



Update on house dust mite immunotherapy: are more studies needed?

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Purpose of review

Although systematic reviews have confirmed the effectiveness of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) for the treatment of allergic rhinitis and allergic asthma, a review of studies employing extracts of house dust mites (HDMs) for immunotherapy found no consensus on basic treatment parameters.

Recent findings

Over the last 2 years nine additional reports on immunotherapy with HDM extract preparations have been published. Six studies were with SLIT, five for allergic rhinitis and one for allergic asthma. The other three studies were all with SCIT in children with allergic asthma.

Summary

The publication of these nine studies supports the efficacy of HDM-SLIT for allergic rhinitis and asthma and for HDM-SCIT for asthma in children. The reported safety data are also reassuring, especially for SLIT. HDM-SLIT tablets under development will have optimal doses established in large, randomized, placebo-controlled trials. The HDM-SCIT trial in children with allergic asthma confirms the efficacy of a commercialized HDM preparation for injection immunotherapy. However, the information that is presented on dosing in the articles on SLIT-liquid is unsatisfactory, as doses are not presented in a form that the clinician can use to guide their practice.

Keywords

allergy immunotherapy, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, house dust mite, subcutaneous, sublingual

INTRODUCTION

Recent systematic reviews have confirmed the presence of moderate to strong evidence for the effectiveness of subcutaneous immunotherapy (SCIT) [1[•]] and sublingual immunotherapy (SLIT) [2[•]] for the treatment of allergic rhinitis and allergic asthma. However, a review of allergen immunotherapy (AIT) articles published in English through March 2013 of studies employing extracts of HDMs for allergic rhinitis and asthma found no consensus on basic treatment parameters [3[•]]. The authors identified 44 randomized, double-blind, placebo-controlled trials of currently available commercial subcutaneous (SCIT) and sublingual (SLIT) preparations; however, the studies were often small, poorly designed, and often did not provide critical information on methods and results. As a result of this review, the authors suggested that more rigorous clinical studies were required. Their specific recommendations were as follows: first, large, well powered studies; second, disease severity and control scores should be used to describe the subjects;

third, dose-ranging studies were needed because of the wide range of doses employed in the reported studies; fourth, trials should be of at least 1 year and preferably longer with observations made at a time of year without conflicting aeroallergen seasons; fifth, outcomes should be measured in patients with asthma in addition to symptoms, such as quality of life, steroid reduction, and pulmonary function; sixth, rhinitis evaluations should include symptom/medication scores and assessment of quality of life; seventh, HDM levels in homes should be measured at baseline and during the course of the study; and eighth, more studies of SCIT in children are needed. This review, written 1 year later, will

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KEY POINTS

- Nine studies published in the last 2 years confirm the efficacy of both SLIT and SCIT with HDM allergens in patients with allergic rhinitis and allergic asthma.
- These studies contain no reports of serious adverse reactions to SLIT, lending further support to its safety.
- Commercial HDM allergen tablets are currently understudy to determine appropriate doses and demonstrate efficacy.
- Despite the fact that four of these studies demonstrated efficacy for HDM-SLIT-liquid therapy, there was little useful information on the doses of HDM liquid preparations that were employed.

assess the extent to which recent studies have addressed these concerns.

RECENT STUDIES OF ALLERGEN IMMUNOTHERAPY WITH HOUSE DUST MITE EXTRACTS

Over the last 2 years, reports on a number of randomized clinical trials with HDM extract preparations have been published (Table 1) [4^{••},5[•],6^{••},7–10,11[•],12–14]. Six studies [4^{••},5[•],6^{••},7–10], all randomized, double-blind, placebo-controlled, were with SLIT, five for allergic rhinitis and one for allergic asthma. The other three studies [11[•],12–14] were all of SCIT in children with allergic asthma.

