

Semi-depot house-dust mite allergen extract for Chinese with allergic rhinitis and asthma

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ABSTRACT

Background: Real-world data of the subcutaneous immunotherapy (SCIT) with semi-depot house-dust mite (HDM) allergen extract (a HDM allergen extract that contains a 50%–50% mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) for allergic rhinitis and asthma was unavailable in China until recently.

Aim: To investigate the effectiveness and safety of a HDM-SCIT for allergic rhinitis and asthma in Chinese patients.

Methods: A multicenter, single-arm, open-label, self-controlled study. Chinese patients with allergic rhinitis or allergic asthma and with a history of symptoms from HDM exposure were included and received allergen-specific immunotherapy for 1 year by subcutaneous injection of HDM-SCIT. The primary outcome measure was the percentage of patients with an improvement in symptom severity assessed at 12 months after initiation of the treatment. The occurrence of adverse events and compliance of treatment were also evaluated.

Results: A total of 272 outpatients were included for effectiveness analysis. The subject-evaluated improvement rate in the visual analog scale (VAS) was 76.1% and 71.3% at 6 and 12 months, respectively; corresponding values for investigator-evaluated VAS were 77.9% and 71.7%, respectively ($p < 0.0001$). Symptom score changes were -2.43 and -3.79 at 6 and 12 months, respectively (both $p < 0.0001$); the VAS improvement rate and symptom score change did not differ significantly between children and adolescents and/or adults. Good injection schedule adherence was found in 98.8% of the patients. No study drug-related serious adverse events or serious systemic allergic reactions occurred.

Conclusion: HDM-SCIT was safe and effective in the treatment of allergic rhinitis and asthma in a Chinese population, with good compliance.

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Allergic rhinitis (AR) and allergic asthma (AA) are chronic diseases that have a substantial economic and psychological burden on the affected individual and his or her family and that also represent an economic burden to medical services, health systems, and society as a whole. The incidence and prevalence of AR and asthma have increased over recent years, with statistical data provided by the World Allergy Organization, which revealed that the global prevalence of these diseases reached 22% in 2007, with prevalence rates of 17% for AR and 11% for AA.¹ Analysis of available data indicated that, despite variations in the prevalence of AR in different regions of China, the prevalence of AR has increased in both adults and children over the past 2 decades. An increase in a “Western” type lifestyle, industrialization, and air pollution over this period may have contributed to the increased prevalence of AR observed in China.¹

The prevalence of childhood allergic diseases in China has increased rapidly from 1990 to 2011.² A China, Children, Homes, Health cross-sectional study in 2011 found that the prevalence of asthma has increased significantly, almost fivefold, from 2.1% in 1990 to 10.2% in 2011.² Another survey showed that the prevalence of self-reported AR

of the rural area (19.1%) was significantly higher than that of the urban area (13.5%).³ A two-stage, clustered, stratified, random sample study showed that the adjusted prevalence of clinical AR was 14.9% (19.5% in urban areas, 10.8% in suburban areas) in preschool children in Beijing.⁴ Subcutaneous immunotherapy (SCIT) currently represents the standard immunotherapy modality, with well-established clinical efficacy.^{5,6} Previous double-blind, placebo-controlled studies confirm the efficacy of subcutaneous injection of allergen SCIT for treatment of both AR and AA.⁷ The house-dust mite (HDM) is a major allergen source and a significant cause of AR and AA.^{8,9}

For HDM standardized SCIT, Novo-Helisen depot, which is a semi-depot HDM allergen extract (HDM-SCIT) (50% *Dermatophagoides pteronyssinus* plus 50% *Dermatophagoides farinae*; Allergopharma GmbH, Germany), is currently the available preparation extract derived from double kinds of mites in China. Analysis of epidemiology data showed that the majority of the patients with mite sensitization respond to different kinds of mites, such as *D. pteronyssinus* and *D. farinae*, but rarely to any single mite species. This product has been used in various European countries, such as Germany and Poland, for >30 years, and its efficacy and safety in the treatment of AR and asthma have been established by a number of clinical trials.^{10–12} However, there were no data available on the clinical effectiveness and safety of HDM-SCIT from a large-scale clinical study in China. This study was conducted to investigate the effectiveness and safety of the HDM-SCIT on AR and AA in a Chinese patient population.

METHODS

Design and Patients

This was a multicenter, single-arm, open-label study to investigate whether HDM-SCIT is safe and effective as a 1-year treatment for AR and asthma in real-world Chinese individuals. The study was conducted in nine centers in China from 2011 to 2013. Inclusion criteria were the following: (1) male and female subjects, ages between 5 and 55 years; (2) a definite diagnosis of AR (according to the Diagnosis and Treatment Guidelines for Allergic Rhinitis, published in 2009¹³) or intermittent AA or mild persistent AA (according to the Diagnosis and Treatment for Bronchial Asthma or the Diagnosis and Treatment

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for Children's Bronchial Asthma, published in 2008^{14,15}); (3) a relevant clinical history of symptoms with HDM exposure; and (4) allergy to *D. pteronyssinus* and/or *D. farinae* identified by skin-prick testing (SPT) or specific immunoglobulin E (IgE) serum testing. A positive SPT result was defined as a *D. pteronyssinus* and/or *D. farinae* wheal of ≥ 3 mm in diameter and larger than that of the positive control (histamine). A positive specific IgE serum test result was defined as an anti-*D. pteronyssinus* IgE level of ≥ 0.7 kU/L and/or an anti-*D. farinae* IgE level of ≥ 0.7 kU/L, measured by the enzyme-linked fluorescent immunoassay method. The exclusion criteria were the following: (1) sensitization to other seasonal or perennial allergens, except for avoidable pets; (2) visual analog scale (VAS) score of ≤ 3 ; (3) a forced expiratory volume in 1 second of $< 80\%$ of the predicted value; (4) severe immunologic, cardiac, liver, renal, or metabolic disease; tumors; or chronic infection; (5) hypersensitivity to alcohol; (6) allergy to recipients (aluminum hydroxide and phenol) used in HDM-SCIT; (7) pregnancy or lactation, or an intention to conceive during the course of the study; (8) an inability to understand the instructions or study documents; (9) previous treatment with specific immunotherapy (SIT); or (10) participation in other studies within the 30 days before enrollment in the present study. Eligible patients were recruited into the study in a continuous manner.

