

Specific immunoglobulin E and immunoglobulin G4 toward major allergens of house-dust mite during allergen-specific immunotherapy

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ABSTRACT

Background: Specific immunoglobulin E (sIgE) and sIgG4 to house-dust mite (HDM) major allergens during allergen immunotherapy (AIT) and their clinical relevance remain unclear.

Objective: To investigate the variation of sIgE and sIgG4 to HDM major allergens and the correlation with clinical responses during AIT in patients with allergic rhinitis.

Methods: Thirty-nine patients with HDM allergy were divided into the AIT group (taking immunotherapy) and the control group (medication only use). The AIT group was subdivided into negative clinical responses to AIT (nAIT) group and positive clinical responses to AIT (pAIT) group according to symptom relief and subjective evaluation. sIgE and sIgG4 to *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df), and their group 1 and group 2 major allergens (Dp1, Df1, Dp2, and Df2) were measured before AIT, at 6 months, and at 1 year after starting AIT.

Results: Dp2, Df, and Df2 sIgE values decreased significantly in the pAIT group versus the nAIT group after 1 year of AIT (median values of delta change were Dp2, -10.09 versus 5.89 kU/L, $p = 0.001$; median values of Df were -9.69 versus 17.54 kU/L, $p = 0.004$; median values of Df2 were -11.06 versus 20.08 kU/L, $p = 0.013$). There was a robust increase in the sIgG4 values to Dp, Df, and their major allergens in both the pAIT and the nAIT groups overall after 1 year of treatment.

Conclusion: Patients with a positive response to AIT showed a significant reduction of HDM group 2 sIgEs compared with those with a negative response to AIT, which indicated that a decrease in group 2 sIgEs could be a marker that reflected AIT clinical efficacy.

(Am J Rhinol Allergy 31, 156–160, 2017; doi: 10.2500/ajra.2017.31.4434)

House-dust mites (HDM), especially *Dermatophagoides pteronyssinus* (Dp) and *Dermatophagoides farinae* (Df), are the predominant indoor allergen sources all over the world.¹ Results of an examination of HDM extracts showed that >30 different proteins could induce immunoglobulin E (IgE) antibody. Major allergens of group 1 (Dp1 and Df1) and group 2 (Dp2 and Df2) account for most of the allergenicity.² HDM group 1 allergens are cysteine proteases that elicit IgE responses in 80% of subjects who are mite sensitized.³ HDM group 2 allergens induce humoral and cellular responses in 80–90% of subjects who are mite sensitive.⁴ Allergen immunotherapy (AIT) by using dust mite extract effectively treats allergic rhinitis and atopic asthma in patients who demonstrate IgE-mediated sensitivity to dust mite.^{5–7} During the course of HDM AIT, serum HDM specific IgE (sIgE) initially increases after a 1-year treatment and then declines to baseline value at 2–3 years of continued AIT.⁸

A significant increase in sIgG4 is usually regarded as a marker for a tolerance to the antigen of interest.^{9–11} Results of some studies indicated that sIgG4 acts as a blocking antibody that competes with sIgE; however, a correlation between sIgG4 change and clinical improvement is not found in most studies.^{9–12} Component testing of sIgE and sIgG4 to major allergens may provide more precise and valuable information for the diagnosis and treatment of allergic airway diseases than measuring IgE or IgG4 to whole allergen extracts of

Dp or Df. The Dp or Df “specific” IgE or IgG4 are actually “total” IgE or IgG4 against the multiple components in the allergens. Some IgG4 responses of unrelated components or contaminant antigens may also interfere with the final results.¹³

Some recent reports indicate that sIgE values to both Dp1 and Dp2 are increased in patients with dust mite allergy and the correlate with total Dp sIgE, although Dp10 sIgE does not increase much in patients who are sensitive to HDM.^{14,15} Although sIgE values to Dp1 and Dp2 during long-term immunotherapy are significantly decreased, the relationship between sIgE and sIgG4 values to Dp1 and Dp2 during AIT, and its clinical relevance, remains unclear.¹⁶ In this study, we investigated sIgE and sIgG4 responses to group 1 and group 2 major allergens of HDM during the first year of subcutaneous Dp AIT. We also analyzed the relationship of sIgE and sIgG4 values with the clinical responses during treatment.

