

The efficacy and safety of two commercial house dust mite extracts for allergic rhinitis: a head-to-head study

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Background: Several studies have demonstrated the efficacy of house dust mite (HDM) immunotherapy in allergic rhinitis (AR). We aimed to compare the efficacy and safety of 2 commercial HDM extracts in a Chinese AR population.

Methods: This was an open-label study. HDM-associated AR patients were randomized into *Dermatophagoides pteronyssinus* (Dp) extracts (Alutard SQ; ALK, Hørsholm, Denmark) and *Dp/Dermatophagoides farinae* (Df) extracts (NovoHelisen Depot [NHD]; Allergopharma, Reinbek, Germany) groups. All patients received subcutaneous injections for 1 year, and were followed every 3 months during that 1-year period. Symptom score, medication score, and adverse reactions were recorded. The primary endpoint was the total combined symptom and medication score (CSMS) during the efficacy evaluation period. Blood samples were taken for specific immunoglobulin E (IgE), IgG4, and IgE-blocking factor tests at baseline and after the 1-year treatment.

Results: A total of 230 AR patients were randomized; 29 patients dropped out. Analysis of the primary endpoint demonstrated significant reductions in CSMS of 1.8 vs 3.1 ($p < 0.001$) in the Alutard group and 1.8 vs 3.3 ($p < 0.001$)

in the NHD group compared with baseline. The 2 groups presented equal effectiveness with regard to CSMS, symptom score, and medication score ($p > 0.05$). The treatment was well tolerated in both groups; 17 (14.8%) patients experienced systemic reactions (SRs) in the Alutard group and 13 (11.3%) in the NHD group. The rates of SRs showed no difference in the 2 groups ($p > 0.05$), and no anaphylaxis occurred. IgG4 and IgE-blocking factor to Dp and Df were increased significantly in both groups after the 1-year treatment.

Conclusion: Our study confirmed the equal efficacy and safety profile of both commercial extracts in HDM-associated AR patients. © 2019 ARS-AAOA, LLC.

Key Words:

allergic rhinitis; immunotherapy; allergens; biomarker; rhinitis

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Allergic rhinitis (AR) is the most common respiratory allergic disease, affecting 10% to 30% of all adults and as many as 40% of children.¹ The prevalence of AR continues to increase worldwide. In China, the self-reported AR in the general Chinese adult population has significantly increased from 11.1% to 17.6% during a 6-year period, becoming the most prevalent chronic disorder in

China.² House dust mites (HDMs) are 1 of the most common sources of indoor allergens and can trigger perennial AR and asthma. Our previous study found that HDMs are the major aeroallergens among AR patients in central China, with a sensitization rate of over 90%.³ The 2 main species of HDMs are *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df); the majority of patients with HDMs are co-sensitized to both species.⁴

Allergen immunotherapy (AIT) is the only treatment option for allergic diseases with disease-modifying effect and is thus a potential for long-term relief of symptoms even after treatment cessation.⁵ AIT has been shown to be effective in the treatment of HDM-associated AR. Clinical benefits of AIT require administration of standardized allergen vaccine in adequate doses and for sufficient periods of time (3 to 5 years).⁶ However, the allergen and protein content of

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commercial extracts is highly variable among manufacturers, and is still based on in-house reference materials with different standardization methods. This makes the comparison among allergen extracts quite difficult,⁷ and represents a major cause of the heterogeneity of clinical studies of AIT. In China, only 2 commercial HDM extracts are available for subcutaneous immunotherapy, *Dp* extracts (Alutard SQ) provided by ALK (Hørsholm, Denmark), and *Dp/Df* (50/50) extracts (NovoHelisen Depot [NHD]) provided by Allergopharma (Reinbek, Germany). The 2 HDM extracts have been demonstrated to be effective in AR treatment through a series of randomized controlled studies and real-life studies, respectively.^{8–12} Because the ingredients of the 2 HDM extracts are different, doctors may be curious about which product will be of greater benefit for their patients. In this study, we compared the efficacy and safety profile of the 2 commercial HDM extracts in a Chinese AR population and investigated the subsequent immunological parameters change after 1 year of AIT.

Patients and methods

Study design

This was an open-label randomized controlled study conducted in Tongji Hospital from January 2016 to May 2018. HDM-associated AR patients were enrolled and 1:1 randomized (4 patients in 1 block) to receive treatment with Alutard or with NHD for 1 year. This study was approved by the Independent Ethical Committee of Tongji Hospital.