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable regulatory requirements in China, and was approved by the ethic committee. All the patients included in the study provided written informed consent. For patients ages of < 14 years (minors), informed consent was obtained from their legal guardians; if the minor was considered capable of making a decision, then additional informed consent from the patient him- or herself was also required.

Treatment with Allergen-SIT

The patients received subcutaneous injection (according to the product label) of HDM-SCIT for 1 year as allergen-SIT, based on their medical history and allergen test results. HDM-SCIT was available in four concentrations: strength 0, 5 therapeutic units per mL (TU/mL); strength 1, 50 TU/mL; strength, 500 TU/mL; and strength 3, 5000 TU/mL. The treatment regimen was divided into two stages: initial treatment and maintenance treatment. The initial treatment (dose escalation phase) started at the minimum dose by using minimal concentrations (strength 1 or strength 0 [equivalent to 10% of strength 1]). For children and subjects who were highly sensitive, strength 0 was used to provide the starting dose. The injection interval during the dose escalation phase was between 7 and 14 days. If the current injection was well tolerated, then the dose was increased step by step to the individual maximum dose (the maintenance treatment dose). If the previous injection was not well tolerated, then the dose was either reduced to the last well-tolerated dose (for intense local reactions) or was reduced by 2–3 steps (for mild systemic reactions); for severe systemic reactions, immunotherapy was either restarted from strength 0 or was discontinued. After the individual maximum tolerated dose was reached, the injection interval was gradually extended to 4–6 weeks for maintenance treatment (maintenance phase). Although the maximum tolerated dose varied among the patients, the absolute maximum dose allowed was 1.0 mL of strength 3. For each patient, the total number of injections and the time, dosage (volume and strength), and site of each injection were recorded.

Visit Schedule

Four visits were planned for each subject in the study: a screening visit (day -30) for collection of demographic and clinical data, pulmonary testing, and allergen testing; visit 1 (day 0, baseline), the first subcutaneous administration of HDM-SCIT and assessment of variables used as outcome measures (see below); and visits 2 (6 months) and 3 (12 months) for assessment of variables used as outcome measures.

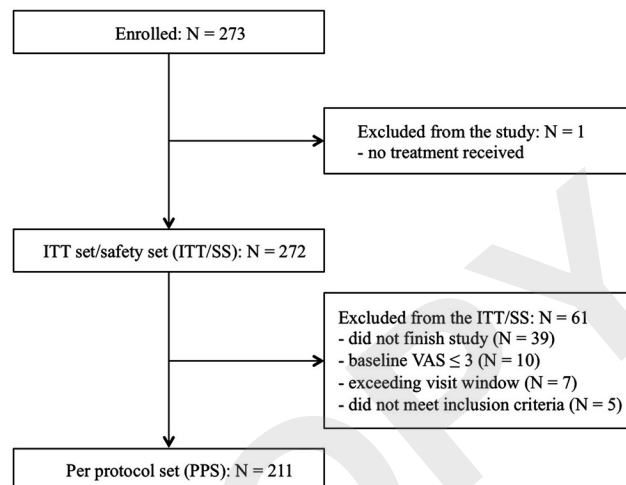


Figure 1. Enrollment of the study population.

Baseline Assessments

The following demographic and clinical data were obtained for all the patients during the screening visit (1 month before the first injection): (1) age, sex, height, weight, blood pressure, heart rate, temperature, and respiration; (2) disease history (history of allergy, including the time of first onset and total disease duration, current state and severity of the disease, complications and family history); and (3) results of the SPT, pulmonary function (PEF/forced expiratory volume in 1 second) and specific IgE serum tests (the times at which the tests were performed and the methods used were also noted). The demographic and clinical data were assessed at both the screening visit and visit 1 (baseline).

Assessments of Effectiveness

The primary outcome was the VAS improvement ratio of patients with AR and patients with asthma before and after 1 year of HDM-SCIT treatment. Improvement was defined as a reduced VAS after treatment compared with baseline: improvement rate = (number of patients who showed improvement)/(total number of patients) $\times$ 100%. The effectiveness of SIT was assessed by using a VAS for the severity of symptoms, symptom scoring, and concomitant use of antiallergy medication at baseline and after 6 and 12 months of treatment. The VAS is recommended by Allergic Rhinitis and its Impact on Asthma guidelines¹⁶ as a method of assessing the efficacy of SIT and was validated in studies.^{17,18} In the present study, the patient was asked to mark his or her own evaluation of severity on a horizontal line (10-cm long, ranging from "no symptoms" on the left to "unbearable" on the right), and the VAS was determined from the distance between the mark and the left-hand end of the line. For symptom scoring, the patient was asked to keep a daily symptom diary for the 2 weeks preceding each visit. As recommended by relevant guidelines,^{19,20} the symptoms assessed were those that affect the nose (nasal congestion, nasal itching, sneezing, runny nose), eyes (itching, tearing, redness and swelling, aching), and lungs (cough, suffocation, wheezing, chest tightness), and were scored as either 0 (no symptoms), 1 (mild, not annoying), 2 (moderate, annoying, yet endurable), or 3 (severe, unbearable).

