

LETTER TO THE EDITOR

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Association between component-resolved diagnosis of house dust mite and efficacy of allergen immunotherapy in allergic rhinitis patients

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Abstract

Data regarding clinical relevance of house dust mite (HDM) components over allergen immunotherapy (AIT) for allergic rhinitis (AR) are lacking. 18 adult AR patients receiving HDM-AIT for 52 weeks were followed up to assess serum levels of sIgE and sIgG4 to HDM components. The study showed that Der p1, p2, p23, Der f1 and f2, are important sensitizing components of HDM, of which Der p1 appears to be the most clinically relevant allergenic component for effective AIT.

Keywords: Allergic rhinitis, Allergen immunotherapy, House dust mite, Component resolved diagnosis

To the editor,

Allergic rhinitis (AR) affects 10–40% of the global population and exerts huge economic and social burdens [1]. The most important allergen responsible for perennial AR (PAR) in China is HDM, including components *Dermatophagoides farina* (Der f) and *Dermatophagoides pteronyssinus* (Der p) [2].

Component resolved diagnostics (CRD) makes it possible for precision medication and individual management, while Der p 1, Der p 2, Der p 23, Der f 1 and Der f 2 are considered to be the main HDM allergens [3–5]. Allergen immunotherapy (AIT), including mainly subcutaneous immunotherapy (SCIT) and sublingual immunotherapy, is the only available etiological treatment for AR. Studies have shown that the levels of sIgE and sIgG4 actually

increase during AIT [6, 7]. The levels of specific IgE present an early increase and a late decrease, while the levels of specific IgG4 show a relatively early increase instead [8]. Indeed, both sIgE and sIgG4 have been documented as potential biomarkers for monitoring clinical efficacy of AIT [9]. However, data regarding the clinical relevance of association between specific components of HDM and sIgE and sIgG4 levels during the course of AIT are still lacking. Thus, the aim of this study was to analyze the different HDM components and the profiles of sIgEs and sIgG4s generated against these components over a 1-year course of AIT in patients with HDM-induced AR.

The study was approved by the ethics review board of the Beijing TongRen Hospital (TRECKY2017-06). Study methods are described in Additional file 1 and a schematic diagram is provided in Additional file 1: Figure S1.

A total of 18 adult AR patients, receiving HDM-AIT for 52 weeks were serially followed up to assess serum levels of sIgE and sIgG4 to allergenic HDM components over the 52-week treatment. The demographic and clinical

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characteristics are shown in Additional file 1: Table S1. Clinically, symptoms were significantly improved during the 52-week HDM-AIT (detailed results were shown in Additional file 1).

Additional file 1: Table S2 shows the sensitization patterns of sIgE and sIgG4 to allergenic HDM components at baseline (W0), and indicate that the prevalence of sensitization to the individual components was in the order Der p 2 (66.7%) = Der f 2 (66.7%) > Der p 1 (55.6%) > Der f 1 (44.4%) > Der p 23 (33.3%); where sensitization to specific allergenic HDM components leading to generation of significant levels of sIgG was in the order Der f 2 (38.9%) > Der p 1 (27.8%) = Der p23 (27.8%) > Der p 2 (22.2%) = Der p 3 (22.2%). All participants were found to be negative (EAST class 0) with respect to significant generation of sIgE against Der p 3, Der p 5 and Der p 10; and generation of sIgG4 against Der p3, Der p10 and Der p23. Moreover, sIgE against Der p 7 and sIgG4 against Der p 7 and Der f 1 was found to be of little relevance, as they demonstrated intensities below 2 (clinically grade 0).

However, 22% patients (4/18) were found to have clinically relevant sIgG4 levels against Der p 3.

