

EXPERT OPINION

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Allergen immunotherapy for house dust mite: clinical efficacy and immunological mechanisms in allergic rhinitis and asthma

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Introduction: There is an increasing prevalence of atopic diseases such as allergic rhinitis and asthma with house dust mite (HDM) being the common allergen that is highly associated with allergic rhinitis and asthma. Allergen avoidance and pharmacotherapy are part of treatment but it has proved difficult to change the course of HDM-related allergic diseases. Allergen immunotherapy (AIT) has been in use for the past century and has been shown to be effective in the treatment of allergic respiratory disease.

Areas covered: This review exclusively focuses on HDM-AIT and discusses the differences in clinical efficacy and safety, long-term effect after discontinuation and immunological changes observed in both HDM-subcutaneous immunotherapy (SCIT) and HDM-sublingual immunotherapy (SLIT) in the treatment of allergic rhinitis and asthma in both pediatric and adult populations.

Expert opinion: The majority of studies involved small numbers of patients, variable doses of major allergens and are of variable quality. There is good evidence for HDM-SCIT efficacy and its long-term effect in adults and children, whereas at the present time, evidence for HDM-SLIT is unconvincing, particularly in children. In carefully selected patients, HDM-SCIT is effective and safe. More definitive trials are needed before HDM-SLIT can be recommended in routine practice for rhinitis and/or asthma.

Keywords: allergy, asthma, dust mite, immunotherapy, rhinitis, subcutaneous, sublingual

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1. Introduction

The prevalence of atopic diseases such as allergic rhinitis (AR) and asthma has increased in the past three decades among children and adults [1]. House dust mites (HDM) are common allergens worldwide and their major allergens (*Dermatophagoides pteronyssinus* [Der p] and *Dermatophagoides farinae* [Der f]) coexist in most geographical regions with a high proportion (up to 85%) of asthmatics being typically HDM allergic; hence, sensitization is attributed as a risk factor for developing asthma [2]. Recently, a birth cohort study showed sensitization to HDM at age 2 years was associated with current wheeze at age 12 years in both monosensitized and polysensitized HDM-sensitized children [3].

A cross-sectional study from the European Community Respiratory Health Survey has shown that only AR with sensitivity to HDM was associated with an increased risk of development of asthma independently of other allergens [4]. Mite allergen avoidance has proven to be difficult, hence different environmental methods, such as chemical and physical methods, for reducing exposure have been explored [2]. According to recent Cochrane meta-analyses on mite avoidance, the use of environmental control measures has been found to be of little benefit in reducing rhinitis symptoms with no effect on asthma symptoms [5,6].

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Article highlights.

- A high proportion of allergic asthma patients are sensitized to HDMs, which are the most common allergens worldwide.
- AIT is currently the only mode of treatment that can change the course of rhinitis and asthma with a long-term effect.
- Based on current data, HMD-SCIT has shown good clinical efficacy; however, we must consider the large clinical and methodological heterogeneity in these studies.
- There is insufficient evidence for recommending the routine use of HDM-SLIT, particularly in children.
- The available head-to-head trials of HDM-SCIT and HDM-SLIT are inadequate to draw any conclusions.
- HDM-SLIT seems to have a better safety profile compared to HDM-SCIT, although this must be balanced against overall insufficient evidence for efficacy of HDM-SLIT.
- A universal grading system to report and to classify both local and systemic adverse reactions due to AIT is needed.
- Both modes of treatment appear to have similar immunological effects, with HDM-SCIT providing an earlier onset of immunological changes.

This box summarizes key points contained in the article.

Pharmacotherapy with topical corticosteroids is effective in the control symptoms of AR and asthma with improvement of lung function in asthmatics but it does not modify the natural course of the disease. Allergen immunotherapy (AIT), involving the administration of gradually increasing concentrations of allergen extract, is the only treatment modality that has the potential to modify the course of allergic disease. AIT has been shown to reduce symptoms and medication usage, prevent asthma development and increase quality of life, with a sustained long-term effect [7-9].

Currently, the only validated administration routes for AIT are subcutaneous (SCIT) and sublingual (SLIT). Subcutaneous immunotherapy (SCIT) has been in use for 100 years and has been shown to be effective in patients with allergic asthma and rhinitis [10,11]. In the past 20 years, SLIT has emerged as an alternative noninjection route and widely used, especially in European countries [12]. Recent systematic reviews and meta-analyses of SLIT have reported variable clinical effects for HDM allergy in both rhinitis and asthma [13-15].

Although AIT has globally been accepted as effective in treating seasonal AR and asthma in both pediatric and adult populations, subanalysis of single allergen extract treatment has not been well documented. This review will focus solely on HDM-AIT, comparing the clinical efficacy and safety, long-term effect and immunological changes observed in SCIT and SLIT. The treatment of both AR and asthma in both pediatric and adult populations has been reviewed.

2. Clinical efficacy

2.1 HDM-SLIT randomized clinical trials and meta-analysis

There are two recently performed meta-analyses that analyzed the efficacy of HDM-SLIT in both children and adults [13,14]. The recent Cochrane analysis on the effect of SLIT in AR performed an individual subgroup analysis for HDM-SLIT [13]. The total standard mean difference (SMD) of symptom scores of nine studies that investigated HDM-induced rhinitis was found to statistically favor active treatment (SDM: -0.97; 95% CI: -1.80 – -0.13; $p = 0.02$). As for medication usage, there was no significant effect of HDM-SLIT in reducing medication, thus concluding that due to a significant heterogeneity between these studies attributed mainly to the treatment duration, scoring system and doses of major allergens, results should be interpreted with considerable caution. A further meta-analysis predominantly evaluated the effect of HDM-SLIT in both children and adults [14]. Overall, nine trials were evaluated and HDM-SLIT was found to be effective in reducing rhinitis and asthma symptoms and medication usage. However, there was very marked heterogeneity among studies, and on subanalysis in either pediatric or adult populations, this effect did not reach significance when compared to placebo for rhinitis symptoms ($p = 0.2$, $p = 0.1$, respectively). Likewise, no reduction in rhinitis medication score was observed for either subgroup. The treatment effect was particularly lacking for rhinitis symptoms within the pediatric subgroup. Asthma symptoms and medication use were shown to be significantly reduced in the pediatric population, but not in the studies in adults – again marked heterogeneity was observed in these studies which emphasized the need for adequately powered large definitive trials for SLIT in mite-allergic subjects, both in adults and children.