Patients' reports and investigators' evaluations were recorded as subject-evaluated VAS and investigator-evaluated VAS, respectively. A record of the concomitant use of antiallergy medication included the frequency, dose, and type (such as antihistamines, glucocorticoids, and leukotriene antagonists) of medication used. The VAS, symptom score, and concomitant use of antiallergy medication were assessed at baseline (visit 1) as well as at 6 months (visit 2) and 12

Table 1 Demographic and clinical characteristics of the patients included in the study

	ITT Set (N = 272)	PPS (N = 211)
Age, mean (SD), y	24.3 ± 14.10	24.6 ± 14.31
Age, no. (%)		
<5 y	1 (0.4)	0
5–14 y	94 (34.6)	74 (35.1)
>14 y	177 (65.1)	137 (64.9)
Sex, no. (%)		
Male	144 (52.9)	113 (53.6)
Female	128 (47.1)	98 (46.4)
FEV ₁ , mean (SD), %	94.6 ± 10.5	95.2 ± 10.2
Diagnosis, no. (%)		
Allergic rhinitis	228 (83.8)	180 (85.3)
Allergic asthma	5 (1.8)	4 (1.9)
Both allergic rhinitis and allergic asthma	39 (14.3)	27 (12.8)
Allergy history, no. (%)*		
History of allergy	272 (100)	211 (100.0)
Rhinitis	267 (98.2)	208 (98.6)
Ocular allergic disease	71 (26.1)	54 (25.6)
Asthma	51 (18.8)	39 (18.5)
Skin allergy	38 (14.0)	25 (11.8)
Others#	10 (3.6)	6 (2.8)
Exposure to treatment, mean (SD) (range), days	331.2 ± 78.4 (1–414)	361.3 ± 12.7 (319–390)
Family history of allergic disease, no. (%)	117 (43.0)	92 (43.6)
History of concomitant serious illness and/or chronic disease, no. (%)		
Infections and infestations	3 (1.1)	
Gastrointestinal disorders	3 (1.1)	
Musculoskeletal and connective tissue disorders	2 (0.7)	
Reproductive system and breast disorders	2 (0.7)	
Metabolism and nutrition disorders	1 (0.4)	
Immune system disorders§	1 (0.4)	
Neoplasms (benign, malignant, and unspecified, including cysts and polyps)	1 (0.4)	
Hepatobiliary disorders	1 (0.4)	
Eye disorders	1 (0.4)	

ITT = intention-to-treat; PPS = per-protocol set; SD = standard deviation; FEV₁ = forced expiratory volume in 1 second.

*Each subject may have a medical history of multiple diseases.

#Includes allergy to seafood, sea crab, beef, food (shrimp), food (unspecified), crab, tomato; urticaria, acute urticaria.

§One patient with allergic purpura, which, on study entry, no longer presented.

months (visit 3) after the initiation of treatment. A secondary outcome included that patient compliance with the therapy was calculated as the percentage of injections performed over time, *i.e.*, $1 - ([\text{number of delayed injections}] / [\text{total number of injections}]) \times 100\%$. Injection schedule fidelities on different levels were defined as follows: <50%, as poor injection schedule fidelity; >50% and <75% as average injection schedule fidelity; and $\geq 75\%$ as good injection schedule fidelity.

Assessments of Safety

Safety outcome included the occurrence and severity of adverse events (AE) and its relationship to treatment and compliance. Records were kept of any AE recorded by the patients. AE was summarized as the occurrence of all AEs, serious adverse events (SAE), treatment-related AEs, and treatment-related SAEs. Allergic reactions after SIT were classified as intense local reactions (wheal diameter of >4 cm; reddening, pruritus, and pseudopodia; no systemic reaction), mild systemic reactions (wheal diameter of >4 cm; reddening, pruritus, pseudopodia; incipient dissemination through lymphocytes and blood concomitant with rhinitis, conjunctivitis, asthma, generalized skin rashes or urticaria), or severe systemic reactions (pruritus and/or heat sensation on and/or underneath the tongue, in the throat, on the palms, and on the soles; vasomotor collapse, with cyanosis, hypotension, tachycardia, loss of consciousness, vomiting, incontinence; pro-

tracted mild systemic reaction with vertigo, exacerbation of asthma, or Quincke edema of the larynx and/or trachea). Allergic reactions were summarized as the occurrence and relationship to treatment.

Statistical Methods

Efficacy analyses were based on the intention-to-treat (ITT) set (all the subjects who received at least one dose of the study drug) population and per-protocol set (PPS) (included all the subjects in ITT except the subjects who had protocol deviation or who withdrew or underwent premature termination from the study). All safety assessments were performed on the safety set. Continuous data are expressed as the mean (standard deviation), or as the median with minimum and maximum values, as appropriate. Categorical variables are expressed as frequencies and percentages. The rate of improvement, *i.e.*, the percentage of patients with improvement (and 95% confidence interval) in the VAS or symptom score (at 6 and 12 months) was calculated as the following: improvement rate = $([\text{number of patients who showed improvement}] / [\text{total number of patients}]) \times 100\%$.

The χ^2 test was performed to compare the percentage of improvements in the VAS, symptom score, concomitant use of antiallergy drugs, and compliance. Changes in the VAS and symptom score from baseline were compared by using the paired-samples Student's *t*-test.

