a total of 102 mite allergens, 39 *D.f* allergens, 38 *D.p* allergens and 21 *Blo.t* allergens [28]. In the *Dermatophagoides* spp, there are 3 major groups of mite allergens—group 1 allergens (cysteine proteases, e.g. *D.p* 1 and *D.f* 1), Group 2 lipid-binding proteins (e.g. *D.p* 2 and *D.f* 2), and Group 23 allergens chitin-binding proteins [29]. There is significant immunoglobulin E (IgE) cross-reactivity between the 2 dominant species *D.p* and

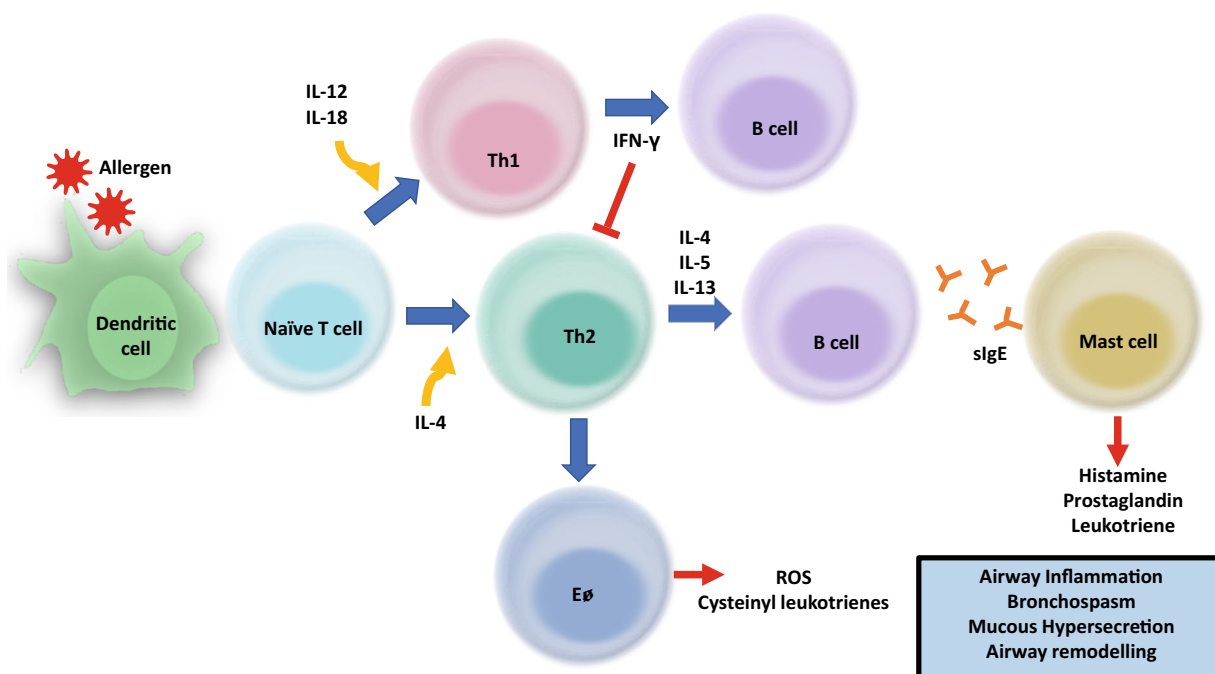


Fig. 1. A naive T cell differentiates into Th1 or Th2 cell depending on the cytokines it is exposed to; IL-12 and IL-18 for Th1 differentiation and IL-4 for Th2 differentiation. Th1 cells produce IFN- γ which in turn downregulates Th2 cells. Th2 cells produce IL-4, IL-5 and IL-13, which downregulate Th1 cells. On exposure to allergens, dendritic cells act as antigen-presenting cells (APC) and produce IL-4, which stimulates naïve T cells to differentiate into Th2 cells. These Th2 cells then go on to produce IL-4, IL-5 and IL-13, activating B cells to differentiate into specific Ig E (sIgE)-producing plasma cells, amplifying the response. sIgE attaches and activates mast cells to degranulate, releasing histamine, prostaglandins and leukotrienes. IL-5 also stimulates and activates eosinophils to produce cysteinyl leukotrienes and reactive oxygen species (ROS). These inflammatory products result in airway inflammation, mucous hypersecretion and smooth muscle bronchoconstriction, which constitute the allergic response. E, eosinophil; IL, interleukin; IFN, interferon; sIgE, specific immunoglobulin E.