We selected and reviewed trials that have been included in previous meta-analyses [13,14] and new trials published from 2008 to December 2012 (Table 1). Double-blind, placebo-controlled randomized trials (DBPCTs) that were conducted to evaluate the clinical efficacy of HDM-SLIT in children and adults with AR and/or asthma [16-35] as shown in Table 1 were evaluated. Twelve trials involved children only (under 18 years) [16,21-23,25,27-29,31-33], while five studies recruited adults only (18 – 75 years) [18,26,30,32,35] and three studies evaluated both children and adults [19,20,24]. Three DBPCTs [21,27,28] evaluated SLIT efficacy on asthma only, while the rest evaluated efficacy on both rhinitis and asthma outcomes. Interestingly, there were no trials that evaluated the effect of HDM-SLIT on isolated rhinitis or its protective effect on the development of asthma. The reported cumulative dose of the major allergen extract used varied extensively from all trials that have mentioned in standard units, which ranged from 0.05 to 17.1 mg and from 3 to 14.7 mg for Der p 1 and Der f 1, respectively. Three trials used a sublingual tablet containing extract [18,26,29], while the rest have

Table 1. HDM-SLIT in children and adults.

Authors	Year	Age	Active/ placebo	Allergen	Duration years	Disease	Main positive results	Other findings
Tari <i>et al.</i> [16].	1990	Children	30/28	Der p	1.5	RA	Reduction of symptoms and medication scores	Decreased BHR
Hirsch <i>et al.</i> [17].	1997	Children	13/14	Der p	1	RA	Reduction of symptoms for asthma only and no change in rhinitis	
Passalacqua <i>et al.</i> [18].	1998	Adults	10/10	Der p, Der f	2	RA	Reduction of symptoms scores	Improved QoL, PFT and BHR in active group
Bousquet <i>et al.</i> [19].	1999	Children and Adults	32/33	Der p, Der f	2	RA	Reduction of rhinitis and asthma symptoms and reduction of medication usage in both groups	No changes in skin prick reactivity
Guez <i>et al.</i> [20].	2000	Children and Adults	36/36	Der p, Der f	2	RA	No difference in symptoms or medication usage	Reduction in skin reactivity and improved lung function
Pajno <i>et al.</i> [21].	2000	Children and Adults	12/12	Der p	2	A	Reduction in symptoms and medication usage	Improved lung function
Bahceciler <i>et al.</i> [22].	2001	Children	8/7	Der p, Der f	0.5	RA	Reduction in asthma and rhinitis symptoms and rescue medication usage. No effect on steroid usage	Reduction in skin reactivity and improved lung function
Ippoliti <i>et al.</i> [23].	2003	Children	47/39	Der p, Der f	0.5	RA	Reduction in rhinitis and asthma symptoms and medication usage	Improved lung function
Tonnel <i>et al.</i> [24].	2004	Children and Adults	15/17	Der p, Der f	2	RA	Reduction in rhinitis and asthma symptoms and no change in medication usage	Reduction in skin reactivity
Marcucci <i>et al.</i> [25].	2005	Children	13/11	Der p, Der f	1	RA	No difference in rhinitis or asthma symptoms and medication usage	Increased sNPT threshold dose
Passalacqua <i>et al.</i> [26].	2006	Adults	34/34	Der p	2	RA	Reduction of total symptoms and medication usage after 1 year but not after 2 years of treatment	No changes in threshold of specific nasal challenge
Niu <i>et al.</i> [27].	2006	Children	56/54	Der p, Der f	0.5	A	Reduction in asthma symptoms and no change in medication usage	No change on QoL
Lue <i>et al.</i> [28].	2006	Children	10/10	Der p, Der f	0.5	A	Reduction in asthma symptoms and medication usage, compared to baseline	Improved lung function
Pham-Ti <i>et al.</i> [29].	2007	Children	54/55	Der p, Der f	1.5	RA	No difference in symptoms or medication usage	No changes in skin reactivity or lung function
O'Hehir <i>et al.</i> [30].	2009	Adults	13/14	Der p, Der f	1	RA	Reduction in rhinitis and asthma symptoms and reduction in medication usage	Improved QoL and reduced skin reactivity
Yonekura <i>et al.</i> [31].	2010	Children	20/11	Der f	1	RA	Reduction in rhinitis symptoms with no changes in medication use	QoL improved in both treatment and no changes in lung function
Bush <i>et al.</i> [32].	2011	Adults	10/11	Der f	1.5	RA	No difference in symptoms or medication use	Increased BHR threshold in high-dose SLIT only
de Bot <i>et al.</i> [33].	2012	Children	110/116	Der p, Der f	2	RA	No difference in symptoms and medication use	No improvement in QoL
Yukselen <i>et al.</i> [34].	2012	Children	10/10	Der p, Der f	1	RA	No difference in rhinitis/asthma symptoms and medication usage	No changes in lung function test, skin reactivity or sBHR
Bozek <i>et al.</i> [35].	2013	Adults	51/57	Der p, Der f	3	RA	Reduction in rhinitis symptoms and medication use	Improved nasal patency post sNPT

Der p: *Dermatophagoides pteronyssinus*; Der f: *Dermatophagoides farinae*; HDM: House dust mite; PFT: Pulmonary function test; QoL: Quality of life; RA: Rhinitis-asthma; SLIT: Sublingual immunotherapy; sNPT: Specific nasal provocation test; sBHR: Specific bronchial hyperreactiveness.