For safety analyses, the number of AEs and the AE occurrence rate (defined as the percentage of subjects with at least one AE) were calculated for all the subjects and for the various subgroups. The number of SIT-related allergic reactions and their rate of occurrence (defined as the percentage of subjects with at least one SIT-related AE) were also determined. The χ^2 test or independent sample *t*-test was performed to compare the change of VAS between the children subgroup (ages 5–14 years) and adolescents and adults subgroup (ages > 14 years). A *p* value of <0.05 was considered to indicate a statistically significant difference, and statistical analysis was performed by using the SAS software version 9.0 (SAS). The *p* values are considered explorative, without multiplicity adjustment.

RESULTS

Baseline Demographic and Clinical Characteristics

Enrollment of the study population is shown in Fig. 1. Of the 273 subjects enrolled, one was excluded due to failure to receive treatment; hence, 272 patients (99.6%), with a mean (standard deviation) age of 24.3 ± 14.1 years (range, 4–55 years) were included in the ITT set, and 211 patients were included in the PPS due to not finishing the study (*n* = 39), having a baseline VAS of ≤ 3 (*n* = 10), exceeding the visit window (*n* = 7), and not meeting inclusion criteria (*n* = 5).

In the ITT set, 228 patients (83.8%) were diagnosed with AR alone, 5 (1.8%) with asthma alone, and 39 (14.3%) with both AR and asthma. All the patients had a history of allergic diseases, and 43.0% had a family history of allergic diseases. Twelve subjects (4.4%) had concomitant serious illness and/or chronic diseases other than allergic diseases. There were three subjects with diseases related to infection and infestation, and three subjects with gastrointestinal diseases. The baseline demographic and clinical characteristics of the ITT set and PPS are shown in Table 1.

Primary Efficacy Outcome Measure: Improvement of VAS after 1 Year of SIT

At 12 months of treatment, 194 of 272 patients (71.3%) in the ITT set and 180 of 211 patients (85.3%) in the PPS showed an improvement in the subject-evaluated VAS compared with baseline (Table 2).

Secondary Efficacy Outcome Measures

Compared with the baseline, 207 of 272 patients (76.1%) in the ITT set and 173 of 211 patients (82.0%) in the PPS showed an improvement in the subject-evaluated VAS at 6 months, whereas 212 of 272 patients (77.9%) in the ITT set and 175 of 211 patients (82.9%) in the PPS showed an improvement in the investigator-evaluated VAS at this time point (Table 2). At 12 months, 195 of 272 patients (71.7%) in the ITT set and 181 of 211 patients (85.8%) in the PPS showed an improvement in the investigator-evaluated VAS (Table 2). Compared with the baseline value, the changes in the subject-evaluated VAS were -1.50 at 6 months and -2.52 at 12 months (*p* < 0.0001 for both) in the ITT set (Table 3). The corresponding changes in the investigator-evaluated VAS were -1.64 at 6 months and -2.61 at 12 months (*p* < 0.0001 for both) in the ITT set (Table 3). The changes in the symptom score compared with baseline were -2.43 at 6 months and -3.79 at 12 months (*p* < 0.0001 for both) in the ITT set (Table 3). At 6 and 12 months, the numbers of patients with improvement in the symptom score were 199 of 272 (73.2%) and 198 of 272 (72.8%), respectively, in the ITT set, respectively (Table 3). Similar results were found in the PPS.

One hundred nineteen subjects (43.7%) used concomitant anti-allergy agents. Among the subjects who used concomitant anti-allergy agents, 64 subjects (23.5%) used one antiallergic agent, 47 subjects (17.3%) used two antiallergic agents, 6 subjects (2.2%) used three antiallergic agents, and 2 subjects (0.7%) used four antiallergic agents. The number of patients who did not require concomitant

Table 2 Rate of improvement in the VAS after specific immunotherapy*

Variable	ITT Set (N = 272), no. (%) (95% CI)			PPS (N = 211), no. (%) (95% CI)		
	All	Age, 5–14 y	Age, >14 y	All	Age, 5–14 y	Age, >14 y
Improvement in subject-evaluated VAS						
6 mo	207 (76.1) (70.6–81.0)	72 (76.6) (66.7–84.7)	134 (75.7) (68.7–81.8)	173 (82.0) (76.1–86.9)	64 (86.5) (76.5–93.3)	109 (79.6) (71.8–86.0)
12 mo	194 (71.3) (65.6–76.6)	71 (75.5) (62.6–83.8)	123 (69.5) (62.1–76.2)	180 (85.3) (79.8–89.8)	66 (89.2) (79.8–95.2)	114 (83.2) (75.9–89.0)
Improvement in investigator-evaluated VAS						
6 mo	212 (77.9) (72.5–82.7)	73 (77.7) (67.9–85.6)	138 (78.0) (71.1–83.8)	175 (82.9) (77.2–87.8)	63 (85.1) (75.0–92.3)	112 (81.8) (74.3–87.8)
12 mo	195 (71.7) (65.9–77.0)	72 (76.6) (66.7–84.7)	123 (69.5) (62.1–76.2)	181 (85.8) (80.3–90.2)	67 (90.5) (81.5–96.1)	114 (83.2) (75.9–89.0)

VAS = visual analog scale; ITT = intention-to-treat; CI = confidence interval; PPS = per-protocol set.
*There were no differences between the age subgroups.