D.f as there is only a 20% amino acid sequence disparity [30]. In contrast, the dominant allergen for *Blo.t* is a lipid binding protein, *Blo.t* 5, which belongs to group 5 allergens; other group 5 allergens include *D.p* 5, *D.f* 5 [31]. The other more recently discovered major *Blo.t* allergen is *Blo.t* 21 (Group 21 allergen). Unlike the high cross-reactivity between *D.p* and *D.f*, there is only low to moderate cross-reactivity (30–50%) between *Blo.t* and *Dermatophagoides* spp, and this is mainly associated with group 5 and group 21 allergens [32–36]. Hence, *Blo.t* is a major and distinct source of HDM allergens.

Besides the airway route, the skin has also recently been identified as a route of mite sensitization, especially when the skin barrier is disrupted [37]. Atopic dermatitis is a prevalent chronic inflammatory skin disease with disturbed epidermal barrier resulting in increased transepidermal water loss and resultant penetrance of aeroallergens. The importance of the epidermal barrier is supported by a study that showed that there is positive correlation between transepidermal water loss and aerosensitisation in infants with atopic dermatitis [38]. The immune mechanisms behind epicutaneous aerosensitisation are likely similar to those at the respiratory airway [37]. This route of sensitization

also forms the basis for the hypothesis of the allergic march, which is characterised by the progression of atopic dermatitis to AA and AR during the early childhood [39, 40].

Disease modifying effect of HDM immunotherapy

The main goal of AIT has been to reprogram the immune system and build immunotolerance against insignificant threats without compromising its ability to respond to real threats. It is the only treatment available that has been shown to prevent the development of asthma [41]. The multiple sequential mechanisms are allowed for the development of long-term peripheral tolerance and are summarised in Fig. 2 [42••, 43].