Study population

Patients with moderate-to-severe HDM-induced AR were enrolled. Inclusion criteria were as follows: (1) age 5 to 60 years; (2) diagnosed with AR with or without allergic asthma according to the Allergic Rhinitis and its Impact on Asthma Guidelines (ARIA)¹³ and Global Initiative for Asthma (GINA) (<https://ginasthma.org/>) guidelines; (3) positive skin-prick tests to *Df* and *Dp* (Macro-Union Pharmaceutical, Beijing, China) and serum specific immunoglobulin Es (IgEs) against *Df* and *Dp* ≥ 0.70 kU/L (Thermo-Fisher, Uppsala, Sweden); and (4) allergic symptoms of rhinitis and/or asthma after exposure to HDM. The exclusion criteria were as follows: (1) sensitized to other allergens (specific IgE ≥ 0.70 kU/L) such as pollens and molds, and experiencing symptoms after allergen exposure; (2) an existing nasal condition such as nasal polyp or deviation of nasal septum that could confound efficacy and safety evaluation; (3) asthma requiring treatment other than inhalant corticosteroids; (4) with autoimmune diseases, cardiovascular disorders, or use of β blockers or angiotensin-converting enzyme (ACE) inhibitors; and (5) prior history of AIT.

Intervention medication

Each subject was randomly assigned to receive Alutard SQ or NHD HDM extracts. Alutard SQ HDM is an allergen extract derived from *Dp* manufactured by ALK-Abello Denmark. NHD HDM is an allergen extract derived from *Dp* and *Df* (50/50) manufactured by Allergopharma, Germany. The manufacturers claim that the major HDM allergen contents (*Dp*) are $9.8 \mu\text{g/mL}$ for Alutard SQ HDM and the major HDM allergen contents (*Dp* and *Df*) are $6.4 \mu\text{g/mL}$ for NHD HDM.

All the patients received allergen injection at Tongji Hospital. The buildup phase was carried out with the conventional schedule provided by the manufacturer. In the Alutard group, patients received injections weekly at a volume of 0.2, 0.4, and 0.8 mL in the No. 1 to 3 vials and 0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 mL in the No. 4 vial, reaching the maintenance dose, 100,000 Standardized Quality Units (SQ-U). In the NHD group, patients received injections weekly at a volume of 0.2, 0.4, and 0.8 mL in the No. 1 to 2 vials and 0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 mL in the No. 3 vial, reaching the maintenance dose, 5000 Treatment Units (TU). Then, the maintenance dose was given on a 6-week basis in both groups according to the manufacturer's instructions. The baseline was defined as the day that patients received the first dose of HDM extract immunotherapy. The evaluation period was every 3 months.

End points and assessments

A total of 4 AR symptoms (sneezing, rhinorrhea, itching, and nasal obstruction) were measured on a scale from 0 to 3 (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe symptom). The symptom score was defined as the average value of the 4 symptom scores (range, 0 to 3). The medication score was defined as follows: 0 = "no rescue medication taken"; 1 = "use of antihistamines (oral, intranasal, ophthalmic, or both)"; 2 = "use of nasal corticosteroids"; and 3 = "use of oral corticosteroids." If more than 1 class of rescue medication was used on a particular day, the highest score was recorded for the medication score. The primary end point was the total combined symptom and medication score (CSMS, which is the sum of rhinitis symptom and medication score; range, 0 to 6). In addition, to determine the potential factors related to AIT response, we defined a reduction of over 30% of CSMS after 1-year treatment as successful AIT.¹⁴ The second end point was the symptom score and medication score.

Adverse reactions related to AIT were recorded. After each injection, patients were kept under observation for 30 minutes. Allergen extract dosage, adjustment in therapy, pulmonary function testing results, and details of local and/or systemic reactions such as onset time, manifestations, and treatment were recorded.

Immunological parameters were measured at baseline and after 1 year of AIT to confirm the AR sensitization profile and to evaluate the specific immunological response

to AIT; the parameters included specific IgE and IgG4 to HDM and IgE-blocking factors.^{15,16}

Statistical analysis

Sample size was calculated using non-inferiority test with a 1-sided 0.05 significance level and a 13% delta. The effective percentage of Alutard SQ and NHD HDM CSMS reduction was 69.7%¹² and 71.3%¹¹ in previous studies; it was calculated that 196 patients (98 per group) were required to achieve a power of 80%.