Table 3 Changes in the VAS and symptom scores after specific immunotherapy*

Variable	ITT Set, mean (SD) (N = 272)			PPS, mean (SD) (N = 211)		
	All	Age, 5–14 y	Age, >14 y	All	Age, 5–14 y	Age, >14 y
Subject-evaluated VAS						
Baseline	5.93 ± 1.56	5.55 ± 1.66	6.12 ± 1.47	6.00 ± 1.39	5.70 ± 1.34	6.15 ± 1.40
6 mo	4.39 ± 1.83	4.14 ± 1.90	4.51 ± 1.78	4.51 ± 1.74	4.14 ± 1.71	4.71 ± 1.73
12 mo	3.32 ± 2.10	2.91 ± 1.90	3.55 ± 2.18	3.41 ± 2.13	3.04 ± 1.91	3.62 ± 2.22
Change in subject-evaluated VAS from baseline						
6 mo	–1.50 ± 1.72#	–1.36 ± 1.64	–2.58 ± 1.77	–1.48 ± 1.68#	–1.56 ± 1.50	–1.44 ± 1.77
12 mo	–2.52 ± 2.26#	–2.53 ± 1.95	–2.51 ± 2.42	–2.58 ± 2.26#	–2.66 ± 1.93	–2.54 ± 2.43
Investigator-evaluated VAS						
Baseline	6.04 ± 1.44	5.76 ± 1.45	6.18 ± 1.42	6.07 ± 1.36	5.81 ± 1.33	6.20 ± 1.36
6 mo	4.37 ± 1.74	4.20 ± 1.74	4.45 ± 1.74	4.46 ± 1.70	4.16 ± 1.59	4.62 ± 1.74
12 mo	3.34 ± 2.09	2.91 ± 1.87	3.57 ± 2.17	3.43 ± 2.11	3.03 ± 1.88	3.65 ± 2.20
Change in investigator-evaluated VAS from baseline						
6 mo	–1.64 ± 1.69#	–1.52 ± 1.51	–1.71 ± 1.78	–1.60 ± 1.68#	–1.64 ± 1.47	–1.58 ± 1.79
12 mo	–2.61 ± 2.24#	–2.73 ± 1.93	–2.55 ± 2.40	–2.63 ± 2.26#	–2.78 ± 1.95	–2.55 ± 2.41
Symptom score						
Baseline	5.61 ± 3.60	4.52 ± 3.26	6.21 ± 3.64	5.76 ± 3.56	4.83 ± 3.37	6.26 ± 3.57
6 mo	3.16 ± 2.41	2.73 ± 1.76	3.41 ± 2.67	3.28 ± 2.44	2.89 ± 1.80	3.49 ± 2.70
12 mo	1.86 ± 2.01	1.58 ± 1.33	2.01 ± 2.28	1.89 ± 2.03	1.61 ± 1.36	2.05 ± 2.31
Change in symptom score from baseline						
6 mo	–2.43 ± 3.42#	–1.90 ± 3.09	–2.72 ± 3.57	–2.48 ± 3.60#	–1.94 ± 3.24	–2.77 ± 3.75
12 mo	–3.79 ± 3.79#	–3.12 ± 3.47	–4.15 ± 3.92	–3.87 ± 3.83#	–3.22 ± 3.54	–4.22 ± 3.94

VAS = visual analog scale; ITT = Intention-to-treat; SD = standard deviation; PPS = per-protocol set.

*There were no differences among the age subgroups.

#Significantly different from baseline, $p < 0.0001$.

Table 4 Changes in concomitant antiallergy medication after specific immunotherapy*

Antiallergy Medication	ITT Set (N = 272), no. patients (%)#			PPS (N = 211), no. patients (%)		
	All	Age, 5–14 y	Age, >14 y	All	Age, 5–14 y	Age, >14 y
At baseline	153 (56.3)	54 (57.4)	98 (55.4)	115 (54.5)	44 (59.5)	71 (51.8)
One	64 (23.5)	19 (20.2)	45 (25.4)	51 (24.2)	13 (17.6)	38 (27.7)
Two	47 (17.3)	17 (18.1)	30 (16.9)	39 (18.5)	15 (20.3)	24 (17.5)
Three	6 (2.2)	4 (4.3)	2 (1.1)	4 (1.9)	2 (2.7)	2 (1.5)
Four	2 (0.7)	0	2 (1.1)	2 (0.9)	0	2 (1.5)
At 6 mo	202 (80.2)	73 (83.0)	129 (79.1)	169 (80.1)	63 (85.1)	106 (77.4)
One	33 (13.1)	9 (10.2)	23 (14.1)	27 (12.8)	6 (8.1)	21 (15.3)
Two	15 (6.0)	6 (6.8)	9 (5.5)	13 (6.2)	5 (6.8)	8 (5.8)
Three	2 (0.8)	0	2 (1.2)	2 (0.9)	0	2 (1.5)
Four	0	0	0	0	0	0
At 12 mo	206 (90.7)	71 (88.8)	135 (91.8)	192 (91.0)	67 (90.5)	125 (91.2)
One	12 (5.3)	6 (7.5)	6 (4.1)	10 (4.7)	4 (5.4)	6 (4.4)
Two	9 (4.0)	3 (3.8)	6 (4.1)	9 (4.3)	3 (4.1)	6 (4.4)
Three	0	0	0	0	0	0
Four	0	0	0	0	0	0

ITT = intention-to-treat; PPS = per-protocol set.

*There were no differences among the age subgroups.

#N = 272 at baseline, 252 at 6 mo (data unavailable for 20 patients), and 227 at 12 mo (data unavailable for 45 patients).

antiallergy medication was 153 of 272 (56.3%) at baseline, 202 of 252 (80.2%) at 6 months (data unavailable for 20 subjects), and 206 of 227 (90.7%) at 12 months (data unavailable for 45 subjects) in the ITT set (Table 4). Details of the types of antiallergy medication used by those patients who required it are presented in Supplemental Table 1. The mean (standard deviation) duration of exposure to HDM-SCIT was 331.2 ± 78.4 days (range, 1–414 days) in the ITT set and was 361.3 ± 12.7 days (range, 319–390 days) in the PPS, respectively. The vast majority of the patients showed good com-

pliance with the treatment: 249 of 252 patients (98.8%) in the ITT set (data not available for 20 patients).