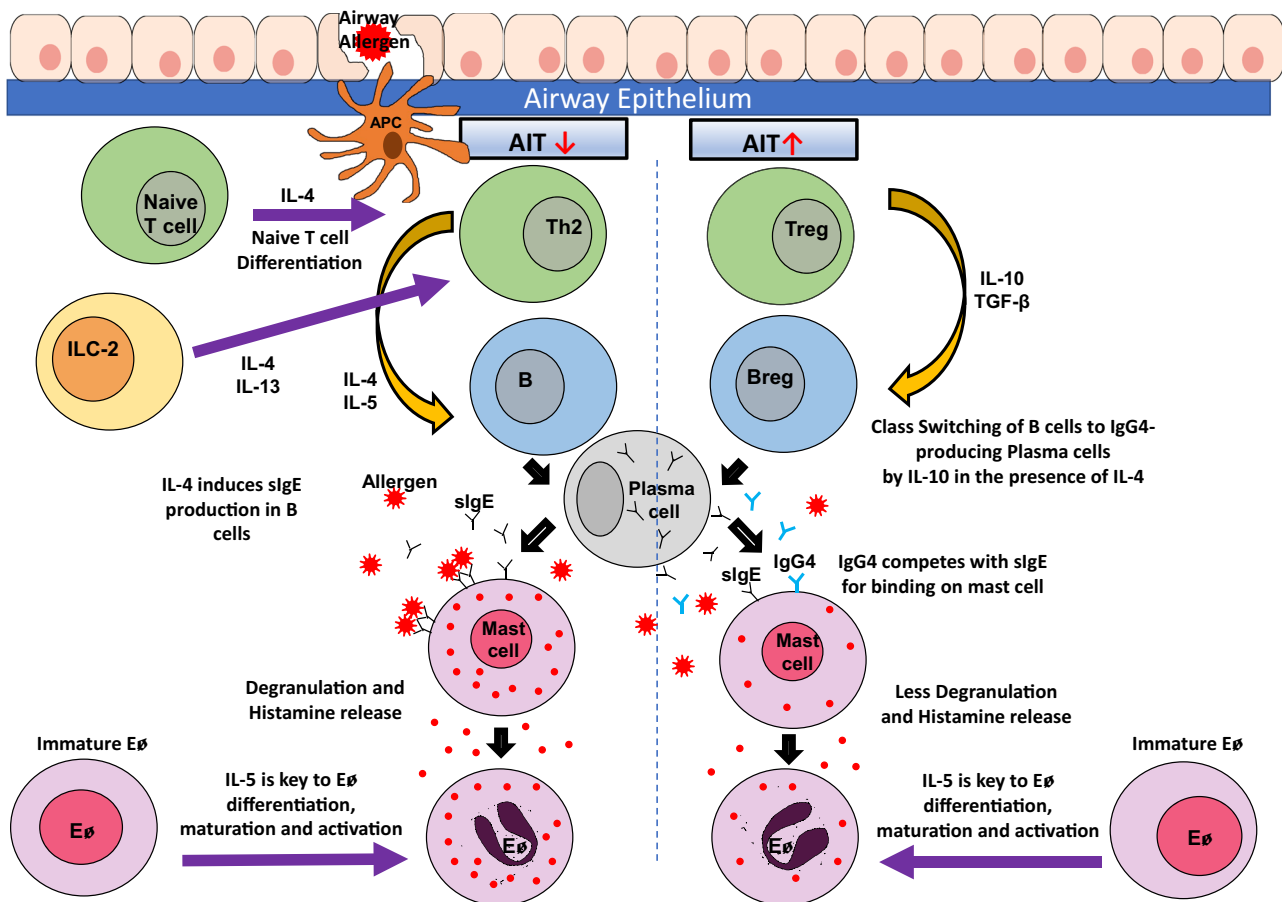


Fig. 2. AIT decreases (AIT↓) the Th2 response to allergen exposure and increases (AIT↑) Treg response which is key to the development of peripheral immune tolerance. These allergen-specific Treg cells secrete IL-10 and TGF-β, which suppress the Th2 response to allergens. IL-10 also induces the development of Breg cells that undergo class-switching to IgG4-producing plasma cells. IgG4 is a blocking type of antibody that competes with IgE with for binding on mast cells, hence reducing further downstream response. ILC-2, type 2 innate lymphoid cell; Treg, T regulatory cell; Breg, B regulatory cell; B, B cell; E, eosinophil; IL, interleukin; TGF, tumour growth factor; sIgE, specific immunoglobulin E; Ig, immunoglobulin.

Treatment strategies for HDM-driven asthma

Assessment of asthma: severity, current control and future risk

Determining asthma control, risk and severity is important before initiating HDM AIT. The Global Initiative of Asthma (GINA), an evidence-based management strategy report recommends that clinicians assess asthma control based on 2 domains: current symptom control and future risks of adverse outcomes, e.g. severe exacerbations, airway remodelling and treatment side effects. Asthma control is assessed using scoring tools such as the GINA symptom control tool, Asthma Control Questionnaire or Asthma Control Test [8, 44] and can aid in titration of asthma treatment. Achieving good asthma control with the appropriate use of inhaled corticosteroids (ICS) is key as it can reduce the future risk of exacerbations and even asthma-related mortality [45, 46]. However, as the reporting of asthma symptom control can be subjective [47], the asthma assessment should include risk assessment based on more objective markers (e.g. recurrent severe exacerbations, history of near-fatal asthma attacks, smoking, poor symptom perception, poor lung function). Finally, asthma severity is assessed retrospectively is based on the level of treatment required to control asthma symptoms [8, 48]. It is crucial to address non-adherence, poor inhaler technique, and mimickers of asthma as contributors to poor asthma control, prior to initiation of HDM AIT.