METHODS

Subjects

Subjects were recruited from the outpatient clinic of the otorhinolaryngology department at Union Hospital, which is affiliated with the University of Science and Technology (Wuhan, China). The inclusion criteria were moderate-severe persistent rhinitis with or without asthma according to the Allergic Rhinitis and its Impact on Asthma guidelines,¹⁷ of at least 1 year's duration, with positive skin-prick test results to HDM extract solutions (Soluprick; ALK-Abello A/S, Hørsholm, Denmark) and/or serum Dp sIgE class 2 or higher (Unicap Pharmacia, Uppsala, Sweden). Patients with nasal polyps, tumors, adenoid hypertrophy, and infectious sinusitis were excluded. Among the subjects who qualified for AIT, the subjects who accepted AIT were assigned to the AIT group, whereas the subjects who did not want AIT were assigned to the control group and received medication treatment alone. Written informed consent was obtained from the participants (ages ≥ 18 years old) or the parents or guardians, and from the participants (ages between 14 and 18 years old) and from the parents or guardians of the participants (ages ≤ 14 years old). The

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Supported by the State Natural Sciences Fund of China (81570898) and the 12th five year science and technology support program (2014BAI07B04)

The authors have no conflicts of interest to declare pertaining to this article

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study was performed in accordance with the tenets of the Declaration of Helsinki and was approved by the ethical committee of the University of Science and Technology.

AIT Treatment Protocol

The subjects in the AIT group were treated with subcutaneous injections of standardized aluminum–formulated Dp Alutard SQ vaccine (ALK-Abello). The treatment protocol included a gradually up-dosing schedule over 16 weeks before reaching a maintenance dose of 100,000 Alutard SQ given every 6 weeks for 3 years. Medications such as antihistamines and nasal sprays were titrated down or discontinued as tolerated during AIT. Serum samples were collected before treatment began, at 6 months, and at 1 year of treatment in both AIT and control groups. All serum samples were stored at -20°C until analysis.

Clinical Evaluation

The subjects completed a survey of symptom scores of major nasal symptoms (nasal obstruction, nasal itching, sneezing, and rhinorrhea: 0, no symptoms; 1, mild; 2, moderate; 3, serious) and medication score the week before treatment, at 6 months, and at 1 year of treatment. The medication score was calculated as follows: 1, oral and/or topical (eyes or nose) non-sedative H1 antihistamines (H1A); 2, intranasal corticosteroids (INS) with/without H1A; 3, oral corticosteroids with or without INS, with or without H1A. The daily Combined Symptom and Medication Score (CSMS) was calculated as follows: (total symptom scores)/4 + medication score.¹⁸ A high CSMS after treatment indicates ineffective treatment, whereas a low CSMS indicates symptomatic improvement. After 1 year of treatment, a subjective evaluation of the efficacy of treatment was also obtained: worse, no change, or better after treatment. The subjects on AIT were divided into the positive clinical response to AIT (pAIT) group and the negative clinical response to AIT (nAIT) group according to the CSMS and subjective evaluation. The criteria of the pAIT group were the following: (CSMS before treatment – CSMS after 1 year)/(CSMS before treatment) $\geq 30\%$, and subjective evaluation was “better” among the choice of worse, no change, and better. The criteria of the nAIT group were the following: (CSMS before treatment – CSMS after 1 year)/(CSMS before treatment) $< 30\%$, and subjective evaluation was “worse” or “no change” among the choice of worse, no change, or better.

sIgE and IgG4 Tests

The sIgE level was measured by using the ADVIA Centaur immunoassay system (Siemens AG, Erlangen, Germany), which was a reversed sandwich immunoassay that uses direct chemiluminescent technology. The routine reagents (biotinylated allergens, calibrators, controls, and universal reagents) were produced by ALK-Abello. The

major group allergens were also produced by ALK-Abello. Dp1 and Df1 were purified from HDM extract, Dp2 and Df2 were recombinant allergens; sIgG4 against HDM extract and major allergens were measured by using UniCAP 100 (Thermo Fisher Scientific Inc, Waltham, MA). Results outside the quantification range of sIgE and sIgG4 were repeated in dilution. Serum samples from the control group were only tested for sIgE and IgG4 against Dp and Df extracts.