Subgroup Analysis

Analysis of the proportion of patients with improvement in the VAS and the changes in the VAS revealed no significant differences for the children subgroup (age range, 5–14 years versus adolescents and adults subgroup (age > 14 years) (Tables 5 and 6). Similarly,

Table 5 Subgroup analyses of the number and fraction of patients with improvement in the VAS (subject evaluated) and the changes in the VAS after specific immunotherapy*

	With Asthma, ITT (N = 44)#	Without Asthma, ITT (N = 228)§	
Rate of improvement in subject- evaluated VAS, no. (%)			
6 mo	27 (61.4)	180 (78.9)	0.0123
12 mo	25 (56.8)	169 (74.1)	0.0201
Change in subject-evaluated VAS from baseline, mean (SD)			
6 mo	-1.38 ± 2.14	-1.52 ± 1.64	0.6847
12 mo	-1.70 ± 2.30	-2.66 ± 2.23	0.0226
Rate of improvement in investigator- evaluated VAS, no. (%)			
6 mo	29 (65.9)	183 (80.3)	0.0355
12 mo	24 (54.5)	171 (75.0)	0.0058
Change in investigator-evaluated VAS from baseline, mean (SD)			
6 mo	-1.61 ± 1.92	-1.65 ± 1.65	0.9041
12 mo	-1.80 ± 2.28	-2.76 ± 2.21	0.0212

VAS = visual analog scale; ITT = intention-to-treat; SD = standard deviation.

*Children: patient ages, 5–14 years; adults: patient ages, >14 years.

#Patients with allergic asthma, with or without allergic rhinitis.

§Patients with allergic rhinitis only.

Table 6 Subgroup analyses of the number and fraction of patients with improvement in the VAS (subject evaluated) and the changes in the VAS after specific immunotherapy*

	Rhinitis Alone ITT (N = 228)#	Rhinitis + Asthma ITT (N = 39)§	
Rate of improvement in subject- evaluated VAS, no. (%)			
6 mo	180 (78.9)	23 (59.0)	0.0069
12 mo	169 (74.1)	21 (53.8)	0.0098
Change in subject-evaluated VAS from baseline, mean (SD)			
6 mo	-1.52 ± 1.64	-1.42 ± 2.26	0.7886
12 mo	-2.66 ± 2.23	-1.65 ± 2.42	0.0231
Rate of improvement in investigator-evaluated VAS, no. (%)			
6 mo	183 (80.3)	25 (64.1)	0.0246
12 mo	171 (75.0)	20 (51.3)	0.0024
Change in investigator-evaluated VAS from baseline, mean (SD)			
6 mo	-1.65 ± 1.65	-1.67 ± 2.01	0.9335
12 mo	-2.76 ± 2.21	-1.76 ± 2.39	0.0236

VAS = visual analog scale; ITT = intention-to-treat; SD = standard deviation.

*Children: patient ages, 5–14 years; adults: patient ages, >14 years.

#Patients with allergic rhinitis only.

§Patients with both allergic rhinitis and allergic asthma.

there were no significant differences between these subgroups with regard to symptom score or concomitant use of antiallergy medications at 6 and 12 months (data not shown). The proportion of patients with improvement in the VAS by subject evaluated (at 6 and 12 months) and the changes in the VAS (at 12 months) were significantly greater ($p < 0.05$) in patients with AR than those with AA (see Tables 5 and 6). However, no differences in symptom scores were identified (data not shown). The use of antiallergy agents was higher in patients with asthma than in those without asthma, at both 6 and 12 months ($p < 0.05$; data not shown).

Safety Outcomes

Among the 272 subjects in the safety set, a total of 12,559 injections were administered. During these injections, a total of 65 patients (23.9%) experienced at least one AE (Table 7); of these, 46 patients (16.9%) were considered to have study drug-related allergic reactions, which accounted for 1% (126/12,559) of the total injections. Among the 126 SCIT-related allergic reactions, there were 59 intense local allergic reactions (26 subjects with adverse reactions), 67 mild systemic allergic reactions (27 subjects with adverse reactions). No

serious systemic allergic reactions were observed, and no study drug-related SAEs occurred (Supplemental Table 2).

DISCUSSION

The common cause of AR and/or AA in Chinese patients was due to *D. pteronyssinus* and/or *D. farina*.^{21,22} In 2009, a cross-sectional survey was performed in 6304 patients with asthma and/or rhinitis in 17 cities from four regions in China.²³ The overall prevalence of positive SPT responses was 57.6% for *D. pteronyssinus* and 59.0% for *D. farina*.¹ In China, HDMs were the most prevalent allergens in patients with asthma and/or rhinitis.²⁴ There were significant differences in the patterns of sensitizations in the patients from different geographic areas, age groups, and manifestation as asthma and/or rhinitis.¹

HDM-SCIT is the only double-mite allergen preparation currently available in China. The present study has two major advantages over previous clinical reports concerning the use of HDM-SCIT in China: (1) the study was performed as a large-scale multicenter study in a population that consisted of children, adolescents, and adults, which had a good representativeness of typical patients with AR; and (2) the

