

An evidence-based analysis of house dust mite allergen immunotherapy: A call for more rigorous clinical studies

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Background: According to meta-analyses and reviews, subcutaneous allergen immunotherapy (SCIT) and sublingual allergen immunotherapy (SLIT) are beneficial in patients with allergic rhinitis (AR) and allergic asthma (AA) induced by house dust mites (HDMs). However, the reported effect sizes have varied greatly from one study to another.

Objective: We sought to perform an evidence-based medicine assessment of commercially available SCIT and SLIT formulations in patients with HDM-induced AA and HDM-induced AR.

Methods: We searched for double-blind, placebo-controlled randomized clinical trials and analyzed study designs, doses, regimens, patient-reported outcomes, safety reporting, and compliance.

Results: Forty-four studies met our inclusion criteria. Some studies tested both SLIT and SCIT or scored both AA and AR outcomes; therefore we reviewed 35 treatment arms in patients with AA (20 for SCIT and 15 for SLIT) and 23 treatment arms in patients with AR (7 for SCIT and 16 for SLIT). The treatment duration ranged from 6 weeks to 3 years. For SCIT, the dose of Der p 1 major allergen (when reported) ranged from 7 to 30 µg for maintenance doses and 60 to 420 µg for cumulative doses. For SLIT, the doses of Der p 1 (when reported) were 0.8 to 70 µg for maintenance doses and 60 to 23,695 µg for cumulative doses. Safety data were often absent or poorly reported. A statistically significant active versus placebo symptom score was observed more frequently for SCIT than for SLIT.

Conclusion: There is no consensus on basic treatment parameters (eg, dose and duration) in HDM SCIT and SLIT.

There is an urgent need for rigorous, long-term, double-blind, placebo-controlled randomized clinical trials with an efficacy criterion that reflects the particular features of HDM-induced allergic disease. (*J Allergy Clin Immunol* 2013;■■■■:■■■-■■■.)

Key words: Evidence-based medicine, house dust mite, allergen immunotherapy, subcutaneous, sublingual, allergic rhinitis, allergic asthma, respiratory allergy

House dust mites (HDMs) have a well-established causal role in patients with persistent allergic respiratory diseases, such as allergic rhinitis (AR) and allergic asthma (AA).^{1,2} These atopic diseases lead to increased burden of disease and health care costs, particularly in patients with uncontrolled or poorly controlled disease.³⁻⁵ Because effective allergen avoidance is not always possible in a domestic setting,^{6,7} HDM-induced respiratory diseases are treated with a range of symptomatic medications or with allergen immunotherapy (AIT) based on purified extracts of HDM bodies, feces, or both.⁸⁻¹⁰ The efficacy of AIT in patients with allergic respiratory conditions has long been acknowledged by national and international guidelines.^{11,12} A meta-analysis¹³ of double-blind, placebo-controlled (DBPC) randomized clinical trials (RCTs) of subcutaneous allergen immunotherapy (SCIT) in adults and children with AA (including asthma induced by allergens other than HDM) has shown that this treatment is effective in relieving symptoms, decreasing rescue medication use, and improving bronchial hyperresponsiveness. Recent meta-analyses and reviews¹⁴⁻¹⁶ suggest that sublingual allergen immunotherapy (SLIT) with HDM extracts might be beneficial in patients with AA, although the effect size reported is small to moderate and varies greatly from one study to another.

With a view toward better informing the practitioner on the quantity and quality of evidence underlying treatment recommendations, we performed an evidence-based medicine (EBM) review of HDM AIT modalities, according to a standardized methodology.¹⁷ We searched MEDLINE, Embase, and the Cochrane Library for DBPC RCTs of currently available commercial HDM SLIT and SCIT preparations for the treatment of AA and AR. Our goal was not to perform a meta-analysis of efficacy or a calculation of the effect size but rather to (1) evaluate the solidity of the research evidence on which the latter analyses are based and (2) identify opportunities for methodological improvements.

METHODS

MEDLINE, Embase, and the Cochrane Library were searched from January 1965 until March 2013 by using logical combinations of the following terms: allerg*, rhinit*, asthma*, desensiti*, immun*, pyroglyphid*, house, dust, mite*, *Dermatophagoides*, *pteronyssinus*, and *farinae*.

We considered only randomized DBPC RCTs of currently available commercial SCIT and SLIT modalities based on purified or semipurified HDM allergens for HDM-induced AR and AA. We excluded studies (1)

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Abbreviations used

AA:	Allergic asthma
AE:	Adverse event
AIT:	Allergen immunotherapy
AR:	Allergic rhinitis
DBPC:	Double-blind, placebo-controlled
EBM:	Evidence-based medicine
HDM:	House dust mite
QoL:	Quality of life
RCT:	Randomized clinical trial
SCIT:	Subcutaneous allergen immunotherapy
SLIT:	Sublingual allergen immunotherapy
SPT:	Skin prick test
TEAE:	Treatment-emergent adverse event
VAS:	Visual analog scale

considering safety only; (2) not reporting any clinical data; (3) with HDM preparations that have never been commercialized or are no longer available, including nonpurified extracts (eg, house dust); (4) involving the simultaneous administration of several unrelated allergens (eg, pollen with HDM extracts) or other active treatments on a regular basis; or (5) not published in English. Articles were cross-checked against those identified in recent meta-analyses and systematic reviews.

From each selected publication, we extracted data concerning study design, patient screening, patient numbers, disease severity on inclusion, maintenance and cumulative doses, the pretreatment baseline period, treatment duration, the primary efficacy criterion, and secondary efficacy criteria (see the [Methods](#) section in this article's Online Repository at www.jacionline.org for the full list). In an exploratory analysis each of the 6 studies published after the issuance of the 2010 CONSORT reporting guidelines¹⁸⁻²⁰ was scored to determine what proportion of the applicable CONSORT items (32-35 items, depending on the study's design) were in compliance.

RESULTS

Our search initially identified a total of 83 potentially relevant publications ([Fig 1](#)). The main reasons for excluding studies ($n = 39$, see [Table E1](#) in this article's Online Repository at www.jacionline.org) were lack of double-blinding, use of preparations that are not currently available commercially, lack of a true placebo group, and systematic adjunction of other therapeutics to AIT (ie, not just the use of rescue medication). Hence we selected a total of 44 publications²¹⁻⁶⁴ for final analysis ([Fig 1](#) and [Tables I-IV](#)), all of which concerned the *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* species only. We also excluded the SCIT subgroup in the study by Mungan et al⁴⁶ because placebo injections were not administered. A study that presented symptom scores for both AR and AA (eg, Bahçeciler et al²²) or studied both SLIT and SCIT or presented separate results for 2 different dose levels (eg, Bush et al,³⁰ which investigated high and low doses of *D farinae* SLIT, containing 70 μg and 1 μg of Der f 1 per day, respectively) was considered as 2 "treatment arms." Hence we reviewed 35 treatment arms in patients with AA (20 for SCIT and 15 for SLIT, [Tables I and II](#)) and 23 treatment arms in patients with AR (7 for SCIT and 16 for SLIT, [Tables III and IV](#)). The vast majority of the studies were performed at single centers in Europe. Only 1 study was multinational, with patients from 3 countries.⁵⁷ We summarize some overall EBM indicators in [Table V](#). For the 6 most recent studies, the percentage compliance with CONSORT items ranged from 38% to 71%. We concluded that studies published before 2010 would be even less compliant in retrospect

and thus did not pursue this approach as a discriminative parameter.

AA induced by HDMs

SCIT in patients with HDM-induced asthma. *Study design.* Nineteen studies (20 treatment arms) met our selection criteria ([Table I](#)) and featured between 22 and 132 randomized participants per study (median number, 46; first-third quartile, 32-56). The severity criteria for inclusion were rarely stated, and only 13 of the 19 studies excluded patients cosensitized to other relevant allergens or with clearly confounding symptoms. None of the studies published before 1997 reported on the major allergen content in micrograms. The maintenance dose of major allergen (Der p 1) ranged from 7 to 17.5 μg , and the cumulative dose ranged from 68 to 250 μg ([Table I](#) and see the [Results](#) section in this article's Online Repository at www.jacionline.org). A wide variety of baseline periods, treatment durations, initiation months, and injection frequencies were noted ([Table I](#) and see the [Results](#) section in this article's Online Repository).

Treatment efficacy. Poor efficacy reporting and lack of standardized parameters limited our ability to compare studies. Only 9 of the 19 studies provided evaluable numeric data on a symptom score or a symptom-related outcome. Nine studies (not the same 9 referred to in the previous sentence) reported a statistically significant active versus placebo difference ([Tables I and V](#)) in a mean $\pm$ SD symptom score or symptom-related parameter,* with maintenance major allergen doses of between 7 and 17.5 μg of Der p 1. Seven of the latter 9 studies featured efficacy scoring periods of a year or more (with just 7 weeks for Bousquet et al²⁵ and 3 months for D'Souza et al³⁴). The secondary efficacy criteria variously included medication scores, skin prick test (SPT) parameters, nasal and bronchial challenges, visual analog scales (VASs) of symptom intensity, peak expiratory flow rate, bronchial hyperresponsiveness to methacholine, FEV₁, forced vital capacity, allergen concentration required to provoke a 25% decrease in FEV₁ (PD₂₅), serum specific and total IgE and IgG₄ levels, and leukocyte histamine release.

Safety. Safety data are summarized in [Table E2](#) in this article's Online Repository at www.jacionline.org. The standard of safety reporting was very poor, even in recent publications. Only 3 studies provided enough numeric information for us to derive the percentages of participants with local and nonlocal treatment-emergent adverse events (TEAEs).^{38,45,64} Several serious TEAEs (some of which required epinephrine) were reported. Pichler et al⁵⁶ mentioned epinephrine use but did not state whether this concerned an active treatment or placebo group participant. The 4 incidents reported by Bousquet et al²⁵ (3 of which required epinephrine) all concerned the active treatment group during the rush up dosing phase. Serious TEAEs were also mentioned, although not in detail, in other reports.^{23,24,28} Warner et al⁶³ mentioned a severe exacerbation of asthma in a placebo-treated patient.

Patient values. The studies by Ameal et al²¹ and Garcia-Robaina et al³⁸ were the only ones to report on quality of life (QoL; by using Marks' Asthma Quality of Life Assessment in both cases), which was significantly better for the active treatment group (vs the placebo group). Three other studies reported on a patient-assessed VAS for overall disease status.^{24,49,54}

*References 21, 24, 25, 34, 38, 49, 53, 62, and 64.