Table 2. HDM-SCIT in children and adults.

Authors	Year	Age	Active/ Placebo	Allergen	Duration years	Disease	Main positive results	Other findings
Ameal <i>et al.</i> [36]	2005	Adults	32/31	Der p	1	RA	Reduction of symptoms and medication usage	Increased QoL and decreased sBHR
Garcia-Robaina <i>et al.</i> [37]	2006	Adults	32/32	Der p, Der f	1	RA	Reduction of asthma, rhinoconjunctivitis symptoms and medication usage	Increased QoL and decreased sBHR
Blumberga <i>et al.</i> [38,40]	2006	Adults	26/28	Der p	3	A	No change of symptoms/rescue medication and reduction of ICSs usage	Decreased sBHR
Wang <i>et al.</i> [39]	2006	Children and Adults	64/65	Der p	1	RA	Reduction of asthma symptoms and medication usage	No change in lung function
Yukselen <i>et al.</i> [34]	2012	Children	10/10	Der p, Der f	1	RA	Reduction of asthma and rhinitis symptoms and medication usage	Decreased in specific nasal and bronchial hyperreactivity

Der P: *Dermatophagoides pteronyssinus*; Der F: *Dermatophagoides farina*; QoL: Quality of life; RA: Rhinitis-asthma; SCIT: Subcutaneous immunotherapy; sBHR: Specific bronchial hyperreactiveness.

used the aqueous extracts in the form of drops as the mode of treatment. Duration of the trials ranged from 6 to 36 months with the age of participants ranging from 5 to 17 years for pediatric and 18 to 75 years for adult trials.

The main outcome measures of the studies were symptoms (total rhinitis and asthma symptoms scores), medication usage and combined symptoms-medication scores. Other parameters evaluated in most trials were visual analog scale, symptom-free days, airway patency with either specific or nonspecific provocations. Overall, the primary outcome measures favored SLIT in 14 studies [16-19,21-24,26-28,30,31,35], by reducing rhinitis in 10 of 17 trials that reported rhinitis symptoms (children = 5 and adults = 5) and asthma symptoms in 12 of 20 trials that reported asthma symptoms (children = 9 and adult = 3; Table 1). Reduction in medication usage attributed to HDM-SLIT was reported in only 7 of 18 studies that evaluated concomitant medication-sparing effect of SLIT (children = 4 and adults = 3) [21-23,26,28,30,35].

Most of the studies did not include power calculations, and only four trials enrolled > 100 patients [27,29,33,35]. A multicentered, DBPC study evaluated the effect of HDM-SLIT for 6 months on children who were mono-sensitized to HDM with mild-to-moderate persistent asthma according to GINA guidelines [27]. Main outcomes were a significant reduction of asthma symptoms and improved lung function measured by spirometry with no effect on medication use. These results were confounded by groups being mismatched for baseline asthma symptom scores and the short duration of treatment.

Recently, two large-scale DBPCTs from Europe evaluated the efficacy of SLIT in AR and asthma in HDM-sensitized children [29,33]. Both studies reported a lack of efficacy in both rhinitis and asthma. Adequate subjects participated in both studies, one involving a high-dose tablet (cumulative dose of Der p 1: 6.9 mg, Der f 1: 14.7 mg) [29], the second a low-dose aqueous

(cumulative dose of Der p 1: 0.44 mg) [33] formulation of HDM-SLIT. Despite 18 and 24 months total duration of treatment, respectively, both studies failed to show efficacy in reducing symptoms or medication usage. A recent large-scale DBPC study (n = 111) with low dropout evaluated the efficacy of HDM-SLIT in mite-allergic elderly patients (mean age over 65 years) with AR [35]. In this study, a reduction in mean weekly nasal symptoms and medication usage with improvement in nasal flow after specific nasal allergen challenge was observed after 3 years of treatment.

2.2 HDM-SCIT clinical trials and meta-analysis for AR and asthma

The efficacy of HDM-SCIT has been evaluated by numerous DBPCTs for the past 5 decades. A recently published Cochrane review meta-analysis that was specifically designed to evaluate the effect of SCIT on asthma has reviewed 42 HDM-SCIT randomized control trials published between 1968 and 2004 [10]. Overall, HDM-SCIT was found to have a moderate effect in reducing asthma symptoms (SMD: -0.48; 95% CI: -0.96 – 0.0; p = 0.048), significantly reducing medication usage (SMD: -0.61; 95% CI: -1.04 – -0.18; p = 0.0058) and specific bronchial hyperresponsiveness (BHR) (SMD: -0.98; 95% CI: -1.39 to -0.58; p < 0.00001). From these results, there is some evidence that HDM-SCIT may have clinical efficacy compared to placebo in reducing asthma symptoms and specific BHR, which should be interpreted with caution due to high heterogeneity between the studies included. This meta-analysis has not reported the effect of HDM-SCIT on rhinitis and currently there are no published systemic reviews or meta-analyses that analyze the effect of SCIT on perennial rhinitis especially HDM-induced rhinitis.