Table 7 AEs reported during specific immunotherapy*

	Total (N = 272)		Age, 5–14 years (N = 94)		Age, >14 y (N = 177)	
	No.	Rate (95% CI), %	No.	Rate, %	No.	Rate, %
At least one AE*	65	23.9 (19.0–29.4)	19	20.2	45	25.4
Treatment-related AE*	46	16.9 (12.7–21.9)	10	10.6	35	19.8
AEs that led to dose reduction	23	8.5 (5.4–12.4)	5	5.3	18	10.2
AEs that led to suspension of treatment	3	1.1 (0.2–3.2)	3	3.2	0	0
AEs that led to treatment discontinuation	4	1.5 (0.4–3.7)	2	2.1	2	1.1
AEs that led to withdrawal from the study	4	1.5 (0.4–3.7)	2	2.1	2	1.1
Significant AEs*#	39	14.3 (10.4–19.1)	11	11.7	27	15.3
SAEs	1	0.4 (0.0–2.0)	1	1.1	0	0
Severe and treatment-related AEs	0	0.0 (0.0–1.3)	0	0	0	0
SAE	2	0.7 (0.1–2.6)	1	1.1	1	0.6
Treatment-related SAEs	0	0.0 (0.0–1.3)	0	0	0	0
AEs that led to death	0	0.0 (0.0–1.3)	0	0	0	0

AE = adverse event; CI = confidence interval; SAE = serious adverse event.

Data are from the safety set (N = 272).

*The age of one patient is missing.

#AEs other than SAEs that affected the study drug dose (dose reduction, or suspension or cessation of treatment) or resulted in other actions (medical treatment or other treatment).

concomitant use of antiallergic agents was not limited during SIT, which allowed a more-comprehensive evaluation of the clinical risks and benefits. Usually, efficacy was evaluated based on reported symptoms and/or medication scores, validated quality-of-life instrument immunologic assays, challenge testing, and AEs.²⁵ In the present noninterventonal study design, the concomitant use of antiallergic agents was added to evaluate the efficacy of SIT. The results were in accordance with the VAS score. That could provide an effective way of gathering real-world evidence, which can be used more directly in the clinical practice.

Although SIT is usually effective within 2–4 months of treatment, a treatment period of at least 3 years is generally recommended to obtain long-term effects after cessation of treatment.²⁶ Currently, the optimal duration of immunotherapy to achieve maximal efficacy is not known, and this may be dependent on the individual subject's specific situation, sensitivity, or allergen type. In the present study, the majority of subjects already showed significant efficacy at 6 months of treatment, with additional benefit observed after 1 year of treatment. This is consistent with a previous report and demonstrated early and consistent efficacy with HDM-SCIT treatment.²⁷

In this study, disease-subgroup analysis showed that the improvement rate was higher in the patients without asthma than in the patients with asthma and that SIT also was more effective at reducing the concomitant use of antiallergy agents in the former subgroup, particularly the use of antihistamines. Since AR and AA are both mediated by similar allergic inflammatory mechanism. More than 40% of patients with AR had asthma and >80% of patients with asthma had concomitant rhinitis. Also, patients with rhinitis have an increased risk of developing asthma.²⁶ The present results indicated that patients with AR should be treated with SIT as soon as possible to gain the reduction in symptoms of rhinitis and potential prevention of asthma, which is also recommended in the latest AR and its Impact on Asthma guideline.²⁶ Analysis between different age groups carried out in this study indicated that the effect of HDM-SCIT did not depend on age. Earlier in life the immune system is more susceptible to sensitization but also to induction of tolerance; it remains possible that the efficacy of SIT is superior in children compared with adults.²⁶ But, in this study, such superiority was not found due to this being a real-world study.

Results obtained with SIT depot preparations in 488 subjects in 14 centers in Spain showed that 3.7% of subjects experienced systemic

reactions during conventional standard allergen immune therapy, and no systemic SAEs were observed.²⁸ In China, a safety study of HDM-SCIT in 256 subjects with AR revealed that the occurrence of local and systemic AEs was 4.5% and 0.31%, respectively.²⁹ In the present study, AEs occurred with 1% of all injections and study-related AEs occurred in 16.9% of all the subjects. There were no study-related SAEs or AEs that led to death. Most AEs were local or mild systemic AEs and were well tolerated by the subjects; the symptoms disappeared after appropriate treatment. Intense local allergic reactions occurred in 9.6% of all the subjects and 0.5% of all the injections. No systemic SAEs were observed, which was consistent with a previous study.³⁰

All the subjects maintained good compliance, with a compliance rate of 98.8%. This may be related because the study was supervised by an experienced medical staff, with active communication maintained between the staff and the patients to ensure that the patients were well informed at all times and with careful evaluation of AEs and clinical symptoms at each visit to ensure that appropriate intervention (including adjustment of subsequent HDM-SCIT dosage) was made when required.

Our study had limitations. First, this was a single-arm, open-label study. There was no randomization and blinding in the study. Second, the heterogeneity of individuals was complex due to combining AR with AA. Third, only patients with AA and with a forced expiratory volume in 1 second value of >80% were included in the study, which is the intermittent or mild persistent AA, therefore, the data record of AA classification was not necessary. Addition bias was a total of 12 subjects of concomitant serious illness and/or chronic diseases other than allergic diseases, which indicated the good physical condition of the subjects. Subgroup analysis in the two allergic diseases could not present high-level evidence. Further research with larger populations should be carried out to verify the present results and validate the changes in patients with AR or asthma.

CONCLUSION

Treating Chinese patients with AR and/or AA by using HDM-SCIT for 1 year resulted in improved disease symptoms and decreased antiallergic medication. The treatment was well tolerated, with a majority of the patients showing good compliance, and raised no safety concerns.