HDM AIT is recommended for mild-moderate AA with AR and forced expiratory volume in the first second (FEV1) > 70% that is suboptimally controlled despite low-moderate dose of ICS-containing therapy [7••, 8]. Severe allergic asthma on the other hand might benefit from omalizumab, an anti-IgE monoclonal antibody [49]

Targeting HDM-driven asthma with suboptimal control

In this group of at-risk mild-moderate AA with suboptimal control despite usual asthma therapy, who might be suitable for HDM AIT, it is important to distinguish between HDM sensitization in asthma versus HDM-driven asthma. This will impact cost-effectiveness in individual patients [7••]. Direct provocation tests—bronchial or nasal provocation tests (NPT) using HDM extracts—is the gold standard test for HDM-driven airway disease but are limited to use in research settings [50, 51]. A positive NPT can diagnosed HDM-driven AR but not necessarily asthma. Bronchial provocation test can also be affected by technical issues and safety concerns, i.e. provocation of asthma exacerbation. Hence, both tests are not employed in clinical settings. Currently, the diagnosis of HDM-driven asthma is based on (a) clinical history demonstrating HDM exposure as the main driver of asthma symptoms and control and (b) objective evidence of HDM sensitisation by SPT or serum HDM-sIgE and (c) supporting evidence of other atopic comorbidities, e.g. AR, allergic conjunctivitis and atopic dermatitis [7••].

Confirming HDM sensitisation

In clinical practice, HDM sensitization is diagnosed using non-purified allergen extracts via 2 methods: (i) skin prick test (SPT) and (ii) serum HDM-specific IgE (HDM-sIgE) [52]. Guidelines recommend either method to confirm HDM

sensitisation [7••, 8]; the choice is largely dependent on clinical practicalities. SPT is comparatively cheap with a rapid turnaround time and can yield results for multiple aeroallergens at the same setting. However, it requires antihistamines to be withheld for at least 3 days, the presence of normal skin for the accurate reading of wheal size. There is a small risk of anaphylaxis and asthma exacerbation especially in uncontrolled asthma cases. The main drawbacks in SPT are the non-standardised methodology and the different concentrations and types of HDM protein extracts employed by various centres. Serum HDM-sIgE measurements can be done by using either the radioallergosorbent test (RAST) or the newer fluorescence enzyme immunoassay (ImmunoCAP™, by Thermo Fisher Scientific, Uppsala, Sweden). The disadvantages of serum sIgE include side effects associated with venepuncture and a slower turnaround time. Nonetheless both tests are dependent on the quality of the extracts used.

Additionally, the 2 methods cannot differentiate HDM monosensitisation from polysensitisation [53] due to cross-reactivity. Different allergens can share common protein epitopes, resulting in the same serum-specific IgE antibody binding to different allergenic proteins with similar structures. For instance, group 1 and group 2 proteins induce cross-reactive IgE antibodies; whereas, group 1 and group 23 induce specific IgE antibodies. As commercially available HDM extracts contain variable amounts of the main allergens (*D.p* 1 and *D.p* 2) testing for 1 HDM species (*D.p* or *D.f*) is usually sufficient in most patients. Consequently, patients, who are only monosensitised to *D.p* 23, will go undetected as group 23 proteins do not cross-react with those in group 1 and 2 [29]. Of note, laboratories in the tropics and subtropics will need to include extracts to test for *Blo.t* sensitization (*Blo.t* 5) since it exhibits low to moderate cross-reactivity with *D.p* or *D.f* [32–36].