Descriptive parameters, such as means and standard deviations for normally distributed continuous data, and frequencies and percentages for categorical data, were calculated. The *t* test was used to evaluate the continuous variable and 95% confidence intervals (CIs) were generated between the 2 groups. The chi-square test and nonparametric test were used to determine the association between categorical variables. All tests were performed 2-tailed, and *p* < 0.05 was considered statistically significant. The Statistical Package for Social Sciences (SPSS version 19.0; IBM, Armonk, NY) was used for all statistical analyses.

Results

Population

A total of 272 AR patients were screened and 230 were randomized in the study; 86 were female. The mean age was 15.0 years. The mean disease duration was 4.0 years. Fifty-one (22.2%) of the patients had a history of asthma. Fourteen patients in the Alutard group (115) and 15 in the NHD group (115) dropped out (Fig. 1). The demographic characteristics of the 2 groups were comparable (*p* > 0.05) (Table 1).

Efficacy

After 1 year of treatment, the CSMS was significantly lower in the 2 groups compared with the baseline (1.8 vs 3.1 in Alutard group and 1.8 vs 3.3 in NHD group). There was no significant difference between the 2 groups. A reduction of CSMS over 30% was observed compared with the baseline after 3-month AIT in both groups. The CSMS decreased continuously with prolonged AIT at 3 months, 6 months, 9 months, and 1 year. No differences of the CSMS of the 2 groups were found at the consecutive time point (*p* > 0.05) (Fig. 2). The proportion of responders (the patients whose CSMS decreased over 30% after 1 year AIT) was 77.2% (78/101) in the ALK group and 74.0% (74/100) in the NHD group (*p* > 0.05).

The secondary end points were AR symptom score and medication score. They presented similar decrease trends as CSMS. The symptom score and medication score were lower than baseline in both groups (*p* < 0.05). However, no differences were found between the 2 groups (*p* > 0.05) (Fig. 2).

TABLE 1. Demographic characteristics of the Alutard and the NHD groups

Characteristic	Alutard	NHD	<i>p</i>
Gender, n (%)			0.413
Male	69 (60.0)	75 (65.2)	
Female	46 (40.0)	40 (34.8)	
Age (years), n (%)			0.625
Children (5–12 years)	75 (65.2)	76 (66.1)	
Adolescents (13–18 years)	5 (4.3)	8 (7.0)	
Adults (>18 years)	35 (30.4)	31 (27.0)	
BMI (kg/m ²), mean ± SD	18.2 ± 4.2	18.7 ± 4.2	0.349
Duration (years), mean ± SD	3.9 ± 4.3	4.2 ± 3.8	0.423
Family history, n			1.000
Yes	71	71	
No	44	44	
Diagnosed, n (%)			
With asthma	23 (20.0)	28 (24.3)	0.427
Without asthma	92 (80.0)	87 (75.7)	0.666
Smoking history, n			
Nonsmoker	104	102	
Smoker (>1 year)	11	13	
Allergen-specific IgE (kU/L), mean ± SD			
<i>Dp</i>	44.9 ± 38.4	48.57 ± 39.0	0.500
<i>Df</i>	50.3 ± 38.3	54.23 ± 39.6	0.469

BMI = body mass index; *Df* = *Dermatophagoides farinae*; *Dp* = *Dermatophagoides pteronyssinus*; IgE = immunoglobulin E; NHD = NovoHelisen Depot; SD = standard deviation.

Safety

In general, the 2 HDM extracts were well tolerated in AR patients. The incidences of local reactions were 58.3% (67/115) in the Alutard group and 57.4% (66/115) in the NHD group. In the Alutard group, 17 (14.8%) experienced systemic reactions, including 7 (6.1%) grade 1, 9 (7.8%) grade 2, 1 (0.9%) grade 3, and no anaphylaxis. In the NHD group, 13 (11.3%) experienced systemic reactions, including 9 (7.8%) grade 1, 4 (3.5%) grade 2, and no anaphylaxis. The incidence of local and systemic reactions showed no differences between the 2 groups (*p* > 0.05).