The trends of the allergenic HDM components leading to production of sIgE are shown in Fig. 1. During the course of AIT, compared with W0 (baseline), the level of Der p sIgE was significantly elevated at W5 (25.27 ± 16.29 versus 20.13 ± 15.19 , $P=0.022$), and then decreased at W19 (15.53 ± 13.79 , $P=0.047$) before progressively attaining levels comparable with baseline at W52 (18.93 ± 16.04 , $P=0.76$). The production of Der p 1 and Der p 2 sIgE followed a trend consistent with Der p sIgE. In contrast, the levels of Der p 23 sIgE were significantly increased from baseline at W2 (25.61 ± 37.73 versus 18.56 ± 27.86 , $P=0.027$), and then remained significantly higher than the baseline throughout the rest of the treatment period (W5, 33.17 ± 43.64 , $P=0.0078$; W7, 30.67 ± 38.31 , $P=0.025$; W19, 28.89 ± 28.40 , $P=0.028$; W35, 30.29 ± 28.10 , $P=0.049$; W52, 37.11 ± 25.2 , $P=0.0174$).

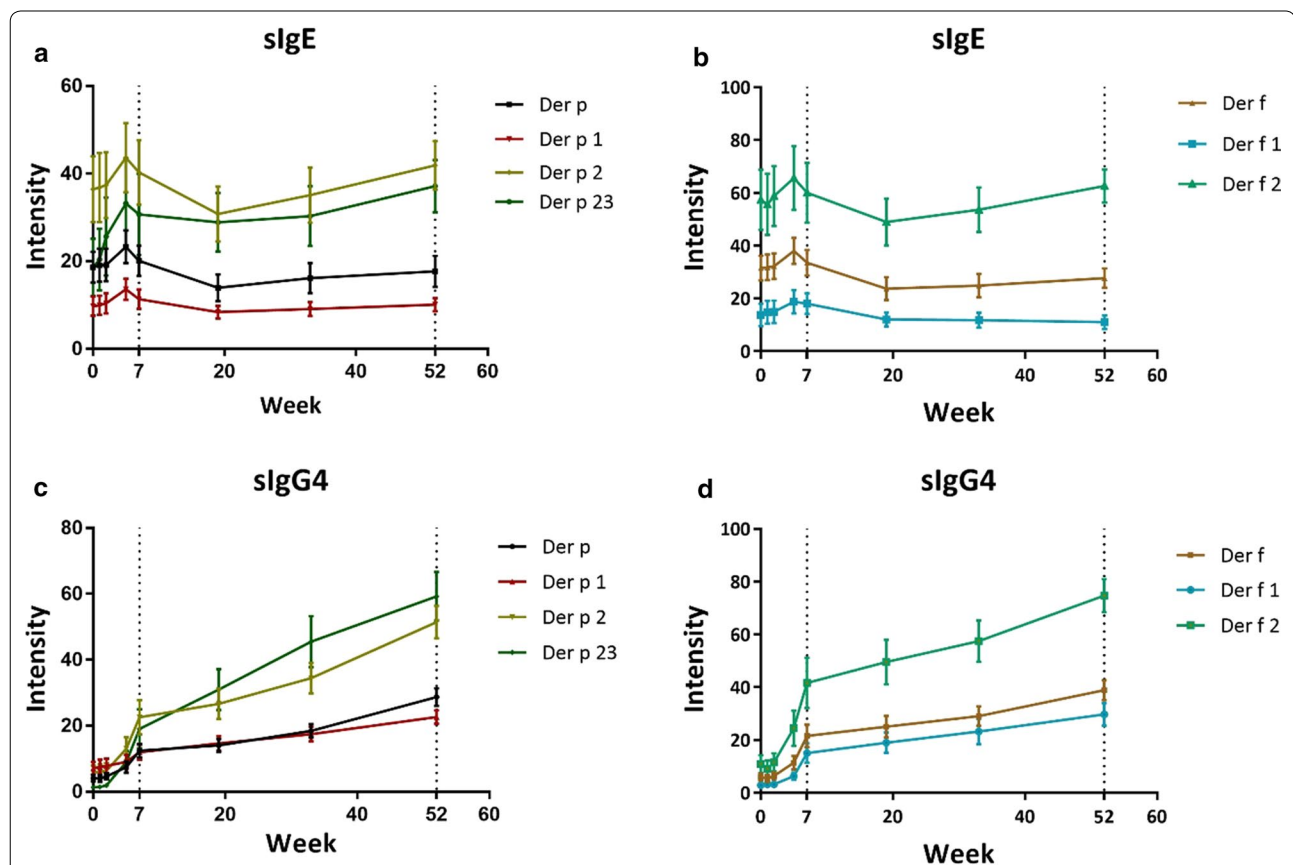