A more specific method, component-resolved diagnosis (CRD), was developed using highly purified native or recombinant allergens to detect IgE sensitivity to individual allergen molecules–specific DNA sequences [54, 55]. Currently, CRD (ImmunoCAP™ ISAC, Phadia/Thermo Fisher Scientific) makes use of modern biochip technology using only a very small quantity of serum (30 µl) to simultaneously determine serum specific IgE towards more than 112 allergen components. In HDM sensitization, Der p 10 (tropomyosin) is highly cross-reactive allergen unlike the major *D.p* allergens (*D.p* 1 and *D.p* 2). CRD helps to distinguish the cross-reactions between antibodies and *D.p* 10 of HDM and rPen a 1 from shrimps, as well as with *Ani s* 2 and *Ani s* 3 from roundworms (*Ascaris*) [56, 57]. Though CRD can distinguish between polysensitisation and false positive results from cross-reactivity, it is mainly reserved for use in research.

Treatment considerations

Treatment strategies for HDM-driven asthma include HDM avoidance [58], nasal and inhaler corticosteroids for AR and AA respectively, and HDM AIT. However, the evidence for HDM reduction and avoidance is weak and has not shown consistent improvement in health outcomes in AA and AR [59–63]. Only AIT has a disease-modifying effect. However, the uptake of AIT is poor at only 10% of children and adults with AR and AA globally [64•]. The contributing factors include [1] physician factors (difficulties with diagnosis and knowledge); [2] lack of standardisation on patient selection, dosing and

schedule; [3] patient factors with adherence and cost; [4] uncertainties with long term efficacy; [5] patient factors with adherence and cost; [6] insufficient data on cost-effectiveness [64, 65].

Prior to the initiation of HDM AIT, physicians have to carefully assess the risk versus benefit, especially in special populations, e.g. elderly and evaluate for demographic and economic factors that might promote adherence [66]. Physicians will have to clearly explain the expected treatment duration (up to 3–5 years) and costs, so that patients can make an informed decision. After treatment initiation, it is important to address early side effects, assess treatment response and monitor long-term adherence. Stepping up AIT dosing gradually, and/or pretreatment with anti-histamines can be used to counteract bothersome side effects in the first 1 month [67].

Differences in HDM AIT therapies/approaches

HDM AIT is divided into 2 routes of administration: subcutaneous (SCIT) and sublingual (SLIT). SLIT comes with 2 alternatives—drops and tablets. Other approaches under investigation include epicutaneous and intralymphatic administration [68, 69]. The recommended treatment duration of either SCIT or SLIT is 3 to 5 years [64•]. Longer treatment duration is associated with persistence of clinical benefit of up to 8 years [70•]; treatment duration of less than 3 years is associated with a higher relapse rate [71•]. Though side effects are common, they are localised and mild (e.g. oral pruritus, throat or eye itchiness) [72•]; severe side effects such as anaphylaxis are rare [73].

SCIT was the first form of AIT used and consists of injecting unmodified or modified allergen extracts, e.g. allergoids or addition of adjuvants. SCIT requires 2 treatment phases: an up-dosing phase, followed by a maintenance phase injection at 4- or 8-week intervals. The up-dosing phase is a titration phase, where the increasing doses are titrated according to patient's sensitivity and tolerance of adverse events (systemic reactions and local injection site reactions). This phase can be reduced by using a cluster or rush schedules, which can achieve earlier clinical and immunologic improvements by the sixth week [74, 75]. Rush schedules are typically safe and well tolerated but may be associated with an increase in adverse reactions despite pre-medications (prednisolone, histamine 1- and 2-receptor blockers) [76]. The maximum tolerated SCIT dose, or maximum dose recommended, whichever is reached first, is then used during the maintenance phase. Conventional SCIT requires typically 30 to 80 injections over 3 to 5 years and are administered by trained medical staff, under monitoring. Nonetheless, SCIT is individualised and an alternative for patients who cannot adhere to daily SLIT. In terms of clinical efficacy, SCIT is associated with a reduction in symptom scores and medication requirements, and improved allergen-specific and non-specific airway hyperresponsiveness [77•].