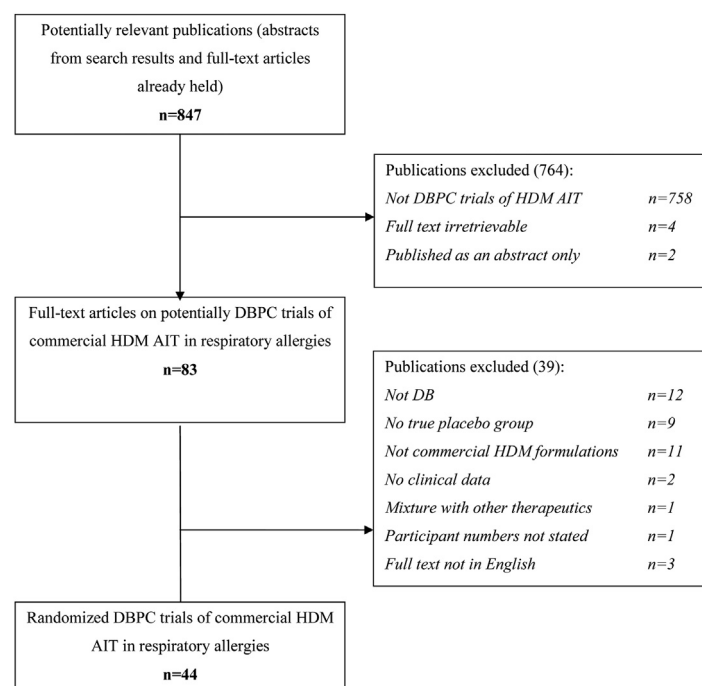


FIG 1. Study selection flow chart. The MEDLINE, Embase, and Cochrane Library databases were searched from January 1965 through March 2013.

Pediatric studies. Three studies were performed in children,^{54,63,64} and all were disadvantaged by small sample sizes (12, 28, and 10 actively treated patients, respectively). The studies by Warner et al⁶³ and Yukselen et al⁶⁴ were further disadvantaged by the lack of screening for confounding sensitizations.

SLIT in patients with HDM-induced asthma. Study design. Fourteen studies (15 treatment arms) met our inclusion criteria (Table II), with between 15 and 465 randomized participants per study (median number, 31; first-third quartile, 24-85). Subjects were screened for specific sensitization by using both SPT and specific IgE assays in all but 1 study.²² Although all studies excluded patients with severe asthma, there was a wide range of inclusion criteria for disease severity (Table II and see the Results section in this article's Online Repository). The maintenance dose varied from 0.8 to 28 µg of Der p 1 and from 1 to 70 µg of Der f 1, and the cumulative major allergen dose ranged from 60 µg of Der p 1⁴¹ to 23,695 µg of Der f 1.³⁰ There was great heterogeneity in the treatment time and month of initiation (Table II and see the Results section in this article's Online Repository).

Treatment efficacy. Ten of the 14 studies provided evaluable numeric data on a symptom score or a symptom-related outcome (Tables II and V). Only 2 studies reported a statistically significant active versus placebo difference in a symptom score or symptom-related efficacy criterion: daily, nighttime, and daytime asthma scores for Niu et al⁴⁷ over 6 months at an unspecified time of year and mean number of asthma attacks per month for Pajno et al,⁵⁰ with 12 months of treatment starting in January. Devillier et al³² found a significantly greater proportion of more well-controlled asthma in a subgroup of treated patients with moderate asthma (vs placebo) over 20 weeks at an unspecified time of year. The primary end point for the overall study population (ie, including patients with mild asthma) was negative. The latter study also stood out because it was the first to use asthma control as an efficacy criterion in HDM SLIT. Given the small number of

studies and the frequent lack of data on major allergen maintenance doses, there was no obvious relationship between dose and efficacy. The study by Pajno et al⁵⁰ featured one of the lowest daily maintenance doses (0.8 µg of Der p 1) but one of the most striking active versus placebo differences ($P = .0001$).

Safety. Most publications did not report on safety at all or merely stated that no or few TEAEs had been observed (see Table E2). The only serious adverse event (AE) reported was a severe exacerbation of asthma in 1 patient in the placebo group in the study by Pham-Thi et al.⁵⁵ In the most detailed report³⁰ the active treatment and placebo groups did not differ markedly in terms of the TEAE rate (55% and 60%, respectively). Treatment compliance was either not measured or not reported, although most publications mention the use of diary cards for recording doses and events.

Patient values. Only 2 publications reported on QoL, with use of the 21-item Childhood Asthma Questionnaire by Pham-Thi et al⁵⁵ and the 20-Item Short Form Health Survey tool (in participants aged ≥15 years) by Bousquet et al.²⁶ Pham-Thi et al⁵⁵ found that the "severity" dimension of QoL was significantly ($P = .04$) better in younger children (age 6-11 years) receiving active treatment (vs placebo) but not in older children (age 12-16 years). Bousquet et al²⁶ reported that after 24 months of treatment, the "general perception of health" and "physical pain" QoL dimensions were significantly better in actively treated participants (vs placebo-treated patients).

Pediatric studies. Strikingly, 10 of the 14 studies were performed in children alone, with 3 performed solely in adults^{30,32,46} and one performed in both children and adults.²⁶

AR induced by HDMs

SCIT in patients with HDM-induced rhinitis. Study design. Seven studies (7 treatment arms) were selected (Table III). The number of randomized participants per study

TABLE I. Study design, study product, and efficacy of SCIT in patients with HDM-induced AA

Lead author, year of publication, study population	Product name and manufacturer, type of mite extract	Reported or calculated maintenance and cumulative doses (μg of major allergen)	Population age (years; mean $\pm$ SD or mean [range])
Yukselen et al, 2012, ⁶⁴ pediatric study	NovoHelisen Depot, Allergopharma, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: NR; cumulative: NR	10.9 $\pm$ 3.2 Ac, 10.1 $\pm$ 2.7 PI
Blumberga et al 2006, ²⁴	ALK-Abelló Alutard SQ, <i>D pteronyssinus</i>	Maintenance: 9.8 μg of Der p 1; cumulative: 68.6 μg of Der p 1	29.8 $\pm$ 10.7 Ac, 28.5 $\pm$ 7.1 PI
Wang et al, 2006 ⁶²	ALK-Abelló Alutard SQ, <i>D pteronyssinus</i>	Maintenance: 9.8 μg of Der p 1; cumulative: 142 μg of Der p 1	16.8 Ac, 17.8 PI
Garcia-Robaina et al, 2006 ³⁸	Laboratorios LETI, <i>D pteronyssinus</i> and <i>D farinae</i> mixture (50:50) of modified extracts	Maintenance: 17.5 μg of "Der p," cumulative: 250 μg of "Der p"	23.5 (9.3) Ac, 23.8 (7.7) PI
Ameal et al, 2005 ²¹	Laboratorios LETI, modified <i>D pteronyssinus</i> extract (allergoid)	Maintenance: NR, cumulative: NR	Mean, 23; no separate Ac and PI data
Maestrelli et al, 2004 ⁴³	ALK-Abelló, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: NR, cumulative: NR	20.2 $\pm$ 8.1 Ac, 23.4 $\pm$ 9.8 PI
Pichler et al, 1997 ⁵⁶	ALK-Abelló, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 9.8 μg of Der p 1, cumulative: NR	28.8 Ac, 31.7 PI
Olsen et al, 1997 ⁴⁹	ALK-Abelló, <i>D pteronyssinus</i> or <i>D farinae</i>	Maintenance: 7 μg of Der p 1 or 10 μg of Der f 1, cumulative: 72 μg of Der p 1	32.0 (18-56) Ac, 40.7 (22-54) PI
Peroni et al, 1995, ⁵⁴ pediatric study	Stallergenes Alpare, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	Not reported separately; 10.8 $\pm$ 2.0 for whole population
Franco et al, 1995 ³⁵	Stallergenes Alpare, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	23 $\pm$ 8.5 Ac, 26 $\pm$ 13.3 PI
Bousquet et al, 1985 ²⁵	Stallergenes, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	29.1 $\pm$ 4.8 Ac, 27.1 $\pm$ 5.9 PI
Pauli et al, 1984 ⁵³	Bencard Migen R, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	28.7 $\pm$ 6.5 Ac, 25.22 $\pm$ 7.3 PI
Blainey et al, 1984 ²³	Bencard, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	NR
Buchanan et al, 1980, ²⁹ group A	Bencard HDM, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	44.3 $\pm$ 8.3 Ac, 40.4 $\pm$ 11.0 PI
British Thoracic Association, 1979, ²⁸ group A	Bencard, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	Not reported separately; 10.8 $\pm$ 2.0 for whole population
British Thoracic Association, 1979, ²⁸ group B	Bencard, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	Not reported separately; 10.8 $\pm$ 2.0 for whole population
Warner et al, ⁶³ 1978, pediatric study	Bencard Migen, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	10.5 Ac, 10 PI
Gaddie et al, ³⁷ 1976	Bencard Migen, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	34 (15-68) Ac, 33 (13-68) PI
D'Souza et al, ³⁴ 1973	Beecham Laboratories, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	NR
Smith and Pizarro, ⁴⁵ 1972	Beecham Laboratories, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	NR

Ac, Active immunotherapy; BH, bronchial hyperresponsiveness; BPT, bronchial provocation test; CPT, conjunctival provocation test; FVC, forced volume capacity; IQR, interquartile range; ISS, individual symptom score; ITT, intention to treat; NR, not reported in the publication; NS, not significant; PEFR, peak expiratory flow rate; PI, placebo; PP, per-protocol; R, randomized; TSS, total symptom score; T3SS, 3-component total symptom score; T4SS, 4-component total symptom score; T6SS, 6-component total symptom score.

*Number of subjects in the active/placebo groups in the randomized, intention-to-treat, and per-protocol populations.