Fig. 1 The profiles of sIgE and sIgG4 levels generated for allergenic HDM components during AIT. **a** sIgE of Der p and its components; **b** sIgE of Der f and its components; **c** sIgG4 of Der p and its components; **d** sIgG4 of Der f and its components. HDM, house dust mite; AIT, allergen immunotherapy

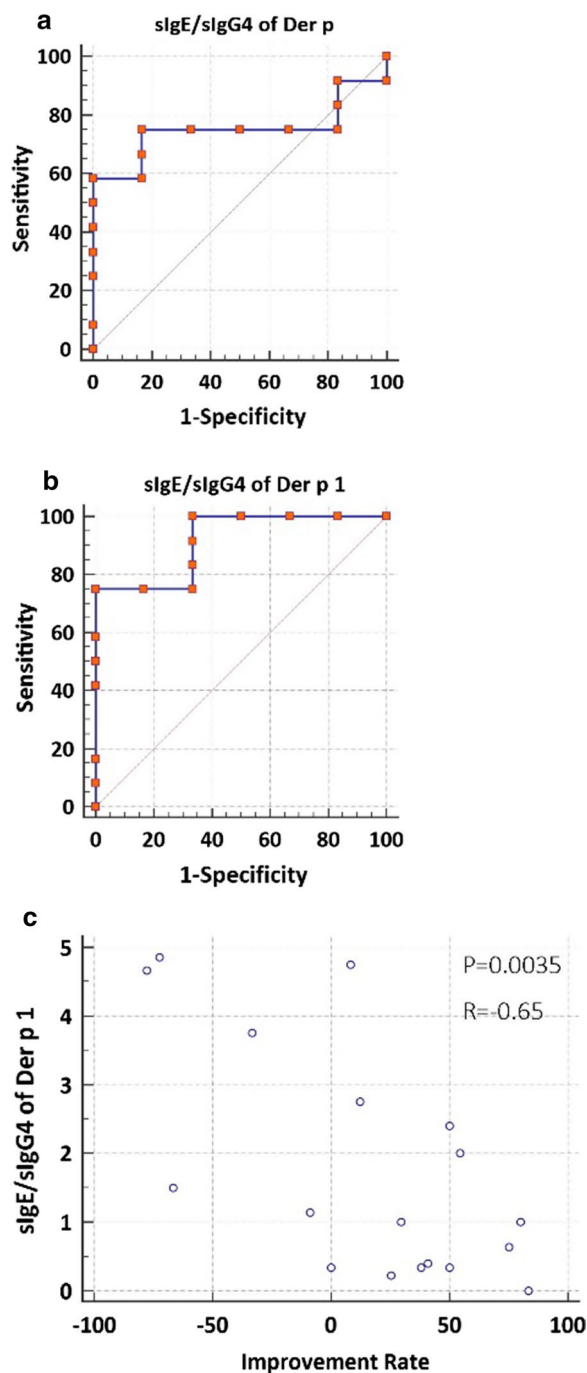


Fig. 2 Receiver operating characteristic (ROC) curve of the baseline sIgE/sIgG4 ratio of Der p (a) and Der p 1 (b) as predictive parameters of clinical responsiveness, and the correlation between baseline sIgE/sIgG4 ratio for Der p 1 and clinical improvement rate for TCS at 52-weeks of AIT (c). AIT, allergen immunotherapy

Similar to Der p sIgE, the level of Der f sIgE was also significantly elevated at W5 compared to baseline level (38.06 ± 20.77 versus 31.56 ± 19.94 , $P=0.0049$), and then

decreased at W19 (23.67 ± 18.56 , $P=0.020$). Likewise, the levels of Der f 1 and Der f 2 sIgE significantly increased at W5 (Der f 1, 18.78 ± 18.87 versus 13.78 ± 18.05 , $P<0.0001$; Der f 2, 65.61 ± 51.3 versus 57.33 ± 48.23 , $P<0.0001$), but remained comparable at the other time-points.