Following the most recent meta-analysis of Abramson *et al.* that reported SCIT studies up until 2006 [10], several

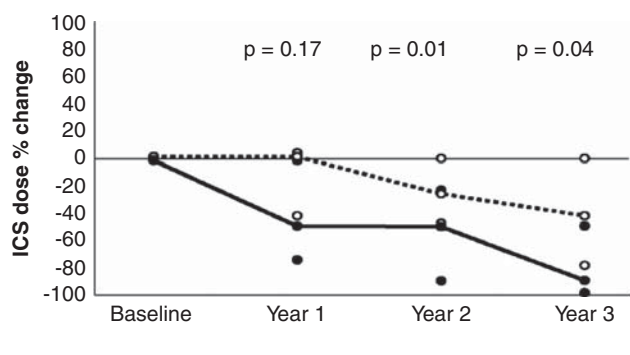


Figure 1. Illustration of median percentage reduction of inhaled steroids in patients with moderate persistent asthma, active --●--, --○-- placebo.

Adapted from [38].

DBPCTs of SCIT with mite extract involving both children and adults with HDM-induced asthma and rhinitis have been reported (Table 2) [34,36-40]. There were three studies in which power calculations confirmed adequate sample sizes [36-38]. Two studies used a depigmented-polymerized HDM extract form of SCIT [36,37]. Only one study recruited > 100 participants including both children and adults [39]. Two of the studies included polysensitized asthmatics [38,39]. Overall, these recent published studies reported significant clinical efficacy of HDM-SCIT in reducing asthma and rhinitis symptoms with reduction in medication scores, reduction in specific BHR and improvement in quality of life (Table 2). A large-scale, multicenter study conducted in both children and adult with mild-persistence rhinitis and asthma, reported a significant reduction in total symptoms and medication use which was evident after just 6 months of SCIT [39]. Another study was designed to evaluate the steroid-sparing effect in adults with moderate-to-severe asthma by giving HDM-SCIT for at least 3 years [38,40]. This randomized, double-blind, placebo study reported a significant reduction in the use of inhaled corticosteroid (ICS) after 1 year of SCIT in moderate asthmatics (Figure 1). Further, significant reduction in specific BHR, late asthmatic reaction post-specific bronchial allergen challenge and intradermal late-phase skin reaction were observed. No changes in asthma symptoms, rescue medications or lung function compared to placebo were observed. Some patients recruited in this study were multisensitized with other pollen and perennial allergens and had severe asthma, which might have reduced the observed effect of SCIT.

3. Safety

3.1 Sublingual immunotherapy

In a recently published systemic review, SLIT was found to be well tolerated [41]. Most of the HDM-SLIT trials reported mild local adverse events such as labial edema, throat irritation and buccal pruritus, which were also observed in a

proportion of patients who received placebo SLIT. In the evaluated controlled trials, there were no severe systemic events, episodes of anaphylaxis or reactions in which adrenaline administration was reported [13]. There is only one case report of systemic severe reactions due to HDM-SLIT in an adolescent patient during the third year of SLIT with a standardized HDM extract solution. After a 3-week treatment gap during the maintenance phase, patient took a dose of 6 times higher than recommended dose. This reaction resulted in loss of consciousness and admission to the intensive care unit [42]. In general, from recent reviews and meta-analyses, there were no definitive predictors for adverse events due to SLIT that could be identified [12,13,43].

3.2 Subcutaneous immunotherapy

The safety profile of SCIT was evaluated in most reported clinical trials. In general, it has been shown that SCIT is safe in patients with AR and mild to-moderate asthma provided that it is administered by experienced and trained physicians in settings with all facilities to treat anaphylaxis [44]. In a recent review of studies published within the past 15 years, systemic reactions to SCIT were found to occur in ~ 0.2% of allergen injection [45]. When comparing the severity of reactions between allergens, a prospective multicentered study found that side effects of HDM-SCIT were in general mild-to-moderate grade 2 – 3 reactions and less than those observed after grass SCIT [46]. A recent Cochrane meta-analysis that evaluated SCIT in allergic bronchial asthma found that the incidence of systemic reactions per patient ranged from 5 to 7% and with 1:1,000,000 injections causing a near-fatal reaction [10]. Although different methods of classification/grading were used to report these adverse reactions, the study shows that SCIT may cause significant systemic effects and that these interventions need to be carefully supervised by trained individuals experienced in recognizing early signs of anaphylaxis and in the immediate presence of a physician. Uncontrolled asthma is an unacceptable major risk factor associated with severe systemic reactions during immunotherapy [45].

4. Head-to-head comparisons of HDM-SCIT versus HDM-SLIT

Currently, there are five randomized controlled trials that have prospectively compared the clinical effectiveness and/or immunological mechanisms of HDM-SCIT versus HDM-SLIT in children and adults having HDM-induced rhinitis and asthma (Table 3) [34,47-50].

In general, these studies were small and inadequately powered to show equivalence. Four of the five studies were either open and/or not placebo-controlled. Three studies included children [34,47,48] and two evaluated adults with both rhinitis and asthma [49,50]. Only one trial including children was designed as a double-blind, double-dummy, placebo-controlled randomized trial [34]. Symptom scores of rhinitis and asthma, total and combined symptoms and medication scores were

Table 3. Effectiveness of HDM-SCIT compared to HDM-SLIT in children and adults with rhinitis and asthma.