Statistics

The Mann-Whitney test was used to compare the data of IgE and IgG4 values to Dp, Df, and major allergens between the two groups. The independent *t*-test was used to compare the data of CSMS between 2 groups. The receiver operating characteristic (ROC) test was performed to analyze the critical biomarkers to predict the success of AIT, with the combination of CSMS and subjective evaluation as the criteria. The 95% confidence interval of the area under ROC (area under ROC curve [AUC]) were calculated and compared between each index. A *p* value of <0.05 was considered statistically significant. SPSS version 21.0 (SPSS, Inc., Chicago, IL) was used for all the analyses.

RESULTS

Subjects

There were 39 subjects included in the study. Twenty-five subjects accepted AIT and 14 subjects were controls. The subjects in the AIT and control groups showed no significant differences in sex, age, sIgE, sIgG4, or CSMS before treatment (Table 1).

Clinical Evaluation

The CSMS of the 25 subjects on AIT significantly declined after 1 year of AIT (1.72 versus 1.06; $p < 0.01$), whereas no significant change was found in the control group (1.85 versus 1.98; $p > 0.05$) (Table 2). After 1 year of treatment, 15 subjects were placed in the pAIT group based on significant CSMS improvement and favorable subjective evaluation. Six patients were placed in the nAIT group based on inadequate CSMS improvement and negative subjective evaluations. The CSMS of the pAIT group were significantly lower than the nAIT group after 1 year of AIT (0.93 ± 0.43 versus 1.5 ± 0.53 ; $p = 0.02$) (Table 3). Two subjects had significant CSMS improvement but negative subjective evaluations (one subject chose “no change,” one subject chose “worse”). Two other subjects had positive subjective evaluations but inadequate CSMS improvement ($<30\%$ of the improvement). These patients were excluded from the analysis.

Levels of sIgE

Before treatment, the median values of sIgE to Dp and Df in the AIT group were 91.94 and 83.25 kU/L, respectively. The median values of

Table 1 Baseline demographic data of the control and AIT groups

	AIT Group (<i>n</i> = 25)	Control Group (<i>n</i> = 14)	<i>p</i> Value*
Male/female, no.	12/13	6/8	>0.05
Age, mean (range), y	17.36 (6–43)	20.01 (9–42)	>0.05
Dp IgE level, kU/L#	91.94 (142.18)	86.42 (107.97)	>0.05
Df IgE level, kU/L#	83.25 (80.68)	60.74 (82.13)	>0.05
Dp IgG4 level, mgA/L#	0.35 (0.62)	0.25 (0.18)	>0.05
Df IgG4, level mgA/L#	0.38 (0.38)	0.27 (0.21)	>0.05
CSMS, mean $\pm$ standardization	1.73 ± 0.4	1.85 ± 0.58	>0.05

AIT = Allergen immunotherapy; Dp = *Dermatophagoides pteronyssinus*; IgE = immunoglobulin E; Df = *Dermatophagoides farinae*; CSMS = Combined Symptom and Medication Score.

*Mann-Whitney test.

#Median (interquartile range).

Table 2 Variation of sIgG4 values and clinical evaluation in the control and AIT groups