Immunological parameters

The blood samples were taken for specific IgE, IgG4 to *Dp/Df* and IgE-blocking factor analyze at baseline and 1-year AIT, 71 patients in the Alutard group and 67 in the NHD group were analyzed. The levels of serum *Dp* and *Df* specific IgG4 and IgE-blocking factor were significantly increased after 1 year AIT in both groups, while specific

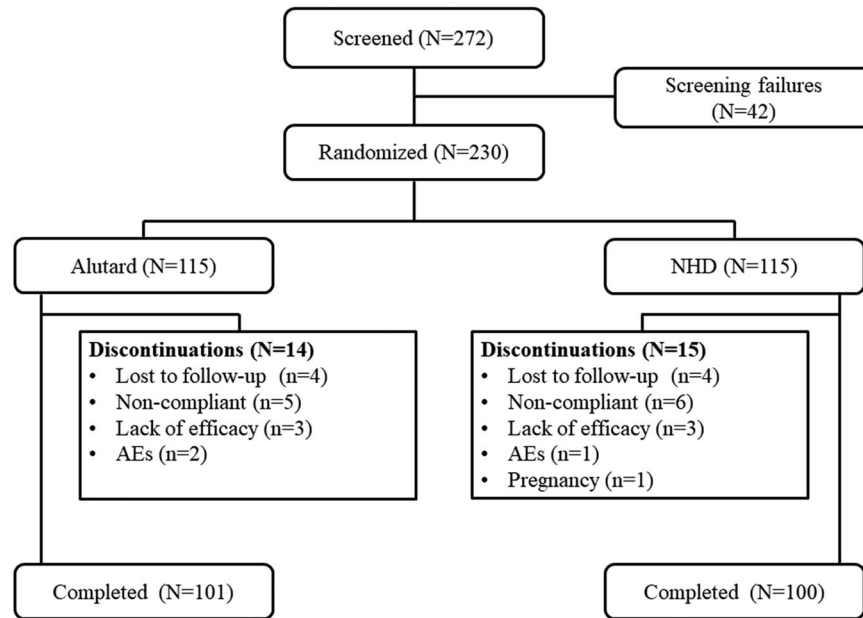


FIGURE 1. Subject disposition showing number of screened, randomized, and completed subjects, as well as reasons for discontinuations.

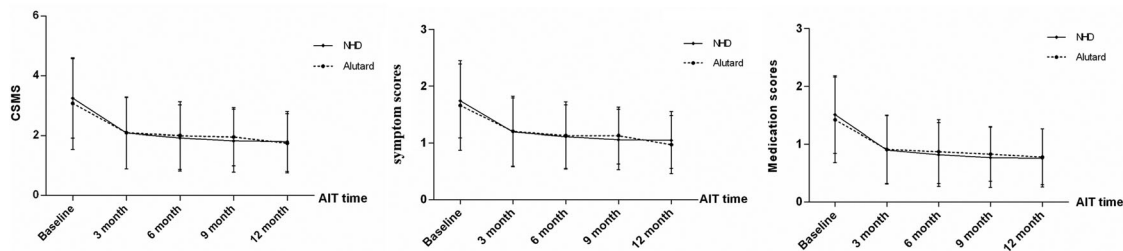


FIGURE 2. Changes of CSMS, symptom score, and medication score at different time points of AIT. Adjusted means with 95% CIs of CSMS, symptom score, and medication score in the Alutard and the NHD groups, there was no statistically difference between the Alutard and the NHD groups. AIT = allergen immunotherapy; CI = confidence interval; CSMS = combined symptom and medication score; NHD = NovoHelisen Depot.

TABLE 2. Changes of immunological parameters after 1-year AIT in Alutard and NHD groups

	Alutard (n = 71)			NHD (n = 67)		
Parameter	Before treatment	After treatment	p	Before treatment	After treatment	p
Dp IgE (kU/L)	41.18 (9.22–146.27)	65.19 (24.73–146.19)	0.105	36.94(9.51–189.66)	127.05 (29.00–258.80)	0.000
Df IgE (kU/L)	45.25 (12.20–131.77)	47.69 (22.64–107.95)	0.683	37.26(15.63–137.34)	79.13 (31.29–210.03)	0.000
Dp IgG4 (mg/L)	0.12 (0.05–0.23)	1.52 (0.65–3.19)	0.000	0.13 (0.05–0.26)	1.46 (0.56–2.70)	0.000
Df IgG4 (mg/L)	0.15 (0.06–0.32)	1.34 (0.53–3.00)	0.000	0.20 (0.08–0.39)	2.28 (1.07–4.96)	0.000
Dp IgE-blocking factor	−0.11 (−0.29 to 0.07)	0.29 (0.20–0.43)	0.000	−0.09 (−0.23 to 0.05)	0.23 (0.12–0.35)	0.000
Df IgE-blocking factor	−0.07 (−0.07 to 0.09)	0.30 (0.17–0.41)	0.000	−0.07 (−0.20 to 0.08)	0.29 (0.13–0.44)	0.000

AIT = allergen immunotherapy; Df = *Dermatophagoides farinae*; Dp = *Dermatophagoides pteronyssinus*; Ig = immunoglobulin; NHD = NovoHelisen Depot.