TABLE I. (Continued)

No. R, ITT (Ac/PI), PP (Ac/PI)*	Mean treatment time (mo) and frequency of administration	Efficacy score (active vs placebo) and P value	Secondary efficacy parameters examined
32, (10,10), (10,10)	12, Monthly	Symptom score, graphic data only, $P = .01$	SPT, NPT, bronchial provocation
54, (26,28), (20,25)	38, Every 6 $\pm$ 2 wk	Inhaled HDM allergen dose required for a 20% decrease in bronchial hyperresponsiveness, graphic data only (year 1: $P = .0089$; year 2: $P = .0001$; year 3: $P = .0319$)	Symptoms (VAS)/rescue use/PEFR/SPT
132, (66,66), (64,65)	11.5, Every 1-6 wk, decreasing in frequency; 22 injections over 12 mo	Daytime T4SS range: 0-20; 0.178 ± 0.032 Ac vs 0.397 ± 0.085 PI, $P = .019$	PEFR, BH, SPT, exacerbation, IgE (total and specific)
64, (NR,NR), (27,27)	12.5, Monthly	Bronchial provocation test (dose for 20% decrease in FEV ₁), 111.06 (IQR, 41.05-686.00) Ac vs 41.00 (IQR, 3.35-311.00) PI, $P = .029$	Bronchial, nasal and ocular, ISSs, TSS, corticoid score, VAS
63, (32,31), (29,26)	12.5, Weekly for 6 wk and then monthly	Bronchial provocation test (PD ₂₀ FEV ₁), 7.14 (IQR, 4.29-14.38) Ac vs 2.76 (IQR, 1.50-10.81) PI, $P = .029$	SPT, symptom score, medication score
95, (NR,NR), (41,31)	36, Every 3 wk	Daytime and nighttime asthma symptoms, 0-3, summed for each month and then averaged for September-November, graphic data only, $P = NS$	Bronchial responsiveness to methacholine, SPTs, morning PEFR
33, (NR,NR), (16,14)	12, Every 8 wk	Subjective VAS, median of 3.5 (range, 2-9) Ac vs median of 7 (range, 4-49), $P = .0903$	CPT, BPT
31, (21,10), (17,6)	12, Every week during up dosing and then every 6 wk	Mean symptom score per week, graphic data only, $P < .05$	FEV ₁ , FVC, SPT, IgE
23, (12,11), (11,10)	12, Every week during up dosing and then every 4 wk	FEV ₁ : 90.9 ± 9.8 Ac vs 85.1 ± 86.6 PI, $P =$ not significant	SPT, BPT
49, (24,25), (20,19)	15, Every 1-2 wk during up dosing and then every 4-6 wk	Daytime asthma severity: 0.3 ± 0.3 Ac vs 0.4 ± 0.6 PI, $P = NR$	VAS of symptom intensity
30, (20,10), (20,10)	1.75, Rush for 3 d and then weekly	PD ₂₀ FEV ₁ : 96.3 ± 82.1 Ac vs 79.1 ± 93.6 PI, $P < .01$	SPT, IgE, IgG
22, (11,11), (9,9)	12, Monthly	T3SS (range, 0-9) but expressed as a percentage, graphic data only, $P < .05$	PEFR, IgE, IgG, leukocyte histamine release
39, (18,21), (14,9)	11.5, Weekly for 6 wk and monthly for a further 10 mo	T4SS (0-3), scores NR, $P = NR$	IgE, IgG, NPT, VAS, overall assessment
37, (19,18), (15,16)	7.5, Weekly for 6 wk and monthly for a further 6 mo	Weekly and monthly questionnaires on symptoms and improvement, 73 Ac vs 77 PI, $P = NS$	Number of asthma attacks
46, (24,22), (14,17)	4.5, Weekly for 18 wk	Daytime asthma at 24 mo, graphic data only, $P = NS$	IgG, IgE, SPT, NPT, daytime asthma, nighttime asthma, FEV ₁
46, (24,22), (15,17)	18, Weekly for 18 wk and then monthly up to 18 mo	Daytime asthma at 24 mo, graphic data only, $P = NS$	IgG, IgE, SPT, NPT, daytime asthma, nighttime asthma, FEV ₁
56, (28,28), (27,24)	12, Weekly for 6 wk and then every 8 wk	T4SS (0-3) over 2 mo, graphic data only, $P = NR$	PEFR, FEV ₁ , thoracic gas volume
55, (26,29), (20,25)	12, Weekly for 6 wk and then monthly	T6SS (0-4), not reported, $P = NS$	FEV ₁ , FVC
96, (48,48), (45,46)	3, Weekly	"Asthma improved" self-assessment, percentage of patients, 62.5 Ac vs 33 PI, $P = .02$	IgE, IgG, leukocyte histamine release, SPT
30, (17,13), (17,13)	3.75, NR	Physician's assessment of improvement, 4 improved and 13 did not Ac vs 7 improved and 6 did not PI, $P = NR$	Patient's assessment, total IgE

TABLE II. Study design, study product, and efficacy of SLIT in patients with HDM-induced AA

Lead author, year of publication, study population	Product name and manufacturer, type of mite extract	Reported or calculated maintenance and cumulative doses (μg of major allergen)	Population age (y; mean $\pm$ SD or mean [range])
Devillier et al, ³² 2013	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 28 μg of Der p 1 and 50 μg of Der f 1; cumulative: 10,267 of μg Der p 1 and 18,333 μg of Der f 1	31.2 $\pm$ 9.0 Ac, 31.3 $\pm$ 8.2 PI
Yukselen et al, ⁶⁴ 2012, pediatric study	Allergopharma, NovoHelisen Oral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: NR; cumulative: NR	9.2 $\pm$ 3.4 Ac; 10.1 $\pm$ 2.7 PI
Bush et al, ³⁰ 2011 (high dose)	Greer Laboratories, <i>D farinae</i>	Maintenance: 70 μg ; cumulative: 23,695 μg	30.6 (18-50)
Bush et al, ³⁰ 2011 (low dose)	Greer Laboratories, <i>D farinae</i>	Maintenance: 1 μg ; cumulative: 338 μg	30.6 (18-50)
Tseng et al, ⁶⁰ 2008, pediatric study	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 12.5 μg ; cumulative: 1,560 μg	9.7 $\pm$ 3.3 Ac, 9.7 $\pm$ 3.0 PI
Pham-Thi et al, ⁵⁵ 2007, pediatric study	Stallergenes, tablets with <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 27 μg of Der p 1 and 57 μg of Der f 1; cumulative: 6,900 μg of Der p 1 and 14,700 μg of Der f 1	9.6 (5-14) Ac, 9.5 (5-16) PI
Niu et al, ⁴⁷ 2006, pediatric study	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i> drops	Maintenance: NR; cumulative: 1,700 μg of Der p 1 and 3,000 μg of Der f 1	7.9 (1.6) Ac, 8.2 (1.7) PI
Lue et al, ⁴² 2006, pediatric study	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i> drops	Maintenance: NR; cumulative: 1,700 μg of Der p 1 and 3,000 μg of Der f 1	7.7 (1.8) Ac, 8.6 (1.8) PI
Marcucci et al, ⁴⁴ 2005, pediatric study	ALK-Abelló, NR	Maintenance: 0.8 μg of mite allergen group 1 and 0.4 μg of mite allergen group 2; cumulative: 110 and 55 μg of mite allergens group 1 and 2	7.7 Ac, 7.3 PI
Ippoliti et al, ⁴¹ 2003, pediatric study	ALK-Abelló, <i>D pteronyssinus</i> ; no information on <i>D farinae</i>	Maintenance: 0.8 μg of Der p 1; cumulative: 60 μg of Der p 1	Median (range): 9 (5-12) Ac, 9 (7-11) PI
Bahçeciler et al, ²² 2001, pediatric study	Stallergenes, <i>D pteronyssinus</i> and <i>D farinae</i> drops	Maintenance: 8 μg of "Der p"; cumulative: 560 μg of "Der p"	11.7 $\pm$ 3.3
Pajno et al, ⁵⁰ 2000, pediatric study	ALK-Abelló, <i>D pteronyssinus</i> ; no information on <i>D farinae</i>	Maintenance: 0.8 μg of Der p 1; cumulative: 249 μg of Der p 1	Mean (range): 11 (8-14) Ac, 12 (8-15) PI
Mungan et al, 1999 ⁴⁶	Stallergenes, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 9 μg of Der p 1; cumulative: 1,018 μg of Der p 1	31.67 $\pm$ 7.28 Ac, 33.27 $\pm$ 8.45 PI
Bousquet et al, ²⁶ 1999	Stallergenes, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 24 μg of Der p 1; cumulative: 4,200 μg of Der p 1	31 $\pm$ 10 Ac, 22 $\pm$ 10 PI
Giovane et al, ³⁹ 1994, pediatric study	Allergopharma, <i>D pteronyssinus</i>	Maintenance: NR; cumulative: NR	6.56 $\pm$ 1.97 Ac, 6.08 $\pm$ 2.39 PI

Ac, Active immunotherapy; ACTH, adrenocorticotrophic hormone; BPT, bronchial provocation test; CPT, conjunctival provocation test; ECP, eosinophil cationic protein; ICS, intranasal corticosteroid; ITT, intention to treat; LFT, lung function test; NR, not reported in the publication; NS, not significant; PEFR, peak expiratory flow rate; PI, placebo; PP, per-protocol; R, randomized; T3SS, 3-component total symptom score; T4NSS, 4-component total nasal symptom score.

*Number of subjects in the active/placebo groups in the randomized, intention-to-treat, and per-protocol populations.

ranged from 32⁶⁴ to 145⁵⁷ (median number, 39; first-third quartile, 34-56), and the treatment duration ranged from 11.5 months²³ to 24 months³³ (Table III and see the Results section in this article's Online Repository). When reported, the maintenance dose of allergen ranged from 7 μg of Der p 1⁶¹ to 30 μg of Der p 2,⁵⁷ and the cumulative dose ranged from approximately 60 μg of Der p 1 to approximately 1420 μg of Der p 2. There was great heterogeneity in injection frequency and the month of

treatment initiation (Table III and see the Results section in this article's Online Repository).

Treatment efficacy. Three of the 7 studies provided evaluable numeric data on a symptom score or a symptom-related outcome (Tables III and V). Three studies (not the same 3 referred to in the previous sentence) reported a statistically significant active versus placebo difference in at least 1 symptom score or symptom-related score: a symptom score over 12 months,⁶⁴ a

TABLE II. (Continued)