Authors	Years	Age	Design	Duration		Disease	Main positive results	Other findings	HDM-SCIT vs HDM-SLIT
				Groups (n)	years				
Eifan <i>et al.</i> [47]	2010	Children	Open-RCT No placebo	SCIT = 16 SLIT = 16 Control = 16	1	RA	Both SCIT and SLIT reduced rhinitis and asthma symptoms compared to controls and SLIT reduced medication usage but not SCIT	2 SCIT patients had grade 3 – 4 adverse reactions and both SCIT and SLIT decreased specific skin and nasal reactivity	SCIT = SLIT
Keles <i>et al.</i> [48]	2011	Children	Open-RCT No placebo	SCIT = 11 SLIT = 13 Control = 12	1	RA	Both SCIT and SLIT reduced ICS dosage and number of asthma attacks	2 SCIT patients had adverse reactions and both SCIT and SLIT decreased specific skin and nasal reactivity	SCIT > SLIT
Yukselen <i>et al.</i> [34]	2012	Children	RCT double-dummy/ blind, placebo	SCIT = 10 SLIT = 10 Placebo = 12	1	RA	Reduction of rhinitis and asthma symptoms and medication usage only in SCIT compared to SLIT and placebo	No severe systemic adverse effects reported in all interventions and both SCIT and SLIT decreased specific skin and nasal reactivity	SCIT > SLIT
Piazza and Bizzaro [49]	1993	Adults	Open-RCT No placebo	SCIT = 17 SLIT = 14 Control = 14	1	R	Significant reduction in rhinitis symptoms was observed in SCIT group compared to SLIT		SCIT > SLIT
Mungan <i>et al.</i> [50]	1999	Adults	RCT, single-blind, placebo	SCIT = 10 SLIT = 15 Placebo = 11	1	RA	Reduction of rhinitis symptoms in both SCIT and SLIT and asthma symptoms decreased in SCIT group only and there was a decreased medication usage in both SCIT & SLIT	2 patients had local reactions and 1 bronchospasm in SCIT. No adverse events in SLIT group were noted. SCIT decreased skin reactivity with effect on BHR	SCIT = SLIT

BHR: Bronchial hyperreactiveness; HDM: House dust mite; ICS: Inhaled corticosteroids; RCT: Randomized controlled trial; RA: Rhinitis-asthma; SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy.

generally the primary outcomes used in most trials that compared these two modes of immunotherapy.

In a recently published prospective randomized three parallel-grouped study, 48 children with HDM-induced rhinitis and asthma were randomized to receive SCIT, SLIT or pharmacotherapy alone. Rhinitis and asthma symptoms were significantly reduced in both SCIT- and SLIT-receiving groups compared to controls, with SCIT having a higher magnitude of effect. Children receiving SLIT had significant reduction in medication usage, which was not observed in SCIT-receiving group. Both modes of immunotherapy were accompanied by a significant decrease in specific nasal and skin reactivity to HDM compared to controls. Severe systemic adverse events were reported in two patients receiving HDM-SCIT [47]. These results were similarly found in a study that was designed to evaluate the novel approach for specific immunotherapy, which is to administer HDM-SCIT in the build-up phase and then switch to HDM-SLIT in the maintenance period [48]. Both SCIT and SLIT reduced the number of asthma attacks and ICSs significantly after treatment compared to controls. Interestingly, SCIT was showed to elicit its clinical effect with induction of allergen-specific TGF- β , IL-10 and IgG4 as early as 4 months of treatment compared to SLIT. Another small study conducted in children using a double-blind, double-dummy, randomized controlled design reported that rhinitis and asthma symptoms with medication usage were significantly reduced in SCIT group but not in SLIT when compared to placebo [34]. Apart from local reactions reported in all three groups, there were no systemic adverse events. Both modes of immunotherapy significantly decrease specific nasal and skin reactivity to HDM compared to controls (Table 3).

A prospective, single-blind, placebo-controlled trial evaluated clinical and immunological outcomes in 36 adult patients who received HDM-SCIT, HDM-SLIT or placebo-SLIT [50]. Rhinitis symptoms were decreased after both SCIT and SLIT treatment, while asthma symptoms decreased in only SCIT group compared to baseline scores. Both modes of treatment significantly reduced medication use after a year of treatment with no effect in placebo group. Skin reactivity decreased significantly in SCIT-receiving group only, with no changes in BHR in both SCIT and SLIT after treatment. Local reactions and bronchospasm reported in one patient were the main adverse events in SCIT, while buccal pruritus and nausea were reported in one patient receiving SLIT. Overall, the magnitude of efficacy in adults was found to be higher in SCIT compared to SLIT treatment.

All studies that evaluated allergen-specific IgG4 after treatment quantitatively found that specific antibodies were increased only after HDM-SCIT but not after HDM-SLIT [34,48-50]. There was no correlation between the increase in specific IgG4 and clinical symptoms. Since both modes of treatment were clinically effective, these results raise the possibility that specific IgG4 measured quantitatively might not be the surrogate marker of effectiveness. However, functional

antibody assays that measured IgG-associated serum inhibitory activity as for pollen immunotherapy [51] were not assessed. In two studies, there were increases in specific IL-10 and TGF- β in both SCIT and SLIT during the early phase of treatment [34,48]. Taken together, these studies give low quality evidence in favor of HDM-SCIT over HDM-SLIT, but more definitive adequately powered head-to-head comparisons are needed.