IgE to Dp and Df were increased only in the NHD group ($p < 0.001$). The NHD group showed a higher Dp and Df IgE and Df IgG4 increment and a lower Dp IgE-blocking factor increment than the Alutard group ($p < 0.05$) (Tables 2 and 3).

To explore the potential immunological parameters for predicting successful AIT, the data in the Alutard group and the NHD group were merged for analysis. All the patients were categorized into AIT responder or nonresponder, by evaluating the reduction of CSMS over 30% compared with

TABLE 3. Comparison of immunological parameters between the Alutard and the NHD groups

Parameter	Alutard (n = 71)	NHD (N = 67)	p
Δ Dp IgE (kU/L)	7.25 (–15.58–34.22)	21.56 (0.76–91.59)	0.011*
Δ Df IgE (kU/L)	0.17 (–26.10–16.80)	16.47 (–1.41–67.28)	0.001*
Δ Dp IgG4, after/before ratio	9.47 (5.52–21.10)	12.16 (6.74–20.45)	0.489
Δ Df IgG4, after/before ratio	7.40 (3.55–13.21)	10.89 (6.13–20.05)	0.014*
Δ Dp IgE-blocking factor	0.41 (0.28–0.53)	0.32 (0.16–0.46)	0.044*
Δ Df IgE-blocking factor	0.38 (0.23–0.47)	0.35 (0.22–0.49)	0.918

*p < 0.05.

Δ = changes before and after 1-year AIT; AIT = allergen immunotherapy; Df = *Dermatophagoides farinae*; Dp = *Dermatophagoides pteronyssinus*; Ig = immunoglobulin; IgG4 ratio = value of the IgG4 concentration after 1-year AIT divided by the IgG4 concentration at baseline; NHD = NovoHelix Depot.

TABLE 4. Changes of immunological parameters in responders and nonresponders

Parameter	Responders (n = 103)	Nonresponders (n = 35)	p
Δ Dp IgE (kU/L)	11.87 (–3.69 to 40.18)	22.95 (–11.84 to 102.98)	0.262
Δ Df IgE (kU/L)	4.64 (–18.69 to 25.04)	14.75 (–11.56 to 86.17)	0.157
Δ Dp IgG4, after/before ratio	10.48 (6.75–17.71)	19.35 (4.56–45.38)	0.095
Δ Df IgG4, after/before ratio	9.00 (4.29–16.53)	12.90 (6.27–41.63)	0.065
Δ Dp IgE-blocking factor	0.37 (0.22–0.49)	0.39 (0.21–0.57)	0.560
Δ Df IgE-blocking factor	0.37 (0.23–0.47)	0.36 (0.18–0.52)	0.723

Δ = changes before and after 1-year AIT; AIT = allergen immunotherapy; Df = *Dermatophagoides farinae*; Dp = *Dermatophagoides pteronyssinus*; Ig = immunoglobulin; IgG4 ratio = value of the IgG4 concentration after 1-year AIT divided by the IgG4 concentration at baseline.

baseline. There were no differences regarding the parameters between AIT responders and nonresponders ($p > 0.05$) (Table 4).

Discussion

Our study indicated an equal efficacy and safety profile of 2 commercial standardized HDM extracts in a Chinese AR population despite a minor difference in AIT immunological changes. Although the 2 HDM extracts have demonstrated their efficacy and safety in several studies, the extracts were usually compared with placebo or even self-control group.^{8–10} In addition, the designs and predefined clinical outcomes varies greatly in different trials, which make the comparison of clinical benefits of different commercial HDM extracts become quite difficult.^{17,18} Until now, there have been very few head-to-head studies for HDM immunotherapy in AR patients. A recommendation for the standardization of clinical outcomes used in AIT trials for AR was purposed recently.¹⁹ In our study, we directly compared the efficacy and safety of the 2 HDM extracts using a predefined protocol according to the recommendation. Because the treatment regimens were different for the 2 HDM extracts, the study was designed as open-label. One reason was the double-dummy HDM extracts were difficult to acquire, and another reason was that our patients, especially children, were

reluctant to receive additional injections of placebo. However, the open-label designation of the study allowed us to recruit enough qualified AR patients in a relatively short time.