No. of R, ITT (Ac/PI), PP (Ac/PI)*	Mean treatment time (mo) and frequency of administration	Efficacy score (active vs placebo) and P value	Secondary efficacy parameters examined
465, (322,162), (308,157)	12, Daily	Number of weeks with well-controlled asthma between treatment weeks 32 and 52; 85.4 Ac and 81.5 PI; $P = \text{NS}$	Totally controlled asthma, ICS dose, number of exacerbations, QoL, LFT, specific IgE
32, (11,10), (10,10)	12, Daily	Symptom score, graphic data only, $P = \text{NS}$	SPT, NPT, BPT
31, (10,11), (9,5)	12, Daily	Symptom score, graphic data only, $P = \text{NS}$	IgG ₄ , BPT
31, (10,11), (7,5)	12, Daily	Symptom score, graphic data only, $P = \text{NS}$	IgG ₄ , BPT
63, (30,3), (28,31)	6, Daily	T4NSS, not reported, NS Ac vs PI difference in β_2 -agonist (puffs/d)	SPT, IgG ₄ , IgE
111, (54,55), (44,48)	18, Daily	"Rhinitis daily score," 0.12 ± 0.14 Ac vs 0.17 ± 0.19 PI, $P = \text{NS}$	Inhaled steroids, PEFR variability, FEV ₁
110, (NR,NR), (49,48)	6, Daily	Daily, nighttime and daytime asthma scores, $0.04 \pm \text{NR}$ Ac vs $0.06 \pm \text{NR}$ PI, $P = .011$	Total serum IgE and specific IgE, global assessment by physician
20, (10,10), (10,10)	6, Daily	Nighttime and daytime asthma scores (0-3 per day), 0.13 ± 0.19 Ac vs 0.49 ± 0.38 PI, $P = .058$	SPT, PEFR, FEV ₁ , eosinophil count, eosinophil cationic protein concentration
24, (13,11), (13,11)	12, Every other day	Rhinitis severity (0-3), monthly sum, $44 \pm (10-103)$ Ac vs $35 \pm (2.5-93.5)$ PI, $P = .8093$	NPT, nasal tryptase, tryptase in sputum, eosinophil cationic protein concentration
86, (47,39), (47,39)	6, 3/wk	Asthma SS: scale described by Tari et al, ⁵⁸ $1.28 \pm \text{NR}$ Ac vs $3.15 \pm \text{NR}$ PI, NR	FEV ₁ , rhinitis, serum prolactin, ACTH, ECP, IL-13, CD40 ⁺ cells
15, (8,7), (8,7)	6, Twice a week	Asthma T3SS for last 4 mo of treatment; median of 0.3 (range, 0.01-1.44) Ac vs median of 0.26 (range, 0-0.7) PI, $P = .77$	LFTs, specific IgE, β_2 -memetic use, patient impression of frequency of symptoms, BPT
24, (12,12), (12,9)	24, 3/wk	Medication score, $0.68 \pm \text{NR}$ Ac vs $1.3 \pm \text{NR}$ PI, $P = .0001$	Number of asthma attacks, nighttime symptoms, VAS overall AA symptoms, IgE
26, (15,11), (15,11)	12, Every day for a month and then 2 d/wk	Eyes, nose, lungs (each 0-3 per day); median in last 6 mo of treatment: $0.41 \pm \text{NR}$ Ac vs $0.88 \pm \text{NR}$ PI (no comparison)	SPT, IgE, BPT
85, (42,43), (23,27)	24, Every day for 4 wk and then 3 d/wk	Daytime asthma (0-3 per day), 0.17 ± 0.5 Ac vs 0.19 ± 0.44 PI, $P = \text{NS}$	FEV ₁ PD ₂₀ , IgE, IgG ₄
18, (10,8), (10,8)	36, 3/wk	Asthma, cough and rhinitis, conjunctivitis, graphic data only, NR	CPT, SPT, IgE, IgG ₄

clinical index over 12 months,⁵⁷ and a patient-scored nasal VAS after 12 months.⁵⁶ Given the small number of studies and the frequent lack of data on major allergen maintenance doses, there was no obvious relationship between dose and efficacy.

Safety. The general quality of safety reporting was very poor (see Table E2). The 2 earliest publications^{23,36} each featured 1 anaphylactic reaction caused by SCIT. More recent trials did not observe anaphylactic reactions. Dokic et al³³ and Yuskelen

et al⁶⁴ stated the complete absence of systemic adverse reactions in their study groups. In the study reported by Varney et al,⁶¹ 7 systemic AEs occurred (in a total of 3 patients) during the updos-ing. The reactions were described as "mild," but at least some were treated with sublingual epinephrine.

Patient values. The study by Riechelmann et al⁵⁷ was the only one to administer a QoL instrument (the Rhinitis Quality of Life Questionnaire⁶⁵), with significantly better scores in the

TABLE III. Study design, study product and efficacy of SCIT in patients with HDM-induced AR

Lead author, year of publication, study population	Product name and manufacturer, type of mite extract	Reported or calculated maintenance and cumulative doses (μg of major allergen)	Population age (y; mean $\pm$ SD or mean [range])
Yukselen et al, 2012, ⁶⁴ pediatric study	NovoHelisen Depot, Allergopharma, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: NR, cumulative: NR	10.9 $\pm$ 3.2 SCIT; 10.1 $\pm$ 2.7 PI
Riechelmann et al, ⁵⁷ 2010	PURETHAL Mites, HAL, glutaraldehyde-modified <i>D pteronyssinus</i>	Maintenance: 30 μg of Der p 2, cumulative: 420 μg of Der p 2	29.31 $\pm$ 8.1 Ac, 30.25 $\pm$ 9.56 PI
Dokic et al, ³³ 2005	NR, <i>D pteronyssinus</i> allergoid	Maintenance: NR, cumulative: NR	27 (18-57) Ac, 33 (18-62) PI
Varney et al, ⁶¹ 2003	ALK-Abelló Alutard-SQ, <i>D pteronyssinus</i>	Maintenance: 7 μg of Der p 1, cumulative: 106 μg of Der p 1	33 (19-48) Ac, 37 (23-55)
Pichler et al, ⁵⁶ 1997	ALK-Abelló, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 9.8 μg of Der p 1, cumulative: 58.8 μg of Der p 1	28.8 Ac, 31.7 PI
Blainey et al, ²³ 1984	Bencard, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	NR
Gabriel et al, ³⁶ 1977	Bencard Migen, <i>D pteronyssinus</i>	Maintenance: NR, cumulative: NR	NR

Ac, Active immunotherapy; BPT, bronchial provocation test; CPT, conjunctival provocation test; ITT, intention to treat; NR, not reported in the publication; NS, not significant; PI, placebo; PP, per protocol; R, randomized; T4SS, 4-component total symptom score.

*Number of subjects in the active/placebo groups in the randomized, intention-to-treat, and per-protocol populations.

active group in the nose-related symptoms, practical problems, and emotional condition domains.

Pediatric studies. The trial by Yukselen et al⁶⁴ was the only children-only study. It yielded a statistically significant active versus placebo difference in symptom score. The study by Gabriel et al³⁶ reportedly included patients as young as 8 years of age but did not report a significant symptom score benefit versus placebo.

SLIT in patients with HDM-induced rhinitis. Study design. Fifteen studies (16 treatment arms) featured between 15 and 257 randomized participants per study (median number, 32; first-third quartile, 29-69; Table IV). The study by de Bot et al³¹ stood out in this respect, with 257 randomized participants. The earliest studies only required a clinical history of AR as an inclusion criterion. More recent studies have featured a variety of inclusion criteria, as follows: a 4-symptom total symptom score of greater than 70 of 168 over the last 2 weeks of a screening period,⁵⁹ mild AR according to the Allergic Rhinitis and its Impact on Asthma classification,⁵² and a rhinitis symptom score of at least 4 of 12 during the 3 months preceding the start of the study.³¹ Nine of the 15 studies incorporated a nasal or bronchial HDM allergen provocation test as an inclusion criterion, efficacy criterion, or both. Only one of the 15 provided information on calculation of the prespecified sample size. Eleven of the 15 excluded patients cosensitized to other relevant allergens or with clearly confounding symptoms. The only 2 studies that did not use drop formulations of SLIT were those performed by Passalacqua et al⁵² (tablets of monomeric carbamylated allergoids) and Pham-Thi et al⁵⁵ (unmodified *D pteronyssinus* and *D farinae* extract tablets). Eleven of the 15 studies reported on the major allergen content in the maintenance dose, which varied from 0.8 μg of Der p 1 to 70 μg of Der f 1 and was mostly between 9 and 27 μg of Der p 1. Given that the treatment periods ranged from 6 months⁶⁰ to 24 months³¹ and treatment frequencies ranged from daily to 2 days a week⁵² and 3 days a week,⁴⁰ the cumulative doses of allergen showed great disparities. The value of 110 μg of

group 1 allergens reported by Marcucci et al⁴⁴ was more than 200-fold lower than the amount of 23,695 μg of Der f 1 reported by Bush et al³⁰ in the 12-month “high-dose” group, even though both studies featured a 12-month treatment period. When stated, the treatment initiation date was variable: November,⁵⁵ November to January,⁴⁰ January,⁴⁴ February to August,³⁰ and April.⁵²

Treatment efficacy. Reporting was poor. Eight of the 15 studies provided evaluable numeric data on a symptom score or a symptom-related outcome (Tables IV and V). Only 2 studies reported a statistically significant active versus placebo difference in a symptom score or symptom-related efficacy criterion. Tonnel et al⁵⁹ found a significant difference in favor of active treatment for the area under the curve of a 4-component total nasal symptom score (<0.03) after 12 months of administration of a maintenance dose with 9 μg of Der p 1 but did not provide numeric data. In the same study the intergroup difference in the medication score was not significant. In the 24-month study by Passalacqua et al⁵³ (starting in November to February) using carbamylated allergoid tablets of undefined dose, the investigators found a statistically significant active versus placebo difference in a 7-component total symptom score (without quoting values) for the first year of the study ($P = .027$) but not the second. The same pattern was seen for the medication score.

Safety. The quality of safety reporting was moderate (see Table E2), although some researchers did not comment in detail on the types of AEs experienced in the active treatment and placebo groups. Bahçeciler et al²² did not observe any AEs of note with a maintenance dose of 8 μg of “Der p” allergens in children and adolescents. In contrast, de Bot et al³¹ studied a maintenance dose of 2 μg of Der p 1 allergen and reported that 96% of both active and placebo group patients experienced TEAEs (including a high proportion of nonlocal AEs). Nevertheless, no immunotherapy-dependent serious AEs were reported in any of the active groups.

TABLE III. (Continued)

No. R, ITT (Ac/PI), PP (Ac/PI)*	Mean treatment time (mo) and frequency of administration	Efficacy score (active vs placebo) and <i>P</i> value	Secondary efficacy parameters examined
32, (10,10), (10,10)	12, Monthly	Symptom score, graphic data only, <i>P</i> = .03	SPT, NPT, BPT
145, (66,74), (62,55)	12, Monthly	Change in clinical index score (combined score), 1.09 ± 0.7 Ac vs 0.75 ± 0.8 PI, <i>P</i> = .011	SSs for eyes, nose, and airways; number of symptom-free persons; threshold of CPT; IgG and IgE
40, (20,20), (20,20)	24, Every 4-8 wk	Composite score: rank sum of VAS of health + physician's assessment of symptoms after 12 and 24 mo, 96.2 ± 10.9 Ac vs 93.3 ± 8.7 PI, <i>P</i> = NS	NPT, SPT, physician's overall assessment
36, (NR,15), (NR,13)	14.5, Weekly for 8-10 wk and then monthly for 1 y	Total symptom score, 72 ± 26 Ac vs 132 ± 48 PI, <i>P</i> = NS	SPT, nasal medication, chest medications
33, (NR,NR), (16,14)	12, Every 2 mo	Subjective VAS: median of 8 (range, 3-21) Ac vs median of 26 (range, 10-45) PI, <i>P</i> = .0393	CPT, BPT
39, (18,21), (17,18)	11.5, Weekly for 6 wk and monthly for a further 10 mo	VAS symptoms, graphic data only, NR	IgE, IgG, NPT
72, (37,35), (27,29)	12, Weekly during up dosing and then monthly	T4SS (0-3), NR, <i>P</i> = NS	SPT, NPT, IgE, IgG, physician's assessment, eosinophil counts

Patient values. Four SLIT studies reported on QoL. de Bot et al³¹ scored the pediatric (6-11 years) and adolescent (12-17 years) versions of the Rhinitis Quality of Life Questionnaire. O'Hehir et al⁴⁸ used the same tool in adults and found that QoL improved more so in the active treatment group (*P* < .001) than in the placebo group (*P* < .01) at 12 and 24 months. Pham-Thi et al⁵⁵ administered the Childhood Asthma Questionnaire but did not observe statistically significant between-group differences. Passalacqua et al⁵² administered the 36-Item Short Form QoL questionnaire and the Satisfaction Profile tool (a nonspecific 32-item questionnaire about daily life); the baseline QoL levels were very high in both groups, and there was no significant between-group difference.