SLIT has overtaken SCIT as the dominant approach in the last 2 decades. The HDM allergen extract is absorbed via the sublingual route, either in liquid or tablet form. SLIT does not have an up-dosing titration phase and involves a fixed standard dose as per manufacturer throughout the duration of treatment. SLIT can be self-administered safely, and the side effects are mild (e.g. oral pruritus) [72•]. The main drawbacks are that the SLIT requires daily dosing and hence long-term adherence is required to maximise treatment response.

Though, SLIT has been shown to reduce asthma symptoms and medication scores in a Cochrane review [78], the majority of the studies did not use validated asthma symptom scores, targeted mainly mild asthmatics and only 2 papers reported impact on clinically important health outcomes [6••, 79••]. Virchow et al. showed that in 834 adults with uncontrolled moderate-persistent asthma, SLIT could improve time to exacerbation during the ICS-reduction phase, though there was no difference in asthma related quality of life scores [6]. In 604 adolescents and adults with mild to moderate-persistent asthma, Mosbech et al. reported a modest reduction of ICS of 81 mcg/day with high dose SLIT [79••]. It is important to note that the efficacy of HDM AIT varies greatly in different clinical trials for different products, and this is likely due to different manufacturers, formulations and variations in allergen content. Hence, the recommendations for AIT in AA should be product-based [80].

Most of the AA patients are polysensitised. Large population surveys in USA and Europe have shown that 50–80% of AA are polysensitised [81, 82]. It has been a long-standing debate as to whether polysensitised patients should receive multiple-allergen immunotherapy (AIT) simultaneously according to their sensitisation profile (or a single allergen according to the most clinically relevant allergy [55]. The single-AIT approach is supported by allergists in Europe, who believe that a polysensitised patient may not be polyallergenic and hence, only the most troublesome allergy needs to target. This is in contrast with the “North American” multiple-AIT approach, which places more emphasis on time-saving since the entire duration of AIT takes years [55]. Consequently, most formulations of AIT in Europe are single-allergen extracts, whereas formulations in the USA contain an average of 8 different components. Other major differences between Europe and the USA include allergen extract regulation, formulation, standardization and types of allergen extracts [83]. Currently, there is insufficient evidence to support multiple—AIT over single—AIT and clearer well-designed clinical trials are required in this [55].

There is currently no data on whether patients who are sensitised to both *Dermatophagoides* spp. and *Blo.t* will do as well with HDM AIT formulations that contain only *Dermatophagoides* allergens. Though the cross reactivity between the major proteins (D.p 1 and D.p 2 and Blo.t 5) is low to moderate, this might be sufficient to promote reduction of T2 response and an increase in Treg cells that can promote immunotolerance. More studies are required to verify this.

Future research needs

There is a need for future research to look into the safety and efficacy of HDM AIT in many areas. Firstly, we need to develop better diagnostic tests and algorithms to differentiate HDM-driven AA from HDM-sensitised individuals with asthma objectively and standardise of patient selection for AIT. Secondly, the impact of different AIT schedules and formulations in polysensitised individuals, and those individuals in the tropics and subtropics who are sensitised with *Blo.t* need to be evaluated. Thirdly, there is a need to focus on the safety and optimal dosing in patients with uncontrolled moderate-persistent to severe HDM-driven asthma, and if there is any long-term disease modifying effects that can reduce their high healthcare burden. Last but not the least, there is a need to standardise the measures of allergen extract potency in studies to assess

AIT effectiveness, as per the recommendations of World Allergy Organisation (WAO) Task Force and the EAACI Task Force [84, 85]. This will help guide and increase physician's confidence in choosing the best-suited and cost-effective AIT for their patients. Nonetheless, the potential benefits of HDM AIT should be weighed against the risk of adverse effects and the cost to the patient and health system.

Compliance with Ethics Guidelines

Conflict of Interest

Mei Fong Liew, Adrian Chan and Hui Fang Lim declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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