The trends of the specific HDM components leading to production of sIgG4 are shown in Fig. 1. The levels of sIgG4 against Der p, Der f and their components (Der p 1, p 2, p 23, f 1 and f 2) were increased rapidly during the first 7 weeks of treatment and then progressively increased at a slower rate over the remaining course of the 52-weeks treatment.

The clinical efficacy of AIT was defined according the percentage improvement observed in total combined score (TCS) at 52 W compared with the baseline (W0) (with $\geq 20\%$ improvement = responder; $< 20\%$ improvement = nonresponder) [10]. 6 out of 18 patients were unresponsive to HDM-SCIT and 12 patients responsive HDM-SCIT. Receiver operating characteristic curve analysis demonstrated that the ratio of sIgE and sIgG4 for Der p and Der p 1 were good predictors for clinical responsiveness, as demonstrated by areas under the curves (AUCs) of 0.75 and 0.92, respectively (Fig. 2a, b). Further, the Der p1 sIgE/sIgG4 was significantly and moderately correlated with the rate of clinical improvement in the patients ($R = -0.65$, $P = 0.0035$; Fig. 2c).

A limitation of the study is that a 52-week course for AIT is relatively short compared to the traditional 3-year course for AIT. Secondly, the study population was relatively small.

In summary, this study has provided preliminary information of the allergenic profiles of major HDM components; especially Der p 1, Der p 2, Der p 23, Der f 1 and Der f 2; at baseline and over a course of 52-week AIT in patients with HDM-induced AR. Furthermore, Der p 1 appears to be the most clinically relevant allergenic component for effective AIT, and the ratio of Der p 1-sIgE/Der p 1-sIgG4 levels may be useful as a biomarker for predicting the clinical responses of AIT.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13601-019-0305-4>.

Additional file 1. Supplemental materials and methods. Demographic and clinical characteristics of the study population at baseline and clinical evaluation. **Table S1.** Demographics and baseline disease characteristics of participants. **Table S2.** Baseline levels of sIgE and sIgG4. **Figure S1.** Schematic diagram showing the SCIT protocol employed. **Figure S2.** The effect of HDM-AIT on nasal/conjunctivitis symptoms (A nasal congestion, B rhinorrhea, C nasal itching, D sneezing, E gritty eyes, F watery eyes) scores over a course of 52-weeks. AIT, allergen immunotherapy. **Figure S3.** The effect of HDM-AIT on DMS (A) and TCS (B) over a course of 52-weeks. DMS, daily medication score; TCS, total combined score; AIT, allergen immunotherapy.

Abbreviations

AR: allergic rhinitis; AIT: allergen immunotherapy; CRD: component resolved diagnostics; Der f: *Dermatophagoides farinae*; Der p: *Dermatophagoides pteronyssinus*; HDM: house dust mite; PAR: perennial allergic rhinitis; SCIT: subcutaneous immunotherapy; slgE: specific immunoglobulin E; slgG4: specific immunoglobulin G4; TCS: total combined score; tlgE: total immunoglobulin E; WAO: World Allergy Organization.

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Not applicable.

Authors' contributions

HY, WC, ZY and ZL performed statistical analyses. All authors collected the data. All authors read and approved the final manuscript.

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Availability of data and materials

We would like to provide the raw data to support the information presented in this publication.