The study by Bergmann enrolled participants 18–50 years with moderate to severe allergic rhinitis confirmed by skin prick test (SPT), at least 0.7 kU/l of serum immunoglobulin E specific for *Dermatophagoides pteronyssinus* or *D. farinae* and a baseline rhinitis score of at least five on a scale of 0–12. The participants were randomized to receive placebo tablets, 300 index of reactivity (IR) tablets containing 16 µg of Der p 1 and 68 µg of Der f 1, or 500 IR tablets containing 28 µg of Der p 1 and 120 µg of Der f 1 on a daily basis (Stallergenes, Antony, France). There was a 3-day and 9-day up-dosing for the 300 IR and 500 IR groups, respectively. Outcomes were assessed from 1 October to 31 December at baseline, after 1 year of treatment with SLIT and after a further year of observation without further treatment. Assessments were based on the occurrence and severity of five rhinitis/conjunctivitis symptoms, medication use and global evaluation. Serum immunoglobulin E and immunoglobulin G4 levels and SPT size were also evaluated. A total of 509 participants were randomized, 427 completed the first year and 397 the second year. The results are presented in Table 2. At the end of 1 year of treatment and an

additional year of observation, there was not a significant difference between active treatment groups. Specific immunoglobulin G4 increased and the SPT to both *D. pteronyssinus* and *D. farinae* was reduced in both active groups. There were no reports of anaphylaxis and no participant received epinephrine, but application-site reactions were common and withdrawals due to treatment emergent adverse events occurred in 2.9% of placebo, 10.0% of 300 IR, and 11.8% of 500 IR participants.

A single-site study was conducted in Poland in participants 60–75 years of age who were diagnosed with allergic rhinitis due to HDM by history, SPT, specific immunoglobulin E, and a positive nasal provocation test with *D. pteronyssinus* and *D. farinae*. The participants were randomized to placebo or a mixed *D. pteronyssinus/D. farinae* liquid preparation 18 puffs, each containing 30 IR, five times weekly sublingually for 3 years (Stallergenes). Treatment was initiated with a 2-week up-dosing. Outcomes were assessed November to January. The outcomes were a seven-point scale of nasal and non-nasal symptoms, medication use, and nasal allergen provocation. A total of 95 participants completed the 3 years of SLIT. The results are presented in Table 3. At the end of the 3 years, total nasal symptoms decreased significantly with active treatment, but there was not a significant difference in non-nasal symptoms. Mean medication scores were also significantly reduced in the active compared with the placebo group. The nasal provocation tests were significantly improved in the active versus the placebo groups when measured by decreases in nasal resistance. No systemic reactions or severe local reactions were reported in either group with only three participants in the active group reporting local adverse reactions.

The efficacy, safety, and time to onset of significant clinical effect for a SLIT-HDM tablet were tested in 124 patients with allergic rhinitis, employing the Vienna Environmental Exposure Chamber (EEC) [6^{••}]. Following a baseline 6-h challenge, qualifying patients were placed on daily treatment with a rapidly dissolving tablet containing 6 development units (DU), 12 DU, or placebo (ALK-Abello, Horsholm, Denmark). The 6-h exposure in the EEC was repeated after 8, 16, and 24 weeks of treatment. The primary outcome was the total nasal symptom score (TNSS). The increase in TNSS was significantly reduced in the 12-DU groups compared with placebo by 8 weeks and in the 6-DU group by 16 weeks (Table 4).

Serum-specific immunoglobulin G4 rose in parallel with the clinical improvement. There were no systemic allergic reactions or reactions requiring epinephrine. In a separate report on the same study,

Table 1. Recent studies of allergen immunotherapy with house dust mite preparations