Pediatric studies. Seven of the 15 studies concerned children, and all had treatment periods of greater than 18 months. However, none reported a statistically significant active versus placebo difference in a symptom score or symptom-related efficacy criterion.

DISCUSSION

This article reports an EBM-based approach to determining the nature and quantity of evidence for commercially available AIT modalities for the treatment of HDM-induced AR and AA. This EBM approach complements previous meta-analyses and systematic reviews because it examines critical quality indicators and identifies opportunities for methodological improvements. There was marked interstudy heterogeneity in terms of primary and secondary efficacy criteria, the detail of reporting, inclusion criteria, population profiles, allergen dose, characterization of the AIT formulation, treatment duration, treatment initiation dates, baseline observation periods, initial disease severity, and primary and secondary efficacy criteria (Tables I-V and see the Results section in this article's Online Repository). Given the frequent lack of detailed numeric information on efficacy outcomes (from often small and sometimes poorly designed studies), a

meta-analysis might not yield an accurate estimation of HDM AIT effect size.

The shortcomings of the clinical studies reviewed here prompted the following summary and suggestions.

- Few multicenter, international, and/or well-powered large trials.** HDM AIT for allergic respiratory diseases is still poorly documented because of limited understanding of the peculiarities of HDM-induced allergies. Most of the 44 selected publications reported on single-center studies, and only 1 study was multinational.⁵⁷ The SLIT studies included more randomized patients in total than the SCIT studies (1960 and 1384, respectively). Only 9 of the 44 selected studies described their prospective statistical power calculations. *Potential improvements:* Today's regulatory framework⁶⁶ requires suppliers of HDM AIT products to perform large multicenter trials with sufficient statistical power. This process now appears to be underway for HDM AIT, with the publication of several abstracts and trial registrations.⁶⁷⁻⁶⁹ Clinical development will produce improvements in pharmaceutical standardization and in manufacturing and treatment regimens. Although DBPC RCTs will remain the gold standard for estimating treatment effects, there is still a role for high-quality open controlled trials.
- Ill-defined criteria for disease status/severity on inclusion.** Most patients in AA trials had AR, and most patients in AR trials had AA, which might modify the efficacy and occurrence of AEs. *Potential improvements:* A poorly detailed "history" of symptoms is not a sufficient inclusion criterion. Disease severity and disease control scores should be used for AA and AR. Although logistically complex, a specific allergen challenge constitutes a more objective proof of the cause of the allergic disease than SPT responses, specific IgE levels, or both. Controlled allergen

TABLE IV. Study design, study product, and efficacy of SLIT in patients with HDM-induced AR

Lead author, year of publication, study population	Product name and manufacturer, type of mite extract	Reported or calculated maintenance and cumulative doses (μg of major allergen)	Population age (y; mean $\pm$ SD or mean [range])
Bozek et al, ²⁷ 2013	Stallergenes Staloral 300, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 48 μg of Der p 1 and 102 μg of Der f 1, cumulative: 37,908 μg of Der p 1 and 80,028 μg of Der f 1	65.78 $\pm$ 4.89 Ac, 66.71 $\pm$ 3.77 PI
Yukselen et al, ⁶⁴ 2012, pediatric study	NovoHelisen Oral, Allergopharma, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: NR, cumulative: NR	9.2 $\pm$ 3.4 SLIT; 10.1 $\pm$ 2.7 PI
de Bot et al, ³¹ 2012, pediatric study	Oralgen Mijten, Artu Biologicals, <i>D pteronyssinus</i>	Maintenance: 2.03 μg of Der p 1, cumulative: 435 μg of Der p 1	11.7 $\pm$ 3.0
Bush et al, ³⁰ 2011 (high dose)	Greer Laboratories, <i>D farinae</i> in 50% glycerinated saline	Maintenance: 70 μg of Der f 1, cumulative: 23,695 μg of Der f 1	30.6 whole group
Bush et al, ³⁰ 2011 (low dose)	Greer Laboratories, <i>D farinae</i> in 50% glycerinated saline	Maintenance: 1 μg of Der f 1, cumulative: 338 μg of Der f 1	30.6
O'Hehir et al, ⁴⁸ 2009	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 48 μg of Der p 1 and 9.6 μg of Der f 1, cumulative: 17,076 μg of Der p 1 and 3,414 μg of Der f 1	28.5 (8.2) Ac, 37.6 (11.1) PI
Tseng et al, ⁶⁰ 2008, pediatric study	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 27 μg of Der p 1 and 57 μg of Der f 1, cumulative: 3,360 μg of Der p 1 and 7,089 μg of Der f 1	9.7 $\pm$ 3.3 Ac, 9.7 $\pm$ 3.0 PI
Pham-Thi et al, ⁵⁵ 2007, pediatric study	Stallergenes, tablets with <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 27 μg of Der p 1 and 57 μg of Der f 1, cumulative: 6,900 μg of Der p 1 and 14,700 μg of Der f 1	9.6 (5-14) Ac, 9.5 (5-16) PI
Passalacqua et al, ⁵² 2006	Lofarma S.p.A., tablets of modified allergen extract (monomeric carbamylated allergoid [Lais])	Maintenance: NR, cumulative: NR	30.64 Ac, 33.64 PI
Marcucci et al, ⁴⁴ 2005, pediatric study	ALK-Abelló, NR	Maintenance: "0.8 μg of mite allergen group 1 and 0.4 μg of mite allergen group 2," cumulative: "110 and 55 μg of mite allergen groups 1 and 2, respectively"	7.7 Ac, 7.3 PI
Tonnel et al, ⁵⁹ 2004	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 9 μg of Der p 1, cumulative: 4,275 μg of Der p 1	23 $\pm$ 8.6 Ac, 20.9 $\pm$ 8.1 PI
Bahçeciler et al, ²² 2001, pediatric study	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 8 μg of "Der p," cumulative: 5,600 μg of "Der p"	11.7 $\pm$ 3.3 for study population
Guez et al, ⁴⁰ 2000	Stallergenes Staloral, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 27 μg of Der p 1 and 57 μg of Der f 1, cumulative: 2,200 μg of Der p 1 and 1,700 μg of Der f 1	29.6 $\pm$ 12.4 Ac, 22.7 $\pm$ 10.7 PI
Mungan et al, ⁴⁶ 1999, SLIT AR	Stallergenes, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: 9 μg of Der p 1, cumulative: 1,018 μg of Der p 1	31.67 $\pm$ 7.28 Ac, 33.27 $\pm$ 8.45 PI
Passalacqua et al, ⁵¹ 1998	Lofarma S.p.A, modified (allergoids) <i>D pteronyssinus</i> and <i>D farinae</i> extract	Maintenance: NR, cumulative: NR	Median (range): 25 (15-37) Ac, 27.2 (17-46) PI
Tari et al, ⁵⁸ 1990, pediatric study	Neo Abelló, <i>D pteronyssinus</i> and <i>D farinae</i>	Maintenance: NR, cumulative: NR	NR

Ac, Active immunotherapy; AUC, area under the curve; BPT, bronchial provocation test; CPT, conjunctival provocation test; ECP, eosinophil cationic protein; ICAM-1, intercellular adhesion molecule 1; ITT, intention to treat; LFT, lung function test; NIPF, nasal inspiratory peak flow; NR, not reported in the publication; NS, not significant; PEFR, peak expiratory flow rate; PI, placebo; PP, per protocol; R, randomized; TSS, total symptom score.

*Number of subjects in the active/placebo groups in the randomized, intention-to-treat, and per-protocol populations.

challenge of a large number of participants in a dedicated facility might be preferable to individual challenges.^{70,71}

- **Lack of consensus on the therapeutic dose used for SCIT and SLIT.** There is no obvious dose-effect

relationship. Unfortunately, after more than 40 years of DBPC HDM AIT investigations, the basic treatment parameters for this modality (dose, duration, and regimen) are still not well established. There are few DBPC

TABLE IV. (Continued)

No. R, ITT (Ac/PI), PP (Ac/PI)*	Mean treatment time (mo) and frequency of administration	Efficacy score (active vs placebo) and <i>P</i> value	Secondary efficacy parameters examined
108, (51,57), (47,48)	28.2, 5/wk	Nasal symptom score (VAS), 2.656 ± 0.634 Ac vs 3.975 ± 0.601 PI, <i>P</i> = .011	IgE, NPT
32, (11,10), (10,10)	12, Daily	Symptom score, graphic data only, <i>P</i> = NS	SPT, NPT, bronchial provocation
257, (110,116), (92,93)	24, Twice weekly	T4NSS, 2.26 ± 1.84 Ac vs 2.02 ± 1.67 PI, <i>P</i> = .08	Well days, symptom-free days, rescue days, eye SS, TSS
31, (10,11), (9,5)	12, Daily	Symptom scores and medication scores, graphic data only, <i>P</i> = NS	IgG ₄ , BPT
31, (10,11), (7,5)	12, Daily	Symptom scores and medication scores, graphic data only, <i>P</i> = NS	IgG ₄ , BPT
30, (15,15), (13,14)	12, Daily	Rhinitis symptom score, graphic data only, NR	Combination score (symptoms + medication) for asthma
63, (30,33), (28,31)	6, Daily	Change in T4NSS, 1.72 ± 1.78 Ac vs 1.89 ± 1.90 PI, <i>P</i> = NS	SPT diameter, IgG ₄ , IgE
111, (54,55), (44,48)	18, Daily	Rhinitis symptom score, 0.71 ± 0.76 Ac vs 0.5 ± 0.58 PI, <i>P</i> = NS	Inhaled steroids, rhinitis score, PEFr variability, FEV ₁
68, (NR,NR), (28,28)	24, 2/wk	T7SS, graphic data only, <i>P</i> = .027 year 1, <i>P</i> = NS year 2	Nasal obstruction
24, (13,11), (13,11)	12, Daily	Rhinitis, 265 (198-684) Ac vs 304 (143-644) PI, <i>P</i> = .9078	NPT, nasal tryptase, tryptase in sputum, eosinophil cationic protein concentration
32, (15,17), (10,8)	24, Daily	AUC T4NSS per month, graphic data only, <i>P</i> < .03	NPT, SPT, IgG ₄ , IgE
15, (8,7), (8,7)	6, Twice a week	Rhinitis for last 4 mo of treatment, median of 0.4 (range, 0.08-1.12) Ac vs median of 0.38 (range, 0-1.02) PI, <i>P</i> = NS	LFTs, specific IgE, β_2 -mimetic use, patient impression of frequency of symptoms, BPT
75, (36,36), (25,14)	24, 3 d/wk	T4NSS, 2.3 ± 1.9 Ac vs 3.2 ± 2.4 PI, <i>P</i> = NS	SPT + IgE
26, (15,11), (15,11)	12, Every day for a month and then 2 d/wk	Eyes, nose, lungs (each 0-3 per day), median in last 6 mo of treatment, 0.5 Ac vs 0.67 PI, NR	SPT, IgE, bronchial provocation
20, (10,10), (10,9)	24, Twice weekly	T8SS, cumulative per month?, graphic data only, NR	CPT, serum ICAM-1, ECP, cell counts
66, (32,34), (30,28)	18, 3/wk	Daily T5SS, summed over a week, graphic data only, NR	NIPF, BPT, IgG ₂ , IgG ₁ , IgG ₄

dose-finding studies⁷²; 2 published dose-finding SCIT trials were not strictly double-blind.^{73,74} Although Bush et al³⁰ did report clinical scores for high- versus low-dose *D farinae* SLIT, their trial was primarily intended to assess safety

and physiologic effects. *Potential improvements.* The maintenance dose in the high-dose group of Bush et al³⁰ (70 μ g of Der f 1 major allergen, the highest maintenance dose used in the selected SLIT studies) was not associated