Ethics approval and consent to participate

The study was approved by the ethics review board of the Beijing TongRen hospital and Beijing Institute of Otolaryngology, P. R. China (TRECKY2017-06); and written informed consent was obtained from all participants before enrolment into the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guide—lines—2016 revision. *J Allergy Clin Immunol*. 2017;140:950.
2. Lou H, Ma S, Zhao Y, Cao F, He F, Liu Z, et al. Sensitization patterns and minimum screening panels for aeroallergens in self-reported allergic rhinitis in China. *Sci Rep*. 2017;7:9286.
3. Zidarn M, Robic M, Krivec A, Silar M, Resch-Marat Y, Vrtala S, et al. Clinical and immunological differences between asymptomatic HDM-sensitized and HDM-allergic rhinitis patients. *Clin Exp Allergy*. 2019;49(6):808–18.
4. Matricardi PM, Dramburg S, Potapova E, Skevaki C, Renz H. Molecular diagnosis for allergen immunotherapy. *J Allergy Clin Immunol*. 2019;143:831–43.
5. Matos Semedo F, Dorofeeva Y, Pires AP, Tomaz E, Taborda Barata L, Inacio F, et al. Der p 23-clinical relevance of molecular monosensitisation in House Dust Mite allergy. *J Investig Allergol Clin Immunol*. 2019;29(4):314–6.
6. Zeng G, Zheng P, Luo W, Huang H, Wei N, Sun B. Longitudinal profiles of serum specific IgE and IgG4 to *Dermatophagoides pteronyssinus* allergen and its major components during allergen immunotherapy in a cohort of southern Chinese children. *Mol Immunol*. 2016;74:1–9.
7. Suarez-Fueyo A, Ramos T, Galan A, Jimeno L, Wurtzen PA, Marin A, et al. Grass tablet sublingual immunotherapy downregulates the TH2 cytokine response followed by regulatory T-cell generation. *J Allergy Clin Immunol*. 2014;133:130–8.
8. Fujita H, Soyka MB, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. *Clin Transl Allergy*. 2012;2:2.
9. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. *Allergy*. 2017;72:1156–73.
10. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy*. 2007;62(3):317–24.

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METHODS

Ethics

This was a prospective cohort study, in which outpatients with HDM-induced AR were enrolled from the Department of Allergy at Beijing TongRen Hospital, from 2017 July to December. The study protocol, shown in Figure S1, was approved by the ethics review board of the Beijing TongRen Hospital and Beijing Institute of Otolaryngology, P.R. China; and written informed consent was obtained from all participants before enrolment into the study.

Study Design

Adult patients with mild to moderate AR, with or without asthma due to HDM, meeting the study inclusion criteria were enrolled into the study and received SCIT for 1 year with standardized extract of HDM (Alutard SQ, ALK company, Denmark). The 1-year clustered SCIT protocol involved a '7-week' up-dosing (up to 100,000 SQ-U) and a '45-week' maintenance period with injection of allergen at intervals of 6 ± 2 weeks. The patients' symptoms were evaluated at baseline and then followed up for a period of one year during the treatment. Blood samples from each patient were collected in 5-ml ethylene-diamine-tetraacetic acid (EDTA)-containing tubes at the initiation of treatment (W0), and the end of week (W)1, W2, W5, W7, W19, W35 and W52; and assessed for serum sIgE and sIgG4 to specific allergenic components of HDM; included Der p, p1, p2, p3, p5, p7, p10, p23, Der f, Der f 1 and f 2. All samples were analyzed using the semiquantified Euroline system (EUROIMMUN, Beijing, China), and the concentration the intensity and grade (EAST class) of each sample was graded as follows: intensity ≤ 2 = grade 0+; ≤ 6 = 1+; ≤ 15 , 2+; ≤ 30 , 3+; ≤ 55 , 4+; ≤ 110 , 5+; ≤ 255 , 6+.