5. Long-term effect of HDM-AIT

5.1 Long-term effect of HDM-SCIT

Long-term efficacy after discontinuation of immunotherapy requires a prolonged duration of treatment. SCIT for 3 – 4 years has been shown to be effective, whereas SCIT given for a short time was associated with relapse of symptoms within 1 year [52-54]. Currently, there are few studies that have examined long-term effect of SCIT (Table 4) [53,55-59]. One early non-randomized long-term HDM-SCIT study retrospectively followed 48 children who received at least 5 years of HDM-SCIT treatment and analyzed their symptoms 9 years after treatment cessation, compared with 42 non-treated asthmatic children [56]. Asthma symptoms were significantly reduced in the HDM-SCIT-receiving group, compared to non-immunotherapy-treated asthmatics. There was no difference in medication use between SCIT-treated and non-treated children. On analyzing the impact of total dose administered, participants who received high dose of HDM-SCIT showed less asthma-related symptoms compared to those who received low dose of HDM-SCIT. Recently, a randomized controlled trial – partly blinded – conducted in both adults and children ($n = 120$) assessed possible differences in long-term effects of either 3 or 5 years' duration of SCIT [58]. After 3 years of treatment with HDM-SCIT, one group continued to be followed for 2 more years without treatment, whereas the other group continued with maintenance to complete 5 years of treatment. The two treatment groups were further compared with a control group receiving pharmacological treatment alone which was included from the third year of study. Clinical efficacy was evaluated in 120 patients (SCIT = 93 and controls = 27) at the end of follow up. After 3 and 5 years of treatment, both groups had significant improvement of symptoms compared with baseline, with > 70% reduction in rhinitis symptoms in the 5-year treated group compared with 50% reduction in the 3-year treatment group. There were no statistical differences between the 3-year or 5-year HDM-SCIT treated groups in terms of visual analog scores, quality of life and global rhinitis and asthma symptoms. These observations suggest that 3 years of HDM-SCIT is sufficient to induce a long-term effect of at least 2 years. Similar results were reported recently in a study conducted among 60 randomly selected children who had received 3 years ($n = 30$) or 5 years ($n = 30$) of HDM-SCIT. The study included a non-immunotherapy-treated asthma control group. Participants were prospectively followed for 3 years after treatment cessation [59].

Table 4. Long-term effect of HDM-specific immunotherapy.

Authors	Year	Age	Design	n	SCIT/SLIT	Duration	Re-evaluation after cessation (years)		Main positive results	Other findings
Des Roches <i>et al.</i> [53,55]	1996, 1997	Children and adults	Prospective open-controlled	40	SCIT	3 – 4 years	3		Asthma remission in 52% and prevented new sensitization in 42% of monosensitized children	
Cools <i>et al.</i> [56]	2000	Children	Retrospective observational	90	SCIT	5 years	9		Reduction in asthma symptoms, no changes in medication use compared to controls after mean of 9 years treatment cessation	Improved lung functions
Pajno <i>et al.</i> [57]	2001	Children	Prospective open-controlled	138	SCIT	3 years	3		Prevented new sensitization in 75% of SCIT-treated children	
Tabar <i>et al.</i> [58]	2011	Children and adults	RCT-partly blind prospective	120	SCIT	3 – 5 years	2		Significant reduction in rhinitis and asthma symptoms after 3 years of treatment that persisted for 2 more years without treatment	Improved QoL
Stelmach <i>et al.</i> [59]	2012	Children	Prospective open-controlled	90	SCIT	3 – 5 years	3		Significant reduction in asthma symptoms and medication use after 3 years of treatment that persisted for 3 more years after treatment	Reduced bronchial hyperreactivity
Di Rienzo <i>et al.</i> [61]	2003	Children	Prospective open-controlled	60	SLIT	4 – 5 years	4 – 5		Significant reduction in asthma symptoms and medication use after 4 – 5 years of treatment that persisted for 4 – 5 more years after treatment	No reduction in new sensitization
Marogna <i>et al.</i> [62]	2010	Children	Prospective open-controlled	78	SLIT	3 – 5 years	10 – 12		Four rather than 3 years of HDM-SLIT might be optimal for long-term tolerance that persists for > 7 years after SLIT discontinuation	

HDM: House dust mite; QoL: Quality of life; RCT: Randomized clinical trial; SLIT: Sublingual immunotherapy; SCIT: Subcutaneous immunotherapy.

Treatment duration for both 3 and 5 years significantly reduced asthma symptoms and medication use for at least 3 years after treatment cessation, and 50% of patients had asthma remission in both treatment duration groups. This is in line with previous studies showing that 3 years of SCIT is adequate treatment duration to induce sustained clinical efficacy in rhinitis and asthma.

5.2 Long-term effect of HDM-SLIT

Recently, a large-scale, 5-year, double-blind, placebo-controlled trial of SLIT with grass pollen extract in a tablet formulation was shown to have long-term sustained effects. Three years treatment resulted in improvement in daily rhinoconjunctivitis symptoms, reduced medication requirements, increased medication-free days and an associated better quality of life during the pollen season which persisted for at least 2 years after discontinuation. These data support that in selected patients with severe seasonal pollinosis, sublingual tablet immunotherapy, unlike usual anti-allergic drugs, is able to modify the course of the underlying disease [60]. There are very few studies that evaluated clinical outcomes after stopping HDM-SLIT; most are open, non-randomized studies.

In a prospective, open, parallel-group controlled study, Di Rienzo *et al.* included 60 asthmatic children, of whom 35 received HDM-SLIT for 4 – 5 years and 25 children who declined immunotherapy were followed on pharmacotherapy alone for the same duration as a control [61]. Patients were prospectively followed for 4 – 5 years after treatment cessation. The clinical efficacy in reducing asthma symptoms was significantly higher in the HDM-SLIT-treated group compared to controls for at least 4 – 5 years post-treatment.

A recent, open, partially randomized study prospectively evaluated the long-term effect of HDM-SLIT in an adult population according to treatment duration (3, 4 or 5 years) [62]. Five drops were sublingually given three times per week. The mean cumulative dose/year given was 390 mg of Der p 1/Der p 2 – about 10 times greater than a corresponding SCIT course. With a minimum duration of 3 years, clinical efficacy could be demonstrated up to 6 years after HDM-SLIT discontinuation, when compared to non-SLIT-treated controls, whereas following both 4 and 5 years of treatment, sustained efficacy could be seen 7 years after discontinuation of SLIT. Authors suggested that 4 rather than 3 years of HDM-SLIT might be optimal for long-term tolerance. However, the small numbers studied, the lack of blinding and only partially randomized design are limitations to the interpretation of these results.