Author (date)	Number of study participants	Disease	Dose	Duration	Efficacy criteria
Bergmann SLIT (2014)	427 first year, 397 second year	Adults with moderate to severe allergic rhinitis	28 µg Der p 1 and 120 µg Der f 1 = 500 IR, also 300 IR and placebo daily	Treated 1 year, observed 1 additional year	Assessed Oct–Dec adjusted symptom score and global evaluation
Bozek SLIT (2013)	95	Allergic rhinitis 60–75 years	540 IR Der p 1/Der f Five days/week	3 years	Assessed Nov–Jan symptoms, medication, PEF, nasal allergen provocation
Horak SLIT (2014)	124	Adults, allergic rhinitis	6 DU and 12 DU	24 weeks	Nasal symptoms in an environmental exposure chamber
Wang DH SLIT (2013)	120	Ages 4–60 years with allergic rhinitis	75 µg <i>Dermatophagoides farinae</i> and <i>D. pteronyssinus</i>	6 months	Symptoms, medication, IgG4
Queiros SLIT (2013)	102	Ages 5–15 years with allergic rhinitis	12 µg Der p 1 three times weekly	18 months	Symptoms, medication, IgG4
Tian SLIT (2014)	60	Ages 4–18 years with asthma	40 µg <i>D. farinae</i> protein	48 weeks	Symptoms, Th17 and CD4 ⁺ CD25 ⁺ T cells
Hui SCIT (2014)	90	Mild to Moderate asthma on ICSs, age 5–14 years	100 000 SQ <i>D. pteronyssinus</i>	3 years	ICS dose, symptoms, PEF, SPT
Ye SCIT (2012, Chinese)	100	Children, mild to moderate asthma, on ICS	Alutard HDM	2 years	ICS dose and pulmonary function tests
Baris SCIT 2014	50	5–15 years, mild to moderate asthma, sensitized to HDM	HDM-SCIT with or without 650 U/day Vitamin D	1 year	Symptoms, medication, Treg cells, IL-10 and TGF-β response in PBMCs

DU, development units; HDM, house dust mite; IgG4, immunoglobulin G4; IL, interleukin; IR, index of reactivity; PBMC, peripheral blood mononucleated cell; PEF, peak expiratory flow; PEF, peak expiratory flow rate; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy; SPT, skin prick test; TGF-β, transforming growth factor beta.

Table 2. Sublingual immunotherapy with house dust mite tablets in allergic rhinitis: average adjusted symptom scores compared with placebo (from reference [4[■]])

Dose	End of treatment year	End of follow-up year
300 IR	–17.9% ($P=0.015$)	–17% ($P<0.05$)
500 IR	–20.2% ($P=0.0066$)	–19.1% ($P<0.05$)

IR, index of reactivity.

34.1% improvement in ocular symptoms compared with placebo was reported by 8 weeks with the 12-DU dose and 67.9% improvement by 24 weeks [7]. There was 41.2% improvement compared with placebo in the 6-DU dose by 24 weeks.

An article from China also examined the onset of action of HDM-SLIT in 120 adults and children with allergic rhinitis. Sixty patients received, following a 5-week build-up, 25 µg if less than 14 years of age or 75 µg if older of an extract of *D. farinae* and *D. pteronyssinus* (Zhejiang Wolwo Bio-Pharmaceutical Co., Deqing, Zhejiang Province, China) or matching placebo for a total of 6 months. Patients maintained a daily symptom/medication diary and at each visit marked a visual analog scale (VAS). Dropout rates were high, 20% of the SLIT and 38% of the placebo group. The total score for four nasal symptoms and the VAS score became significantly lower in the active treatment compared with the placebo group by the 14th week and the difference for both became increasingly pronounced until the end of treatment. Specific immunoglobulin G4 increased significantly in the active compared with the placebo groups. There were no serious adverse reactions.

A study from Brazil examined the response to HDM-SLIT with or without a mixed bacterial vaccine compared to placebo in 102 children 5–15 years of age with allergic rhinitis due to HDMs. Following up-dosing, two groups received a sublingual extract containing 12 µg Der p 1 (FDA Allergenic Ltda, Rio de Janeiro, Brazil) three times weekly and one group received, in addition, a mixed respiratory bacterial vaccine (FDA Allergenic Ltda) for a total of 18 months of treatment. Only 68.6% completed the study, but only three on the active treatment withdrew because of drug-related reactions,

none serious. After 18 months, all three groups had a decrease in symptoms, but the decrease was significant only in the two groups receiving active treatment. Immunoglobulin G4 levels were significantly increased only in those receiving HDM extract alone.