Patients

A total of 18 outpatients, 10 males (55.6%) and 8 females (44.4%), aged 18 to 40 years with a confirmed diagnosis of AR were enrolled into the study. Each patient fulfilled the inclusion criteria as follows: (1) adult patients aged ≥ 18 years; (2) a history of atopy to HDM and a physician-diagnosis of mild to moderate rhinitis with

or without asthma based on ARIA 2016 revision (1); and (3) patients with significant nasal symptoms (nasal congestion, rhinorrhea, itching and sneezing) and sensitization to HDM, as indicated by skin prick test (SPT) and confirmed by serum sIgE $\geq$ 3.5 kU/L using the Pharmacia UniCAP system (Thermo Fisher Scientific Co., Ltd., Shanghai, China). During AIT, patients only used rescue medication (antihistamines, nasal corticosteroids) if necessary.

Patients with severe uncontrolled systemic diseases, including active systemic/immunologic disease, were excluded; as were pregnant women.

Clinical Efficacy of AIT

The clinical efficacy of treatment was evaluated by assessing symptoms and rescue medication usage. Nasal symptoms of congestion, rhinorrhea, itching and sneezing, together with eye discomfort (gritty eyes and watery eyes) were assessed using a 4-point visual analogue scale (VAS) ranging from 0 (asymptomatic) to 3 (severe). Daily medication score (DMS), ranging from 0 to 6, was calculated based on the total daily medicine intake, with 0 = “without taking any medicine”, 1= “using antihistamines”, 2= “using nasal corticosteroids”, 3= “using oral corticosteroids”. Total combined score (TCS) (2), ranging from 0 to 6, was calculated as the sum of the average score of 6 nasal conjunctivitis symptoms and DMS.

According to the position paper of World Allergy Organization in 2007 (3), a $\geq$ 20% improvement in outcome is considered to be clinically efficacious for AIT. Thus, the clinical efficacy of AIT was defined according the percentage improvement observed in TCS at 52W compared with the baseline (W0) (with $\geq$ 20% improvement= responder; $<$ 20% improvement= nonresponder).

Statistical analysis

Data were analyzed using SPSS V.19 software package (IBM Corp., Armonk, NewYork, USA) and MedCalc V.15.2.2 (MedCalc Software, Mariakerke, Belgium). Descriptive statistics were used for general information of the study population. For normally distributed data the results were expressed as mean $\pm$ standard deviation (SD). Paired Student t test or Wilcoxon test were used to analyze the significance of

differences in symptoms and medication scores between baseline and at different time points, for normally and non-normally distributed data. Receiver operating characteristic (ROC) curves were used to assess the predictive value of clinical responsiveness. Correlations were assessed using Spearman correlation. A value of $P < 0.05$ was considered to be significant.

RESULTS

Demographic and Clinical Characteristics of the Study Population at baseline

The demographic and clinical characteristics of the study population are shown in Table S1. All 18 participants completed the 52-week SCIT treatment. The mean age of the patients was 30.17 ± 9.67 years. Only 1 patient had history of asthma. There was no significant difference in patient number regarding gender. The baseline levels of sIgE to Der p and Der f were 18.61 ± 14.85 and 31.56 ± 19.94 , respectively; and of sIgG4 to Der p and Der f were 4.11 ± 4.42 and 5.94 ± 5.79 , respectively.

Der p and Der f were 4.11 ± 4.42 and 5.94 ± 5.79 , respectively.