TABLE V. Population size, efficacy reporting, study duration, and patient-reported outcomes in trials of commercially available HDM AIT modalities in patients with AR and AA

Modality	No. of randomized patients (median [first-third quartile]) per study and total no.	Percentage of "large" studies*	Percentage of studies with more than 12 mo of treatment	Percentage of studies evaluating QoL
SCIT in HDM-induced AA, 19 studies	46 (32-56), total = 987	5%	21%	10%
SLIT in HDM-induced AA, 14 studies	31 (24-85), total = 1110	21%	14%	14%
SCIT in HDM-induced AR, 7 studies	39 (34-56), total = 397	14%	28%	14%
SLIT in HDM-induced AR, 15 studies	32 (29-69), total = 958	13%	46%	26%

Values are rounded down to the nearest whole number.

gp, Group; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

*Percentage of studies in which at least 100 subjects were randomized.

with any allergen-dependent serious AEs. By analogy with the known dose dependency of efficacy and safety profiles in grass pollen SLIT and SCIT, this observation suggests that even higher doses could at least be tested ethically. Large phase IIb dose-ranging studies and phase III pivotal studies^{75,76} of HDM AIT should be performed in adults and (separately) children. If HDM SLIT with even higher doses of major allergens is both effective and safe, one could then conclude that previous studies were significantly underdosed.

- **Differing trial timelines and duration of treatment.** The duration of the clinical studies reviewed here ranged from 6 weeks to 3 years, with a baseline observation period of between 2 weeks and 12 months. The treatment initiation month varied from October to May (ie, every time of year except summer in the northern hemisphere). *Potential improvements:* Trials of HDM AIT should probably run for at least 1 year and preferably 2 to 3 years. The calendar period of treatment initiation should be standardized.
- **Lack of standardized efficacy criteria in asthmatic patients.** Patients with HDM allergy might be used to "coping" with chronic symptoms and downplaying the latter's intensity. Symptom scores could fail to take account of complications of HDM-induced allergic disease, such as poor QoL, poor sleep, the influence of concomitant viral and nonallergic conditions, the use of inhaled corticosteroids, the potential steroid-sparing effect of AIT, and even differences related to asthma phenotypes. *Potential improvements:* The widespread acceptance of the Global Initiative for Asthma classification means that the concept of disease control^{77,78} merits further consideration as a primary end point.^{4,10} Performance of a reliable lung function test (eg, peak expiratory flow rate) by the (trained) patient would then be required in trials with home-based AIT administration.
- **Lack of standardized efficacy criteria in patients with rhinitis.** One can question whether a rhinitis total or nasal symptom score on a 0- to 3-point scale is sufficiently discriminative and responsive in patients with HDM-induced perennial AR. *Potential improvements:* A combined symptom and medication score should be included in HDM AIT trials. The assessment of QoL, disease control, or both in patients with AR could also be

considered because validated, disease-specific tools are available.⁷⁹

- **Lack of information on allergen exposure.** Few of the studies reviewed here measured HDM levels in individual dwellings. With one exception,³⁰ the studies that reported on domestic HDM allergen levels measured baseline (ie, pretreatment) values only. *Potential improvements:* HDM allergen levels should be measured at least once before treatment and once during or after treatment.
- **Few SCIT trials in pediatric populations.** The low number of pediatric SCIT studies selected here might be related to our strict inclusion criteria, notably the need for a true placebo group. In contrast, a high proportion of the selected HDM SLIT studies were performed in children. *Potential improvements:* Ethical concerns and parental wishes make it difficult to gain approval for studies involving placebo injections in children. A strong and positive outcome in just one good study as part of a pediatric investigation plan would justify the use of HDM AIT in children.⁸⁰

The present study has a number of methodological limitations, although many are shared by other systematic reviews, such as poor reporting in the original publications, lack of publication of negative findings, use of publications with abstracts in English, and irretrievable full texts. Many older publications do not report extensively on design and outcomes; this reduces the quality of the evidence for SCIT (as the historically predominant AIT modality) relative to SLIT. As noted above, all the selected studies were based in the northern hemisphere and likely investigated predominantly white populations.

In conclusion, our results show that the most basic parameters of HDM AIT (eg, dose and duration of administration) have yet to be reliably defined. The specific phenotypic features of HDM-induced respiratory disease must be taken into account when designing clinical trials. A statistically significant active versus placebo symptom score was observed more frequently for SCIT than for SLIT. However, the SLIT trials might well have been significantly underdosed in terms of major allergen. For both SLIT and SCIT, there is an urgent need for rigorous, long-term, well-powered RCTs with well-characterized, standardized HDM allergen extracts.⁸¹ This process appears to be underway, with studies examining dosing, treatment onset, effect size, and QoL for sublingual tablet formulations in both patients with AR and

TABLE V. (Continued)

No. (%) of studies reporting a symptom-related outcome	Of those reporting, the percentage with a significant Ac vs PI difference	Maintenance/cumulative doses (μ g of major allergen) in studies with a significant Ac vs PI difference	Maintenance/cumulative doses (μ g of major allergen) in studies without a significant Ac vs PI difference
15 (78%)	9 (60%)	9.9, 9.8, 17.5, 7/68.6, 142, 250, 72	None reported
11 (73%)	2 (19%)	NR, 0.8/1,700, 249	78, 70, 1, 84, 0.8, 8, 24/28,600, 23,698, 338, 21,600, 4,700, 110, 560, 4,200
6 (85%)	3 (50%)	30 (gp 2), 9.8/420 (gp 2), 58.8	7/106
11 (73%)	2 (18%)	150, 9/117,936, 4,275	2.03, 70, 84, 84, 0.8, 8, 84/435, 23,695, 10,449, 21,600, 110, 5,600, 3,900

those with AA.⁶⁷⁻⁶⁹ Although much work remains to be done, this field is moving ahead.

Key messages

- We reviewed 44 studies of HDM immunotherapy for AR and AA.
- There was marked interstudy heterogeneity in terms of primary and secondary efficacy criteria, the detail of reporting, inclusion criteria, population profiles, doses, formulations, and treatment duration for both the subcutaneous and sublingual formulations.
- We identified potential improvements for the clinical investigation of HDM immunotherapy.

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Online Repository.

Search strategy, selection criteria and data extraction

MEDLINE, Embase and the Cochrane Library were searched from January 1965 up until March 2013 using logical combinations of the following terms: allerg*, rhinit*, asthma*, desensiti*, immun*, pyroglyphid*, house, dust, mite*, *Dermatophagoides*, *pteronysinus*, *farinae*.

We considered only randomized DBPC RCTs of currently available commercially SCIT and SLIT modalities based on purified or semi-purified HDM allergens for HDM-induced AR and AA. We excluded studies (i) considering safety only, (ii) not reporting any clinical data, (iii) of HDM preparations that have never been commercialized or are no longer available, including non-purified extracts (e.g. house dust), (iv) involving the simultaneous administration of several unrelated allergens (e.g. pollen with HDM extracts) or other active treatments on a regular basis or (vi) lacking an abstract in English. Articles were cross-checked against those identified in recent meta-analyses and reviews.

From each selected publication, we extracted the following data (if reported):

1. the country or countries in which the study was performed.
2. the mean and/or median age and the variance (SD and/or range) in each treatment arm (active and placebo).
3. the allergen sensitization test method(s) used as an inclusion criteria (skin prick testing (SPT), a serum specific IgE assay, nasal or bronchial provocation tests, etc.).
4. the criteria for disease severity on inclusion.
5. the manufacturer and brand name of the AIT formulation and its overall composition (mite species extracted, the presence of other components, etc.).
6. the reported or calculated maintenance dose and the reported or calculated cumulative dose, in both the proprietary units used in the publication and in µg of major allergen).
7. the mean treatment time (in months).
8. the duration of any baseline or observational period
9. the month of the year in which AIT was initiated
10. the administration regimen (daily, weekly, monthly, etc.) and the presence or absence of an up-dosing phase before the maintenance phase
11. the total number of randomized participants

12. the intention-to-treat (ITT) and per-protocol (PP) populations in the active treatment and placebo arms.
13. the primary efficacy criterion and secondary efficacy criteria, with a special focus on patient-reported outcomes (such as quality of life and satisfaction with treatment, for example).
14. the nature and number of symptoms scored, the symptom scale (min/max), the symptom score and variance for active and placebo groups and the reported p value for active vs. placebo differences.
15. the medication scale (min/max), the medication score and variance for active and placebo groups and the p value for active vs. placebo differences.
16. the combined symptom and medication scale (min/max), the overall combined score and variance for active and placebo groups and the p value for active vs. placebo differences.
17. the percentage of participants with treatment-emergent adverse events (TEAEs), local and non-local TEAEs.
18. the occurrence of any serious TEAEs.
19. the patient's quality of life and satisfaction with the treatment.
20. treatment compliance (criteria and, if provided, descriptive values).
21. The proportion of the CONSORT checklist items [E1] met by the study report (for trials published in 2010 or later).

Results: detailed comments on study designs.

SCIT in HDM asthma

Nineteen studies (20 treatment arms) met our selection criteria (Table I) and featured between 22 and 132 randomized participants per study (median number (1st/3rd quartile): 46 (32-56)). The severity criteria for inclusion were rarely stated, although Bousquet mentioned a score of 3 on Charpin's scale [reference 25 in the main text]. Ten of the 19 studies incorporated a nasal or bronchial HDM allergen provocation test as an inclusion and/or efficacy criterion, 4 of the 19 gave information on calculation of the pre-specified sample size and 13 of the 19 excluded patients co-sensitized to other relevant allergens or with clearly confounding symptoms. None of the studies published before 1997 reported on the major allergen content in µg. Five later studies reported the major allergen content (Der p 1) of the maintenance dose (between 7 µg and 17.5 µg) (Table I). Likewise, only four recent studies reported on cumulative doses, with values of 68, 72, 142 and 250 µg Der p 1 (Table I). However, this four-fold difference between the lowest and highest observed doses in SCIT studies was far smaller than the almost 400-fold difference observed from one SLIT study to another (see the following section). A wide variety of baseline periods (from 2 weeks to 12 months), treatment durations (from 7 weeks [25] to 38 months [24]) and initiation months (October to December [32], October or November [37], November to March [43], December [29] and February [24]) were noted. Injections were given every three weeks [43], every four weeks [38], every six weeks [64] or every eight weeks [56].