Sixty Chinese children, ages 4–18 years, with mild to moderate asthma and sensitivity to *D. farinae* by both SPT and in-vitro testing, were randomized into a double-blind, placebo-controlled 48-week SLIT study in which the active group received 4 weeks of up-dosing followed by 44 weeks of maintenance with 40 µg *D. farinae* protein daily (Zhejiang Wolwo Bio-Pharmaceutical Co.). The outcomes were asthma symptoms, and the percentages of Th17 and CD4⁺CD25⁺ T cells in the peripheral blood at 12-week intervals. Symptom scores declined significantly more in the active than in the placebo group beginning at the 12-week assessment. The Th17 cell population gradually declined, becoming significantly lower than in the placebo group after 24 weeks of treatment. The percentage of CD4⁺CD25⁺ Treg cells significantly increased over the study period in the active group and was significantly higher than the placebo group at 24, 36, and 48 weeks of treatment.

A 3-year randomized, double-blind, placebo-controlled study [11[■]] of the efficacy of treating HDM-allergic children with injections of a standardized HDM extract was conducted in China. The children, ages 5–14 years, all of whom required inhaled corticosteroid treatment to control their asthma, were randomized to receive treatment with Alutard SQ *D. pteronyssinus* (ALK-Abello[®]) or placebo injections. After a 15-visit up-dosing, maintenance

Table 3. Sublingual immunotherapy with house dust mite liquid in allergic rhinitis. Comparison with placebo after 3 years of treatment (from reference [5[■]])

Outcome	Change compared with placebo	P-value
Weekly nasal symptom score	–33%	0.011
Weekly medication score	–26%	0.034
Nasal peak flow after NPT with Der p	–14%	0.023
Nasal peak flow after NPT with Der f	–20%	0.013

NPT, nasal provocation test.

Table 4. Response to house dust mite-sublingual immunotherapy tablets compared with placebo in an Environmental Exposure Chamber (from reference [6**])

Dose	8 weeks	16 weeks	24 weeks
6 DU	NS	–17.8%, <i>P</i> = 0.032	–26.2%, <i>P</i> = 0.003
12 DU	–20.3%, <i>P</i> = 0.007	–30.1%, <i>P</i> = <0.001	–48.4%, <i>P</i> = <0.001

DU, development units; NS, not significant.

injections of 100 000 SQ (9.8 µg Der p 1) were administered every 6 weeks for a total of 3 years. The dose of inhaled corticosteroids (ICS) was adjusted by the degree of asthma control. The results are presented in Table 5. Both groups exhibited a steady decline in ICS dose, but the doses were significantly lower in the active treatment group after 2 and 3 years. There was also a progressive decline in asthma symptom scores over the 3 years in both groups, but the scores were significantly lower, both for daytime and for nighttime in the active treatment group for all 3 years. Peak expiratory flows were also significantly higher in the active treatment group for the second and third years. Five children withdrew from the active group because of systemic reactions, all mild.

A similar study [12], published in Chinese, reports 2 years of SCIT treatment of 100 children with the same Alutard HDM extract in a randomized, but open study. Again, a significant difference was found in ICS doses between SCIT group and control group after 9 months of treatment and the difference increased as the treatment progressed. Pulmonary function studies were also higher in the active treatment group beginning after 3 months of treatment.

Fifty Turkish children with asthma were randomized into a study comparing HDM-SCIT with or without the addition of vitamin D to pharmacotherapy alone [13].

Information on the dose of HDM extract was not provided in the study. Although not placebo controlled, none of the outcome parameters required any clinician assessment. There was a 6-week observation period beginning in November, and assessment of treatment was for 1 year. At 6 and 12 months, total asthma score and dose of ICS were

significantly better in both active groups compared with the pharmacotherapy alone. At 6 months, the improvement in asthma symptoms with added vitamin D was superior to SCIT alone, but after 12 months there were no significant differences between active treatments.