The symptoms and medication use were significantly improved after 1 year of AIT with the 2 HDM extracts. The efficacy of AIT could be observed at 3 months and the CSMS scores decreased consecutively at 6, 9, and 12 months, which was consistent with previous studies.^{11,12} Our study implied that the subcutaneous immunotherapy had an early effect on AR symptoms. However, there is still no consensus of the correlation of the cutoff value of CSMS change and the degree of patient perceived AR improvement (eg, worse, or slight, moderate, or significant improvement). In a recent HDM tablet AIT trial, a predefined absolute difference of total combined rhinitis score (range, 0 to 24) of 1.00 with placebo was regarded as improved (clinically relevant).¹⁷ In our study, the changes of CSMS in the 2 groups were comparable (1.10 and 1.12 after AIT, respectively). We were not able to determine the absolute difference of the 2 HDM extracts due to the lack of a placebo control group. Another issue of the study was to define the responder to AIT. The change of CSMS after AIT relies on the scoring system (eg, range from 0 to 24 or 0 to 12),^{17,18} which makes a predefined absolute uniformed score change of responder impractical. Thus, a relative change of CSMS compared with baseline is more

acceptable to describe responders.^{12,18} In our study, we also defined a decrease of 30% as a responder for the subsequent analysis. Of the AR patients in the ALK group, 77.2% (78/101) were responders, and 74.0% (74/100) in NHD group were responders, which also implied the efficacy of the 2 HDM extracts.

The 2 HDM extracts were well tolerated. Although local reactions were found in the majority of the AR patients, they were mild and tolerable. Systemic reactions were observed in 14.8% of the AR patients in the Alutard group and in 11.3% of the NHD group, which were similar to our previous studies.²⁰ No anaphylaxis was observed and there was no difference between the 2 groups in terms of asthma exacerbation or onset. The incidence of systemic reactions (SRs) in our study was higher than other studies in Europe,²¹ while similar to the studies in China,²⁰ which might be due to ethnic differences, study population, and level of HDM exposure.^{22,23} Two patients in the Alutard group and 1 patient in NHD group dropped out because of SRs. The findings suggested that the 2 HDM extracts were safe in AR patients, in addition to similar efficacy.

Immune responses to AIT in the 2 groups were also similar. HDM specific IgG4 and IgE-blocking factor were significantly increased after 1 year AIT. These changes were in consistent with other studies.^{15,16} Minor differences in immunological parameters were observed in the 2 groups, eg, specific IgG4 to *Df* increased higher in the NHD group while *Dp* specific IgE-blocking factor increased higher in the Alutard group, which might account for the different formula of the 2 HDM extracts (*Dp/Df* 50/50 in NHD and single *Dp* in Alutard). However, these differences had no impact on the efficacy of the 2 extracts. In addition, we merged the data of the 2 groups and tried to figure out the immunological parameters in the AIT responders and nonresponders. We found no difference regarding the parameters, which was also consistent with previous studies.²⁴

These findings indicated that IgE, IgG4, and IgE-blocking factors might be not suitable for predicting successful AIT.

This is the first head-to-head study concerning to the efficacy and safety of the 2 commercial HDM extracts in China, as far as we know. However, some limitations may hamper our study. First, the study was a single-center study and observational bias of AIT might exist. Second, the study lacked a placebo control group, so the absolute efficacy of AIT over placebo could not be documented and the efficacy results of the 2 HDM extracts should be interpreted with caution. Third, the study duration was relatively short (1 year). In general, AIT is suggested to last for 3 to 5 years according to current guidelines. Thus, the persistent efficacy during AIT and the long-term efficacy after treatment were not clear. Moreover, we suggest that the product consistency of different batches of the HDM extracts should be a consideration in 3-year to 5-year AIT studies. Finally, only 68.7% of the patients received blood tests, which might have had an impact on the immunological parameters analysis. In addition, the sera samples were collected only in baseline and after 1 year of AIT, which might not be enough to reflect the trend of immunological parameters changes during AIT.