SLIT in HDM asthma

Fourteen studies (15 treatment arms) met our inclusion criteria (Table II), with between 15 and 465 randomized participants per study (median number (1st/3rd quartile): 31 (24-85)). The study by Devillier et al. [32] stood out because of the large number of randomized participants (n=465), which contrast sharply with the presence of only 5 per-protocol placebo group patients in the (admittedly preliminary) study by Bush et al. [30]. Subjects were screened for specific sensitization using both SPT and specific IgE assays in all but one study [22]. Although all studies excluded patients with severe asthma, there was a wide range of inclusion criteria for disease severity: lung function test values (FEV1 >70% or 80% predicted [22,30,41]; a PC20 (the histamine provocation concentration producing a 20% fall in FEV1) of no lower than 2 mg/ml [50]; the reversal of bronchial obstruction by more than 15% with albuterol [55], severity classifications (the Global Initiative for Asthma (GINA) classification [42,47,64], the National

Heart, Lung and Blood Institute classification [30] and the Aas score [26]), medication used (a daily budesonide equivalent of 200-1000 mg [55] or the need for inhaled corticosteroids [22]) and a clinical history of asthma for at least one year (Giovane 1994) or two years [60]. Five of the 14 studies incorporated a nasal or bronchial HDM allergen provocation test as an inclusion and/or efficacy criterion, 2 of the 14 gave information on calculation of the pre-specified sample size and 12 of the 14 excluded patients co-sensitized to other relevant allergens or with clearly confounding symptoms. Ten of the 14 studies reported on the major allergen content in the maintenance dose, which varied from 0.8 µg of Der p 1 and from 1 µg to 70 µg of Der f 1. The cumulative major allergen dose ranged from 60 µg Der p 1 in the 6-month study by Ippoliti et al. [41] to 23,695 µg Der f 1 in the 12-month "high-dose" group studied by Bush et al. [30]. This almost 400-fold difference in cumulative dose observed from one SLIT study to another was much greater than the (four-fold) difference between the lowest and highest observed doses in SCIT studies (see the previous section). All but one [44] of the studies featured a baseline period (ranging from 2 weeks to 12 months) prior to initiation of AIT. When stated, treatment was initiated in November [55], January [39,44,50], February to August [30] and September to May [26]. The treatment time ranged from 6 months [22,41,42,47,60] to 36 months [39].

SCIT in HDM rhinitis

Seven studies (7 treatment arms) were selected (Table III). The number of randomized participants per study ranged from 32 [64] to 145 [57] (median number (1st/3rd quartile): 39 (34- 56)). The disease severity criteria on inclusion were poorly defined (often merely a clinical history of perennial symptoms). Five of the seven studies incorporated a nasal or bronchial HDM allergen provocation test as an inclusion and/or efficacy criterion, 2 of the seven gave information on calculation of the pre-specified sample size and 4 of the seven excluded patients co-sensitized to other relevant allergens or with clearly confounding symptoms. The treatment duration ranged from 11.5 months [23] to 24 months [33]. Three studies reported on the major allergen content in the maintenance dose (30 µg Der p 2 for [57], 7 µg Der p 1 for [61] and 9.8 µg Der p 1 for [56]. The latter trials all had overall treatment periods of 12 to 14 months but injections were administered monthly by [57] and Varney et al. [61] and every two months by Pichler et al. ([56], leading to cumulative doses of around 420 µg Der p 2, 106 µg Der p 1 and 60 µg Der p 1, respectively.

SLIT in HDM rhinitis

Fifteen studies (16 treatment arms) featured between 15 and 257 randomized participants per study (median number (1st/3rd quartile): 32 (29-69)) (Table IV). The study by de Bot 2012 [31] stood out in this respect, with 257 randomized participants. The earliest studies only required a clinical history of AR as an inclusion criterion. More recent studies have featured a variety of inclusion criteria, as follows: a four-symptom total symptom score (T4SS) of more than 70 out of 168 over the last 2 weeks of a screening period [59], mild AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification [52] and a rhinitis symptom score of at least 4 out of 12 during the three months preceding the start of the study [31]. Nine of the 15 studies incorporated a nasal or bronchial HDM allergen provocation test as an inclusion and/or efficacy criterion. Only one of the 15 gave information on calculation of the pre-specified sample size. Eleven of the 15 excluded patients co-sensitized to other relevant allergens or with clearly confounding symptoms. The only two studies that did not use drop formulations of SLIT were those performed by Passalacqua et al. [52] (tablets of monomeric, carbamylated allergoids) and Pham-Thi et al. [55] (unmodified *D pte* and *D far* extract tablets). Eleven of the 15 studies reported on the major allergen content in the maintenance dose, which varied from 0.8 µg Der p 1 to 70 µg of Der f 1 and was mostly between 9 µg and 27 µg of Der p 1. Given that the treatment periods ranged from 6 months (e.g. [60]) to 24 months (e.g. [31]) and treatment frequencies ranged from daily to 2 days a week [52] and 3 days a week (e.g. [40]), the cumulative doses of allergen showed great disparities. The value of 110 µg of group 1 allergens reported by Marcucci et al. [44] was more than 200-fold lower than the amount of 23,695 µg of Der f 1 reported by Bush et al. in the 12-month "high-dose" group [30], even though both studies featured a 12-month treatment period. When stated, the treatment initiation date was variable: November [55], November to January [40], January [44], February to August [30] and April [51]).

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Table EI. Studies notably excluded from the analysis and reasons for exclusion.

<u>Study</u>	<u>AIT modality</u>	<u>Reason for exclusion</u>
British Tuberculosis Association 1968 [E2]	SCIT	Active treatment was a dust extract
Aas 1971 [E3]	SCIT	Active treatment was a dust extract
Smith 1971 [E4]	SCIT	Non-commercial preparation ("prepared by Dr K. Maunsell")
Taylor 1974 [E5]	SCIT	Non-commercial preparation (house dust preparation with additional <i>D far</i>)
Amaral Marques 1978 [E6]	SCIT	Two different active groups (different regimens), both of which had corresponding placebo groups, but pooled results are presented. The Active group is therefore inhomogeneous
Newton 1978 [E7]	SCIT	Dome Laboratories Allpyral product not currently available
Price 1984 [E8]	SCIT	Randomization of the active group from Warner et al. 1978 for a further 12 months of active or placebo treatment. Hence, the placebo patients had already received a year of active D pte treatment. Hence, the patients in the placebo group had received active treatment.
Scadding 1986 [E9]	SLIT	Cross-over design, the results of which were not reported separately before and after cross-over; no truly "placebo-only" group.
Pastorello 1987 [E10]	SCIT	No clinical data (study of IgG levels)
Ewan 1988 [E11]	SCIT	Pharmalgen product not currently available
Corrado 1989 [E12]	SCIT	Miles/Bayer Conjuvac product not currently available
Mosbech 1989 [E13]	SCIT	No placebo
McHugh 1990 [E14]	SCIT	Pharmalgen product not currently available. Allpyral patient groups were single-blind only (not the same regimen as for Pharmalgen).
Novembre 1991 [E15]	SLIT	Full text in Italian

Sabbah 1991 [E16]	SLIT	Full text in French
Van Bever 1992 [E17]	SCIT	First year not DBPC. All patients were on active treatment prior to randomization.
Haugaard 1993 [E18]	SCIT	No strictly placebo injections (control group was low-dose SCIT)
Sin 1996 [E19]	SCIT	Not DB: "cross-over randomized single-blind, placebo-controlled"
Hirsch 1997 [E20]	SLIT	Mixture of AA, AR and AA+AR patients. No report of how many of each in the active treatment and placebo groups, respectively. Scores reported for undetermined numbers of subjects.
Mungan 1999 (SCIT subgroup) [E21]	SCIT	No placebo injections - the placebo was SLIT
Altıntaş 1999 [E22]	SCIT	Not a blind trial, although a placebo was used (5 patients). Three types of SCIT formulation were used, with different regimens (weekly vs. monthly) and appearances.
Grembiale 2000 [E23]	SCIT	Miles/Bayer Conjuvac product not currently available
Alvarez 2002 [E24]	SCIT	Liposome-encapsulated formulation, not commercially available
Basomba 2002 [E25]	SCIT	Liposome-encapsulated formulation, not commercially available
Marcucci 2002 [E26]	nasal IT	Nasal administration, not a commercially available modality
Marcucci 2003 [E27]	SLIT	Same population as Marcucci 2005; immunological outcomes after 1 year; no comparison of post-treatment scores for Ac. vs. Pl.
Sambugaro 2003 [E28]	SLIT	Not DB or PC (open study)
Marogna 2004 [E29]	SLIT	Not DB or PC (open study)
Rodriguez Santos 2004 [E30]	SLIT	Not DB or PC
Gómez Vera 2005 [E31]	SLIT	Not DB (single-blind)
Tabar 2005 [E32]	SCIT	"The study design did not include a separate placebo or control group" (this was a comparison of a cluster regimen vs. a conventional regimen).
Cao 2007 [E33]	SLIT	Full text not in English

Guimarães Junqueir de Queirós 2008 [E34]	SCIT	Not a commercially available preparation
Kopp 2009 [E35]	SCIT	Combination therapy: Xolair® + allergoid vs. Xolair® + placebo
Yonekura 2010 [E36]	SLIT	Active treatment was a dust extract
Majak 2010 [E37]	SCIT	No placebo group for SCIT. The trial compared [montelukast + SCIT] with [placebo tablet + SCIT]
Blumberga 2011 [E38]	SCIT	Same patients as Blumberga 2006. The 2011 report covers immunomodulatory parameters.
Keles 2011 [E39]	SCIT and/or SLIT	Not DB or PC. The treatment groups were "(1) subcutaneous immunotherapy (SCIT), (2) sublingual immunotherapy (SLIT), (3) SCIT plus SLIT, or (4) pharmacotherapy."
Tabar 2011 [E40]	SCIT	Same patients as Tabar 2005, not fully DB, no placebo group (control was pharmacotherapy)
Stelmach 2012 [E41]	SCIT	Not DB, not PC. Treatment groups: 3 years of SCIT vs. 5 years of SCIT vs. pharmacotherapy

Abbreviations: SCIT: subcutaneous allergen immunotherapy; SLIT: sublingual allergen immunotherapy; D far: *Dermatophagoides farinae*; Ig: immunoglobulin; DBPC: double-blind, placebo-controlled; AA: allergic asthma; AR: allergic rhinitis