6. Immunological changes associated with HDM-AIT

AIT has been shown to be clinically effective in treating AR and/or asthma through induction of T_H1, T_H2 and T-regulatory (Treg) cells (Figure 2) [63]. Studies of grass pollen AIT have found a significant increase in serum-specific IgG4 [64,65] and serum

allergen-specific IgA after AIT, which were associated with an increase in local and systemic IL-10 and TGF- β [66–68]. Induction of Treg s were also shown to increase in the nasal and sublingual mucosa of grass pollen rhinitic patients after specific immunotherapy [69,70], thus supporting a potential role for Tregs in the induction of human allergen-specific tolerance. Further, the induction of tolerance is species-specific as was recently shown in a small, double-blind, placebo-controlled crossover study of HDM-SCIT and grass pollen-SCIT in dual-allergic mite and grass-sensitive patients with AR [71]. A specific immunomodulating effect of AIT has been found not to trigger autoimmune or ischemic heart diseases in a 10-year follow-up study. The study revealed an actual lower risk mortality rate, incidence of heart disease and autoimmune disease in patients receiving SCIT compared to conventional treatment [72].

High dose HDM-SLIT was associated with elevated allergen-specific IgG4 antibody with no or little correlation with clinical efficacy [28,29,32,73]. Conversely, there are studies that have shown clinical effectiveness of SLIT, but no difference in specific IgG4 levels [20,21,24,30]. These discrepancies might be due to different treatment durations, differing doses or alternative methodologies for detecting IgG antibodies. It is possible that further functional assays might reveal differences relevant to a role of specific antibodies in perennial as observed for seasonal allergy [60]. Secretory specific-IgA antibodies have been found to be increased after HDM-SLIT in asthmatic children from baseline to those detectable in healthy controls [74], whereas another study in adult asthmatics found no differences between active and placebo groups [30]. Recently, it was shown that HDM-SLIT decreases allergen-specific CD4⁺ T-cell proliferation and induces transient Treg cells (CD4⁺CD25⁺ Foxp3/CD127^{lo}) which actively suppress allergen-specific T-effector proliferation and cytokine production [30]. This suppression was detectable after 6 months of treatment and found to be mediated, at least in part, by TGF- β but not IL-10. Other studies have shown that HDM-SLIT increases antigen-specific IL-10 in AR with suppression of T-cell proliferation without induction of antigen-TGF- β [75,76] as was observed in birch pollen-SLIT-treated patients [77]; however, since these studies were non-randomized, results should be interpreted with caution.

Recently, Swamy *et al.* demonstrated that dual-SLIT with two allergens (HDM and timothy grass) was clinically effective in polysensitized AR patients. Actively treated patients who developed tolerance, which is defined as a lack of allergic reaction after nasal allergen re-challenge with timothy grass allergen, were compared to non-responders. The tolerant group had Foxp3⁺ suppressive memory Treg cells with reduced DNA methylation of CpG sites within the Foxp3 locus. This implies that expression of memory Treg cell markers might be predictive of clinical tolerance [78].

HDM-SCIT has been shown to decrease the proportion of IL-4 with an increase in allergen-specific CD4⁺CD25⁺ T cells expressing IL-10. It was not clear if these cells were regulatory/suppressor or activated conventional T cells [79]. Recently, in a

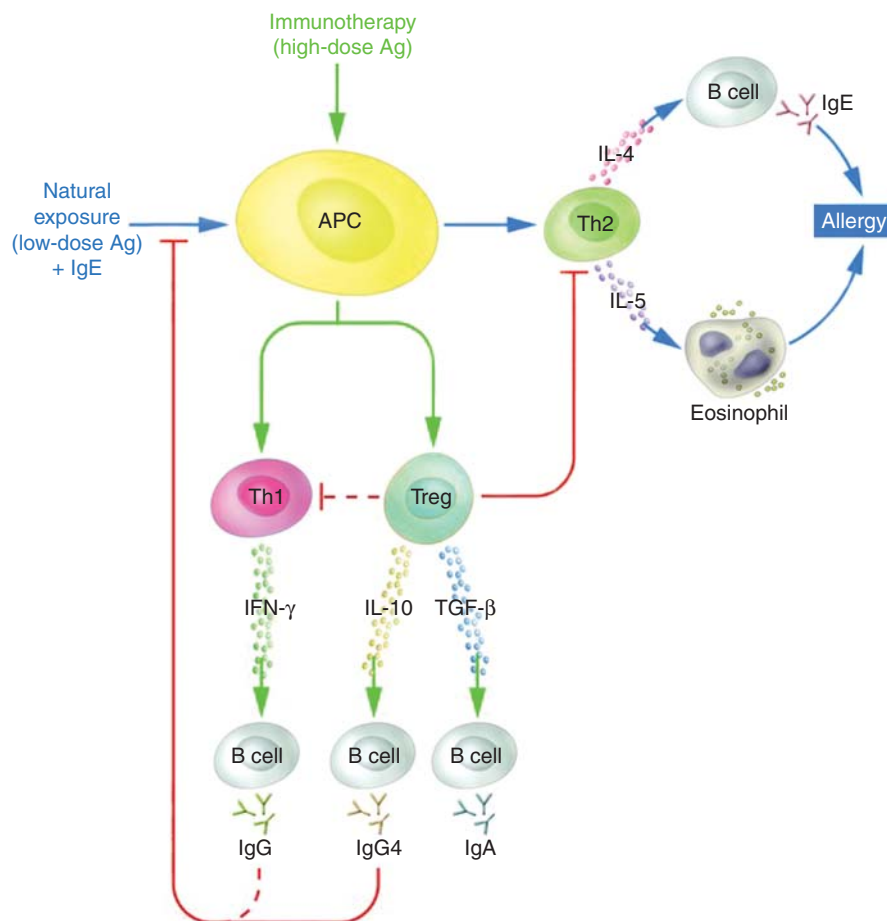


Figure 2. Immunological mechanisms of AIT are shown.