Conclusion

This study confirmed the equal efficacy and safety of both Alutard and NHD extracts in Chinese HDM-induced AR patients. More studies are needed to elucidate the mechanism of AIT and ascertain potential biomarkers for successful AIT. 📌

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References

- Pawankar R, Holgate ST, Canonica GW, et al. *WAO White Book on Allergy 2013 Update*. Milwaukee, WI: World Allergy Organization; 2013.
- Wang XD, Zheng M, Lou HF, et al. An increased prevalence of self-reported allergic rhinitis in major Chinese cities from 2005 to 2011. *Allergy*. 2016;71:1170–1180.
- Wang J, Wu Y, Li J, Huang X, et al. Eight aeroallergen skin extracts may be the optimal panel for allergic rhinitis patients in Central China. *Int Arch Allergy Immunol*. 2017;173:193–198.
- Gregory LG, Lloyd CM. Orchestrating house dust mite-associated allergy in the lung. *Trends Immunol*. 2011;32:402–411.
- Durham SR, Emminger W, Kapp A, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol*. 2012;129:717–725.e5.
- Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol*. 2011;127(1 Suppl):S1–S55.
- van Kampen V, de Blay F, Folletti I, et al. Evaluation of commercial skin prick test solutions for selected occupational allergens. *Allergy*. 2013;68:651–658.
- Cools M, Van Bever HP, Weyler JJ, et al. Long-term effects of specific immunotherapy, administered during childhood, in asthmatic patients allergic to either house-dust mite or to both house-dust mite and grass pollen. *Allergy*. 2000;55:69–73.
- Olsen OT, Larsen KR, Jacobsen L, et al. A 1-year, placebo-controlled, double-blind house-dust-mite immunotherapy study in asthmatic adults. *Allergy*. 1997;52:853–859.
- Jutel M, Rudert M, Kreimendahl F, et al. Efficacy and tolerability of a house dust mite allergoid in allergic bronchial asthma: a randomized dose-ranging trial. *Immunotherapy*. 2018;10:1149–1161.
- Li X, Wang X, Lin X, et al. Semi-depot house-dust mite allergen extract for Chinese with allergic rhinitis and asthma. *Am J Rhinol Allergy*. 2016;30:201–208.
- Qi S, Chen H, Huang N, et al. Early intervention improves clinical responses to house dust mite immunotherapy in allergic rhinitis patients. *Int Arch Allergy Immunol*. 2016;171:234–240.
- 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*. 2008;63(Suppl 86):8–160.
- Di Lorenzo G, Mansueto P, Pacor ML, et al. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to allergen-specific immunotherapy. *J Allergy Clin Immunol*. 2009;123:1103–1110.
- Zhao D, Lai X, Tian M, et al. The functional IgE-blocking factor induced by allergen-specific immunotherapy correlates with IgG4 antibodies and a decrease of symptoms in house dust mite-allergic children. *Int Arch Allergy Immunol*. 2016;169:113–120.
- Didier A, Campo P, Moreno F, et al. Dose-dependent immunological responses after a 6-month course of sublingual house dust mite immunotherapy in patients with allergic rhinitis. *Int Arch Allergy Immunol*. 2015;168:182–192.
- Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. 2016;137:444–451.
- Roux M, Devillier P, Yang WH, et al. Efficacy and safety of sublingual tablets of house dust mite allergen extracts: results of a dose-ranging study in an environmental exposure chamber. *J Allergy Clin Immunol*. 2016;138:451–458.
- Pfaar O, Demoly P, van Wijk RG, et al. Recommendations for the standardization of clinical outcomes

- used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI position paper. *Allergy*. 2014;69:854–867.
20. Dong X, Huang N, Li W, et al. Systemic reactions to dust mite subcutaneous immunotherapy: a 3-year follow-up study. *Allergy Asthma Immunol Res*. 2016;8:421–427.
21. Nacaroglu HT, Erdem SB, Sumer O, et al. Local and systemic reactions to subcutaneous allergen immunotherapy. *Ann Allergy Asthma Immunol*. 2016;116:349–353.
22. Nettis E, Giordano D, Pannofino A, et al. Safety of inhalant allergen immunotherapy with mass units-standardized extracts. *Clin Exp Allergy*. 2002;32:1745–1749.
23. Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol*. 1998;102:558–562.
24. Ciprandi G, Tosca MA, Silvestri M. The practical role of serum allergen-specific IgE as potential biomarker for predicting responder to allergen immunotherapy. *Expert Rev Clin Immunol*. 2014;10:321–324.