Clinical evaluation

Except for nasal congestion, the other 3 common nasal symptoms (rhinorrhea, itching and sneezing) and gritty eyes were significantly improved (0.78 ± 0.73 versus 1.50 ± 1.04 , $P=0.03$; 1.22 ± 1.00 versus 1.72 ± 1.18 , $P=0.047$; 1.06 ± 0.80 versus 1.83 ± 0.99 , $P=0.002$; 0.83 ± 0.71 versus 1.56 ± 1.50 , $P=0.034$; respectively) at the end of the 52-week SCIT treatment compared to the baseline (W0) (Figure.S2). Nasal congestion was found to significantly decrease at the W35 compared with W0 (0.94 ± 0.83 versus 1.72 ± 1.13 , $P=0.02$). At W7, nasal itching and sneezing were shown to be the earliest effectively alleviated among the 6 nasal conjunctivitis symptoms (0.94 ± 0.90 versus 1.72 ± 1.18 , $P=0.027$; 0.94 ± 0.75 , $P=0.0078$; respectively). However, no significant difference could be found in watery eyes (Figure S2F) and DMS during the 1-year treatment (Figure S3A). Combining symptoms and medication usage, TCS (Figure S3B) was found to significantly decrease at W35 and W52 compared with W0

(1.33 ± 1.08 , 1.50 ± 0.99 , respectively; versus 2.20 ± 1.24 (W0); $P=0.012$ and 0.042 , respectively).

References

1. Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines—2016 revision. *Journal of Allergy & Clinical Immunology* 2017;**140**(4):950.
2. Baris S, Kiykim A, Ozen A, Tulunay A, Karakocaydiner E, Barlan IB. Vitamin D as an adjunct to subcutaneous allergen immunotherapy in asthmatic children sensitized to house dust mite. *Allergy* 2014;**69**(2):246–253.
3. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy* 2007;**62**(3):317-324.

TABLES

Table S1. Demographics and baseline disease characteristics of participants

Characteristics	Number
Total subjects, n	18
Gender (%), male/female	10(55.6)/8(44.4)
Age (years; mean±SD)	30.17±9.67
Asthma (%), yes/no	1(5.6)/17(94.4)
Baseline sIgE (mean±SD)	
Der p	18.61±14.85
Der f	31.56±19.94
Baseline sIgG4 (mean±SD)	
Der p	4.11±4.42
Der f	5.94±5.79

Table S2. Baseline levels of sIgE and sIgG4

Components of HDM	sIgE		sIgG4	
	Positive	Negative	Positive	Negative
Der p 1	10 (55.6%)	8 (44.4%)	5 (27.8%)	13 (72.2%)
Der p 2	12 (66.7%)	6 (33.3%)	4 (22.2%)	14 (77.8%)
Der p 3	-	18 (100%)	4 (22.2%)	14 (77.8%)
Der p 5	-	18 (100%)	-	18 (100%)
Der p 7	1 (5.6%)	17 (94.4%)	1 (5.6%)	17 (94.4%)
Der p 10	-	18 (100%)	-	18 (100%)
Der p 23	6 (33.3%)	12 (66.7%)	5 (27.8%)	13 (72.2%)
Der f 1	8 (44.4%)	10 (55.6%)	2 (11.1%)	16 (88.9%)
Der f 2	12 (66.7%)	6 (33.3%)	7 (38.9%)	11 (61.1%)

FIGURES

Figure legends

Figure S1. Schematic diagram showing the SCIT protocol employed.

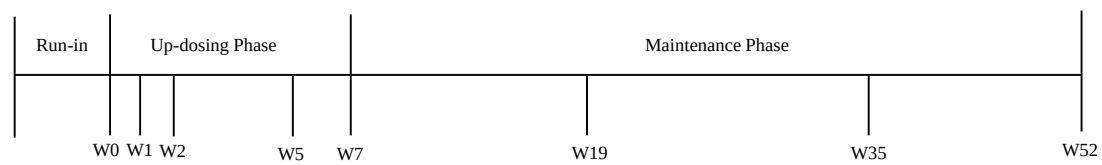


Figure S2. The effect of HDM-AIT on nasal/conjunctivitis symptoms (A nasal congestion, B rhinorrhea, C nasal itching, D sneezing, E gritty eyes, F watery eyes) scores over a course of 52-weeks. AIT, allergen immunotherapy.