Table EII: Safety, quality of life and treatment compliance for HDM allergen immunotherapy (SCIT and SLIT) in allergic asthma and allergic rhinitis

Lead author, year of publication, study population	Percentage of patients with TEAEs (Ac/PI), local AEs (Ac/PI) and non-local AEs (Ac/PI)	Medication-driven serious AEs	QoL or other PROs?	Compliance
SCIT in HDM asthma				
Yukselen 2012 [64] <i>Pediatric study</i>	Ac 20 / PI 20, Ac 20 / PI 20 , Ac 0 / PI 0	no	no	Presumably 100% in PP populations
Blumberga 2006 [24]	Ac NR / PI NR, Ac NR / PI NR, Ac 38 / PI 29	Yes, 1	disease evaluation VAS	Presumably 100% in PP populations
Wang 2006 [62]	Ac NR / PI NR, Ac NR / PI NR, Ac NR / PI NR	NR	no	Presumably 100% in PP populations
Garcia-Robaina 2006 [38]	Ac 8/ PI 8, Ac 8 / PI 8 , Ac 0 / PI 0	no	AQLQ	Presumably 100% in PP populations
Ameal 2005 [21]	Ac NR / PI NR, Ac NR / PI NR, Ac 17 / PI 11	no	Marks' Asthma Quality of Life Questionnaire	Presumably 100% in PP populations
Maestrelli 2004 [43]	Ac NR / PI NR, Ac NR / PI NR, Ac NR / PI NR	no	no	Presumably 100% in PP populations
Pichler 1997 [56]	Ac NR / PI NR, Ac NR / PI NR,	epinephrine use in one case (not	no	Presumably 100% in PP

	Ac NR / Pl NR	stated whether Ac or Pl)		populations
Olsen 1997 [49]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	no	overall treatment effect	Presumably 100% in PP populations
Peroni 1995 [54] <i>Pediatric study</i>	Ac NR / Pl NR, Ac NR / Pl NR, Ac 0 / Pl 0	no	overall treatment effect	Presumably 100% in PP populations
Franco 1995 [35]	Ac 17 / Pl 20, Ac NR / Pl NR, Ac 4 / Pl 4	NR	no	Presumably 100% in PP populations
Bousquet 1985 [25]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	Yes, 4 during rush, all in active group, 3 required epinephrine	no	Presumably 100% in PP populations
Pauli 1984 [53]	Ac NR / Pl NR, Ac 55 / Pl 75, Ac NR / Pl NR	NR	no	Presumably 100% in PP populations
Blainey 1984 [23]	Ac NR / Pl NR, Ac 29 / Pl 33, Ac NR / Pl NR	Yes, 1 severe reaction, group not stated	no	Presumably 100% in PP populations
Buchanan 1981 Group A [29]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	NR	no	Presumably 100% in PP populations
British Thor. Asso. 1979 Group A [28]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	Yes but group not specified	no	Presumably 100% in PP populations
British Thor. Asso. 1979 Group B [28]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	Yes but group not specified	no	Presumably 100% in PP populations
Warner 1978 [63]	Ac NR / Pl NR, Ac 48 / Pl 41, Ac	Yes, 1 severe exacerbation of	no	Presumably 100% in PP

<i>Pediatric study</i>	NR / Pl NR	asthma (placebo).		populations
Gaddie 1976 [37]	Ac NR / Pl NR, Ac NR / Pl NR, Ac 35 / Pl 17	NR	no	Presumably 100% in PP populations
D'Souza 1973 [34]	Ac NR / Pl NR, Ac NR / Pl NR, Ac 40 / Pl NR	mild case of asthma exacerbation after an injection but did not specify the group.	overall satisfaction	Presumably 100% in PP populations
Smith 1972 [45]	Ac 12/ Pl 0, Ac 12 / Pl 0 , Ac 0 / Pl 0	NR	no	Presumably 100% in PP populations
SLIT in HDM asthma				
Devillier 2013 [32]	Ac 87 / Pl 76, Ac 27 / Pl 14 , Ac 47 / Pl 48	no	Asthma Quality of Life Questionnaire	yes, compliance during the maintenance phase was 90.9% and 93.0% in the active and placebo groups, respectively
Yukselen 2012 <i>Pediatric study</i> [64]	Ac 30 / Pl 20, Ac 30 / Pl 20 , Ac 0 / Pl 0	no	no	NR
Bush 2011 (high dose) [30]	Ac 55 / Pl 60, Ac 44 / Pl 22, Ac 22 / Pl 11	no	no	NR
Bush 2011 (low dose) [30]	Ac 57 / Pl 60, Ac 33 / Pl 22, Ac 22 / Pl 11	no	no	NR

Tseng 2008 [60] <i>Pediatric study</i>	Ac 67 / Pl 22, Ac NR / Pl NR, Ac NR / Pl NR	no	no	diary card
Pham-Thi 2007 [55] <i>Pediatric study</i>	Ac 71 / Pl 66, Ac NR / Pl NR, Ac NR / Pl NR	yes (severe exacerbation of asthma in a placebo patient,)	Childhood Asthma Questionnaire	diary card and physician assessment
Niu 2006 [47] <i>Pediatric study</i>	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	no	"global assessment" by patient	diary card
Lue 2006 [42] <i>Pediatric study</i>	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	no	no	diary card
Marcucci 2005 [44] <i>Pediatric study</i>	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	NR	no	NR
Ippoliti 2003 [41] <i>Pediatric study</i>	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	no	no	diary card
Bahçeciler 2001 [22] <i>Pediatric study</i>	Ac 0 / Pl 0, Ac 0 / Pl 0, Ac 0 / Pl 0	no	no	diary card
Pajno 2000 [50] <i>Pediatric study</i>	Ac NR / Pl 0, Ac 6 / Pl 0, Ac 6 / Pl 0	no	no	diary card
Mungan 1999 [46]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	NR	no	diary
Bousquet 1999 [26]	Ac 35 / Pl 32, Ac NR / Pl NR, Ac NR / Pl NR	NR	SF20	diary

Giovane 1994 [39] <i>Pediatric study</i>	Ac 0 / Pl 0, Ac 0 / Pl 0, Ac 0 / Pl 0	no	no	diary
SCIT in HDM rhinitis				
Yukselen 2012 [64] <i>Pediatric study</i>	Ac 20 / Pl 20, Ac 20 / Pl 20, Ac 0 / Pl 0	no	no	Presumably 100% in PP populations
Riechelmann 2010 [57]	Ac 77 / Pl 66, Ac NR / Pl NR, Ac NR / Pl NR	no	Rhinoconjunctivitis Quality of Life Questionnaire	Presumably 100% in PP populations
Dokic 2005 [33]	Ac 35 / Pl 40, Ac 35 / Pl 40, Ac 0 / Pl 0	no	VAS status	Presumably 100% in PP populations
Varney 2003 [61]	Ac NR / Pl NR, Ac NR / Pl NR, Ac 20 / Pl 0	yes, sublingual epinephrine from a Medihaler EpiSpray	no	Diary cards. Presumably 100% in PP populations
Pichler 1997 [56]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	epinephrine use in one case (not stated whether Ac or Pl)	no	Presumably 100% in PP populations
Blainey 1984 [23]	Ac NR / Pl NR, Ac 28 / Pl 29, Ac 17 / Pl 14	yes, one	overall treatment effect	Presumably 100% in PP populations
Gabriel 1977 [36]	Ac 91 / Pl 33, Ac 79 / Pl 9, Ac 33 / Pl 24	yes, 1 anaphylactic event in Ac	no	Presumably 100% in PP populations
SLIT in HDM rhinitis				

Bozek 2012 [27]	Ac 6 / Pl 2, Ac 6 / Pl 0, Ac 0 / Pl 2	no	symptom VAS included "mental function and QoL"	NR
Yukselen 2012 [64] <i>Pediatric study</i>	Ac 30 / Pl 20, Ac 30 / Pl 20, Ac 0 / Pl 0	no	no	NR
de Bot 2012 [31] <i>Pediatric study</i>	Ac 96 / Pl 96, Ac 68 / Pl 60, Ac 92 / Pl 97	no	Pediatric (6–11 years) and Adolescent (12–17 years) Rhinoconjunctivitis Quality of Life Questionnaire	study diary, telephone follow-up and weighing any returned medication
Bush 2011 (high dose) [30]	Ac 55 / Pl 60, Ac 44 / Pl 22, Ac 22 / Pl 11	no	no	NR
Bush 2011 (low dose) [30]	Ac 57 / Pl 60, Ac 33 / Pl 22, Ac 22 / Pl 11	no	no	NR
O'Hehir 2009 [48]	Ac NR / Pl NR, Ac 60 / Pl 7, Ac 7 / Pl 7	no	Juniper Rhinoconjunctivitis QoL Questionnaire and AR and AS VASs	"Returned vials were inspected and all were empty"
Tseng 2008 [60] <i>Pediatric study</i>	Ac 67 / Pl 22, Ac NR / Pl NR, Ac NR / Pl NR	no	no	diary card
Pham-Thi 2007 [55] <i>Pediatric study</i>	Ac 71 / Pl 66, Ac NR / Pl NR, Ac NR / Pl NR	yes (placebo patient, severe exacerbation of asthma)	Childhood Asthma Questionnaire	diary cards and physician assessment
Passalacqua 2006 [52]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	NR	QoL (SF-36), general satisfaction and SAT-P (nondisease specific,	NR

			32 questions about daily life)	
Marcucci 2005 [44] <i>Pediatric study</i>	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	NR	no	NR
Tonnel [59] 2004	Ac 6 / Pl 11, Ac NR / Pl NR, Ac NR / Pl NR	no	no	diary
Bahçeciler 2001 [22] <i>Pediatric study</i>	Ac 0 / Pl 0, Ac 0 / Pl 0, Ac 0 / Pl 0	no	no	diary card
Guez 2000 [40]	Ac 5 / Pl 5, Ac 5 / Pl 2, Ac 0 / Pl 2	no	no	diary
Mungan 1999 SLIT AR [46]	Ac NR / Pl NR, Ac NR / Pl NR, Ac NR / Pl NR	NR	no	diary
Passalacqua 1998 [51]	Ac 10 / Pl 20, Ac 10 / Pl 20, Ac 0 / Pl 0	no	no	diary
Tari 1990 [58] <i>Pediatric study</i>	Ac NR / Pl 0, Ac 9 / Pl 0, Ac 12 / Pl 0	no	no	diary card

Abbreviations: AA: allergic asthma; Ac: active immunotherapy; AE: adverse event; AR: allergic rhinitis; AQLQ: Asthma Quality of Life Questionnaire; NR: not reported in the publication; Pl: placebo; PRO: patient-reported outcome; PP: per-protocol; QoL: quality of life; TEAE: treatment-emergent adverse event; VAS: visual analog scale