REFERENCES

- Li J, Sun B, Huang Y, et al. A multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. *Allergy* 64:1083–1092, 2009.
- Huang C, Liu W, Hu Y, et al. Updated prevalences of asthma, allergy, and airway symptoms, and a systematic review of trends over time for childhood asthma in Shanghai, China. *PLoS One* 10:e0121577, 2015.
- Zheng M, Wang X, Bo M, et al. Prevalence of allergic rhinitis among adults in urban and rural areas of china: A population-based cross-sectional survey. *Allergy Asthma Immunol Res* 7:148–157, 2015.
- Zhang YM, Zhang J, Liu SL, et al. Prevalence and associated risk factors of allergic rhinitis in preschool children in Beijing. *Laryngoscope* 123:28–35, 2013.
- Knisely AJ, and Lee S. Advances in subcutaneous immunotherapy. *Curr Opin Otolaryngol Head Neck Surg* 22:216–220, 2014.
- Feng S, Xu Y, Ma R, et al. Cluster subcutaneous allergen specific immunotherapy for the treatment of allergic rhinitis: A systematic review and meta-analysis. *PLoS One* 9:e86529, 2014.
- Canonica GW, Bousquet J, Casale T, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 64(suppl. 91):1–59, 2009.
- Pfaar O, and Gerth van Wijk R. Mite-allergic rhinitis: How to evaluate clinical efficacy in allergen-specific immunotherapy trials? *Curr Treat Options Allergy* 2:1–9, 2015.
- Calderon MA, Linneberg A, Kleine-Tebbe J, et al. Respiratory allergy caused by house dust mites: What do we really know? *J Allergy Clin Immunol* 136:38–48, 2015.
- Chyrek-Borowska S, Rogalewska A, Szymanski W, et al. Efficacy and tolerance of allergenic extracts Allergovit and Novo-Helisen depot in immunotherapy of allergic diseases [in Polish with English abstract]. *Pneumonol Alergol Pol* 63(suppl. 2):32–41, 1995.
- Ullrich D, Thum-Oltmer S, Mussler S, et al. Successful specific subcutaneous immunotherapy (SCIT) with non-modified semi-depot pollen and mite preparations: Results of a post-marketing surveillance study. *Allergo J* 16:193–198, 2007.
- Kettner J, Narkus A, Meyer H, et al. Efficacious management of house dust mite allergy by 3 years of specific immunotherapy with allergen extract. *Allergy Clin Immunol Int—J World Allergy Org* 62:s264–s265, 2007.
- Subspecialty Group of Rhinology, Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery, and Subspecialty Group of Rhinology, Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association. Guidelines for diagnosis and treatment of allergic rhinitis (2009, Wuyishan) [in Chinese]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi* 44:977–978, 2009.
- Subspecialty Group of Respiratory Diseases Society of Pediatrics, Chinese Medical Association, and Chinese Journal of Pediatrics Editorial Board. Guideline for the diagnosis and optimal management of asthma in children. *Zhonghua Er Ke Za Zhi* 46:745–753, 2008.
- Ukena D, Fishman L, and Niebling WB. Bronchial asthma: Diagnosis and long-term treatment in adults. *Dtsch Arztebl Int* 105:385–394, 2008.
- Bousquet J, Khaltaev N, Cruz AA, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 63(suppl. 86):8–160, 2008.
- Senti G, Vavricka BM, Graf N, et al. Evaluation of visual analog scales for the assessment of symptom severity in allergic rhinoconjunctivitis. *Ann Allergy Asthma Immunol* 98:134–138, 2007.
- Bousquet PJ, Combescure C, Neukirch F, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 62:367–372, 2007.
- European Medicines Agency. Pre-Authorisation Evaluation of Medicines for Human Use. Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. Doc. Ref. CHMP/EWP/18504/2006, 2008.
- Colas C, Monzon S, Venturini M, and Lezaun A. Double-blind, placebo-controlled study with a modified therapeutic vaccine of *Sal-sola kali* (Russian thistle) administered through use of a cluster schedule. *J Allergy Clin Immunol* 117:810–816, 2006.
- Yu JM, Luo QH, Sun JL, et al. Diversity of house dust mite species in Xishuangbanna Dai, a tropical rainforest region in southwest China. *Biomed Res Int* 2015:421716, 2015.
- Zhang C, Li J, Lai X, et al. House dust mite and storage mite IgE reactivity in allergic patients from Guangzhou, China. *Asian Pac J Allergy Immunol* 30:294–300, 2012.
- Li J, Huang Y, Lin X, et al. Factors associated with allergen sensitizations in patients with asthma and/or rhinitis in China. *Am J Rhinol Allergy* 26:85–91, 2012.
- Hong H, Yang Q, Zuo K, et al. A hospital-based survey on the prevalence of bronchial asthma in patients with allergic rhinitis in southern China. *Am J Rhinol Allergy* 27:502–505, 2013.
- Purkey MT, Smith TL, Ferguson BJ, et al. Subcutaneous immunotherapy for allergic rhinitis: An evidence based review of the recent literature with recommendations. *Int Forum Allergy Rhinol* 3:519–531, 2013.
- Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 126:466–476, 2010.
- Wang H, Lin X, Hao C, et al. A double-blind, placebo-controlled study of house dust mite immunotherapy in Chinese asthmatic patients. *Allergy* 61:191–197, 2006.
- Moreno C, Cuesta-Herranz J, Fernandez-Tavora L, et al. Immunotherapy safety: A prospective multi-centric monitoring study of biologically standardized therapeutic vaccines for allergic diseases. *Clin Exp Allergy* 34:527–531, 2004.
- Chen J, Xiang J, Kong W, et al. Safety analysis of Allergovit immunotherapy in patients of allergic rhinitis. *Lin Chuang Er Bi Yan Hou Ke Za Zhi* 20:208–209, 2006.
- Wang HY, Lin XP, Hao CL, et al. Effect of 1-year specific immunotherapy with standardized house dust mite vaccine on mild to moderate allergic asthmatic patients. *Zhonghua Jie He He Hu Xi Za Zhi* 29:679–687, 2006. □

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