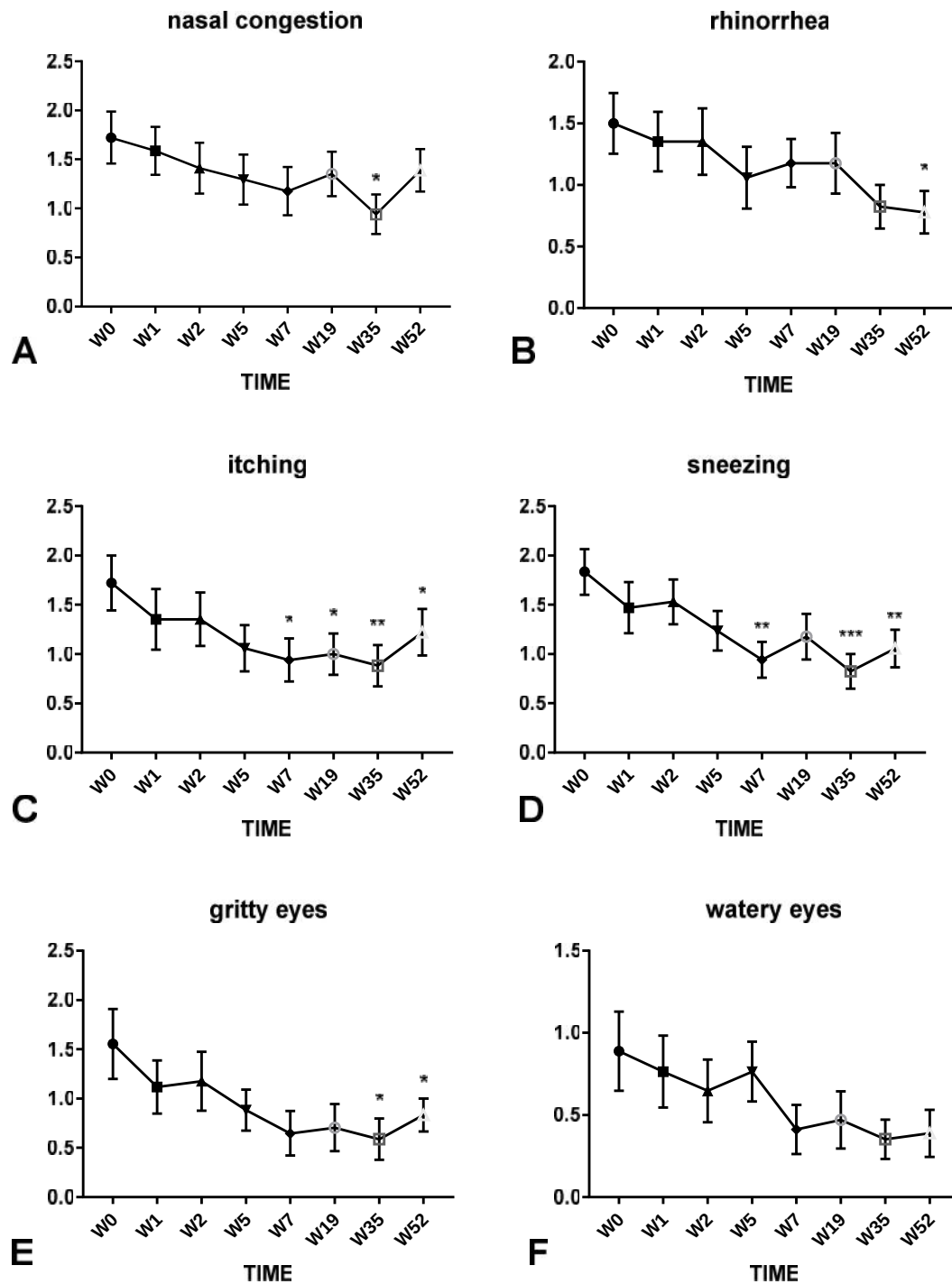


Figure S3. The effect of HDM-AIT on DMS (A) and TCS (B) over a course of 52-weeks. DMS, daily medication score; TCS, total combined score. AIT, allergen immunotherapy.