Adapted from [63].

APC: Allergen-presenting cells; IFN- γ : Interferon gamma; TGF- β : Transforming growth factor-beta; Th: T-helper cell; Treg: T-regulatory cell.

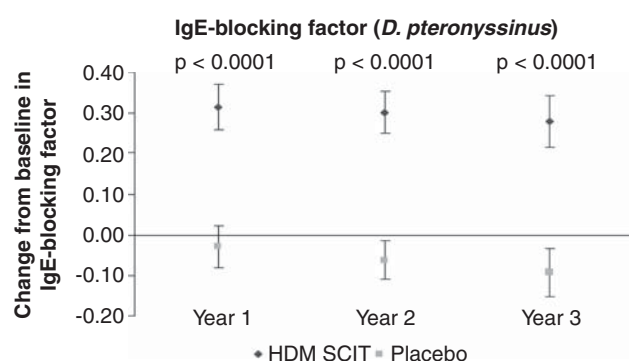


Figure 3. Change from baseline in IgE-blocking factor after 1, 2 and 3 years of treatment are depicted.

Adapted from [40].

study of mite-allergic children with rhinitis treated with HDM-SCIT, there was a correlation between increases in Tr1 cells (IL-10⁺IL-4⁺CD4⁺ T cells) and suppression of nasal symptoms, whereas no change in either CD4⁺CD25⁺Foxp3⁺,

Th1 or Th2 cells were observed [80]. In conjunction with a steroid-sparing effect and suppression of early and late phase skin responses, HDM-SCIT was found to be associated with an increase serum-specific IgE-blocking factor consistently for all 3 years of treatment with a decrease in specific IgE after the first year of treatment (Figure 3) [40]. Allergen-specific IgG4 antibodies were found to be significantly increased during HDM-SCIT [58,80] without any change in specific IgE, which then decreased significantly 2 years after treatment discontinuation [58].

7. Conclusion

Overall, based on currently published studies on HDM-AIT, there is good evidence showing the clinical effectiveness and safety of HDM-SCIT in treating HDM-allergic subjects with rhinitis mild-to-moderate asthma both in adults and children. There is currently insufficient evidence for the effectiveness of HDM-SLIT in treating rhinitis or asthma in either adults or children. The large clinical and methodological heterogeneity found in the SLIT meta-analyses prevent us from

making recommendations for use of HDM-SLIT in routine clinical practice.

When evaluating a single and complex allergen, such as HDM, in a clinical trial, we must consider the study design *per se*, the statistical power of the study, the criteria for inclusion of patients, the use of validated outcomes and the quality of the extracts used for SCIT or SLIT. Most of these parameters are not well established in many of the currently published studies. We consider that there is an urgent need for large adequately powered placebo-controlled 'definitive' trials of HDM-SLIT in both children and adults.

At present, no conclusion can be drawn in studies that compare HDM-SCIT and HDM-SLIT head to head, due to inadequate number of patients and studies conducted.

The safety profile of HDM-AIT on asthmatic patients and in the pediatric population seems to be better in HDM-SLIT compared to HDM-SCIT, although this is not clinically relevant unless accompanied by consistent and convincing data for efficacy, which at present is not the case for HDM-SLIT.

Both modes of treatment seem to have similar mechanisms of action with SCIT providing earlier immunological changes compared to SLIT.

8. Expert opinion

Currently, according to local and international guidelines, recommendations on the treatment of HDM-induced asthma and/rhinitis have focused on the use of antihistamines/inhaled β -agonists and intranasal/ICSs. These approaches have not been shown to be effective in inducing long-term remission or preventing disease progression. At present, AIT is the only available option with the potential to induce long-term tolerance and modify the natural course of allergic disease.

Since perennial asthma and/or rhinitis may have multiple underlying etiological factors and since a high proportion of the general population is sensitized to HDM, it is difficult

to select those sensitized candidates in whom HDM is the major driver of their disease and who are therefore likely to respond optimally to HDM-AIT. At present, there is good evidence for use of HDM-SCIT in selected patients with rhinitis with or without mild asthma, whereas the evidence for the routine use of HDM-SLIT is inadequate. However, this is largely an absence of high-quality evidence rather than 'evidence against', and further well-designed well-powered studies, including head-to-head comparisons of HDM-SCIT and HDM-SLIT are needed.

These studies should be focused on those patients who give a history of symptoms on exposure as well as clear-cut HDM sensitization. Provocation testing in the target organ may represent an alternative method to demonstrate clinical relevance of mite exposure. Treatment duration and optimal dosage are required to be evaluated for both short-term efficacy and long-term tolerance. Effectiveness of HDM-AIT in monosensitized compared with multisensitized individuals needs to be assessed. Similarly, a comparison of efficacy in those patients with rhinitis alone compared with those with associated asthma needs to be evaluated. A better understanding of mechanisms of HDM-SCIT and HDM-SLIT might afford the development of biomarkers to monitor response to treatment.

Declaration of interest

M Calderon has received lecture fees from ALK, Stallergenes and Merck. S R Durham has received honoraria via Imperial College London from ALK-Abello, Glaxo-Smith-Kline, Merck, Ono Pharmaceuticals and Circassia, and lecture fees from ALK-Abello, Glaxo-Smith-Kline and Torii Pharmaceuticals, and research funds via Imperial College from Glaxo-Smith-Kline and ALK-Abello. None of the remaining authors have any conflict of interest to declare and no funding was received in support of this manuscript.

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