ARE MORE STUDIES NEEDED?

Many studies have been reported in the last 2 years on the subjects of AIT for HDM sensitivity. These have addressed the treatment of both rhinitis and asthma by both the sublingual and subcutaneous route and have particularly addressed AIT in children. Have these studies adequately addressed the issues raised by Calderon *et al.* [3*] regarding the quality of the research?

Few large, multicenter, well powered trials

The six HDM-SLIT trials were all of reasonable size but four of six were single-site studies. They included a total of 928 participants, but 427 of these were in one multicenter trial [4**]. The three SCIT trials included a total of 240 participants and all were single-site studies.

Ill-defined criteria for disease status/severity: use of allergen challenges

Two studies used nasal challenges to establish eligibility and to assess response, one with individual challenges [5*], the other used an EEC [6**]. Otherwise, eligibility was established by history, often following international guidelines, and evidence of sensitization to HDM by SPT and/or specific immunoglobulin E.

Table 5. Treatment of asthma in children with house dust mite-sublingual immunotherapy, difference from placebo (from reference [11*])

Outcome	First year	Second year	Third year
Symptoms Day/night <i>P</i> -value	–20%/–27% 0.013/0.024	–31%/–33% 0.012/0.011	–30%/–43% 0.009/0.007
ICS dose <i>P</i> -value	NS	–22% 0.015	–30% 0.027
Peak expiratory flow	NS	+19% 0.018	+12% 0.007

NS, not significant.

Lack of consensus on the therapeutic dose for subcutaneous immunotherapy and sublingual immunotherapy

There was a disappointing lack of usable information on dosing. Only the large, multicenter study [4[■]] of SLIT-HDM tablets provided a comparison of two major allergen doses and both were quite high, without a clear differentiation in response. The EEC study [6[■]] employed two doses, with a clear-cut dose response, but the doses are expressed in 'DU' without giving major allergen content. In the SCIT studies, the dose in major allergen content is provided in one of the studies [11[■]] and is consistent with doses that have been reported to be clinically effective in the past [14].

Differing times of year of initiation of studies and differing durations of studies

Three of the studies [4[■], 5[■], 13] clearly stated periods of enrollment that corresponded to periods of major HDM allergen exposure not confounded by seasonal aeroallergen exposure. For most studies, baseline and outcome assessments were made 1, 2, or 3 years apart, ensuring similar exposures each time.

Lack of standardized efficacy criteria in both asthma and rhinitis patients

In general, the studies employed assessments of rhinitis or asthma symptoms, use of rescue medication for rhinitis, and dose of inhaled corticosteroids for asthma. The two studies employing nasal allergen challenge at baseline used repeat challenge as an outcome. Many of the studies measured the specific immunoglobulin G4 antibody response and repeated the SPTs as secondary outcomes.

Lack of information on allergen exposure

Except for the study [6[■]] conducted in the EEC, none of the studies provided any information on HDM allergen exposure of the participants.

Few subcutaneous immunotherapy trials in pediatric populations

All three of the SCIT studies [11[■], 12, 13] were conducted in children with asthma, greatly increasing the experience in this population.

CONCLUSION

The publication of these nine studies reinforces the previous conclusions regarding the efficacy of

HDM-SLIT for allergic rhinitis and asthma and for HDM-SCIT for allergic asthma in children. The reported safety data are also reassuring, especially for SLIT.

HDM-SLIT tablets are under development that will have optimal clinically effective doses established in large, randomized, placebo-controlled trials. The HDM-SCIT trial in children with allergic asthma confirms the efficacy of a commercialized HDM preparation for injection immunotherapy. The information that is presented in the articles for effective SLIT-liquid dosing is unsatisfactory, as doses are not presented in a form that the clinician can use to guide their practice. What is especially lacking is evidence as to what are effective doses of currently available United States HDM allergen extracts, should a physician decide to use these 'off-label' extracts for treatment of HDM sensitive patients.

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Conflicts of interest

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- of special interest
- of outstanding interest

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