	Before Treatment		At 6 Months		At 1 Year	
	Control	AIT	Control	AIT	Control	AIT
Dp sIgG4, median (range), AU/L	0.25 (0.04–1.02)	0.35 (0.14–1.71)	0.22 (0.08–1.26)	1.33 (0.21–13.2)*#	0.20 (0.08–0.94)	3.09 (0.23–36.5)*#
Dp1 sIgG4, median (range), AU/L	0.18 (0.04–0.54)	0.27 (0.1–1.2)	0.17 (0.04–0.68)	0.66 (0.17–7.42)*#	0.15 (0.04–0.59)	1.96 (0.14–25.4)*#
Dp2 sIgG4, median (range), AU/L	0.04 (0.04–0.40)	0.08 (0.02–1.47)	0.04 (0.04–0.48)	0.36 (0.07–10)§	0.04 (0.04–0.38)	1.39 (0.07–19.7)*#
Df sIgG4, median (range), AU/L	0.27 (0.09–1.09)	0.38 (0.14–1.85)	0.25 (0.09–1.35)	0.99 (0.25–12.5)*#	0.24 (0.09–1.03)	2.11 (0.24–30.9)*#
Df1 sIgG4, median (range), AU/L	¶	0.19 (0.06–1.02)	¶	0.56 (0.1–6.72)*	¶	1.81 (0.07–19.9)*
Df2 sIgG4, median (range), AU/L	¶	0.10 (0.01–1.66)	¶	0.44 (0.09–15.3)§	¶	1.27 (0.07–21.0)*
CSMS, mean $\pm$ standardization	1.85 $\pm$ 0.58	1.73 $\pm$ 0.4	1.89 $\pm$ 0.54	1.15 $\pm$ 0.51*¶	1.98 $\pm$ 0.61	1.06 $\pm$ 0.46*¶

sIgG4 = Specific immunoglobulin G4; AIT = allergen immunotherapy; Dp = *Dermatophagoides pteronyssinus*; Df = *Dermatophagoides farinae*; CSMS = Combined Symptom and Medication Score.

*Significantly increased compared with data at day 0 of the same group, $p < 0.01$.

#Significant difference between the two groups of the same stage, $p < 0.05$.

§Significantly increased compared with data at day 0 of the same group, $p < 0.05$.

¶ Not measured.

||Significant difference between the two groups of the same stage, $p < 0.01$.

sIgE to group 1 allergens were 26.05 kU/L for Dp1 and 46.13 kU/L for Df1. The median values of sIgE to group 2 allergens were 50.72 kU/L for Dp2 and 63.99 kU/L for Df2. During the year of AIT treatment, there was no significant change of the median sIgE value to Dp (before, 91.94 kU/L; at 6 months, 85.55 kU/L; at 1 year, 101.37 kU/L), Dp1 (before, 26.05 kU/L; at 6 months, 30.57 kU/L; at 1 year, 45.39 kU/L) and Dp2 (before, 50.72 kU/L; at 6 months, 38.51 kU/L; at 1 year, 43.68 kU/L). Very similar results were seen in Df, Df1, and Df2 sIgE values (data not shown).

Although sIgE values to Dp, Df, and major allergens in the whole AIT group did not change before and after treatment, significant differences between the pAIT group and the nAIT group were identified. The subtracted levels of sIgE to Dp, Df, and their major allergens from the baseline levels versus after 1 year of treatment in the pAIT group were significantly lower than those of the nAIT group, especially for the delta change of Dp2, Df, and Df2 IgE values (median values of Dp2, -10.09 versus 5.89 kU/L [$p = 0.001$]; median values of Df, -9.69 versus 17.54 kU/L [$p = 0.004$]; and median values of Df2, -11.06 versus 20.08 kU/L [$p = 0.013$]) (Table 3). We performed ROC analyses with different indexes and found that the delta changes of Dp2, Df, and Df2 IgE were good biomarkers to predict success of AIT (Fig. 1). The AUC was 0.956 of the delta change of the Dp2 IgE value, 0.911 of the delta change of the Df IgE value, and 0.856 of the delta change of the Df2 IgE value (Table 4).

Levels and Changes of sIgG4

After 6 months of AIT, there was a significant increase in the concentrations of sIgG4 to Dp and Df as well as to HDM group 1 and group 2 allergens. The sIgG4 levels increased even further after 1 year of AIT and showed statistical significance compared with the IgG4 levels before AIT ($p < 0.01$). The IgG4 levels in the control group did not change significantly at 6 months or at 1 year compared with baseline (Table 2). An increasing tendency was found of sIgG4 levels to Dp, Df, and major allergens after 1 year of treatment in both the pAIT and nAIT groups (Table 3).

DISCUSSION

In most studies, sIgE levels did not change significantly during 1 year of AIT treatment.^{10–12} Blumberga *et al.*⁸ demonstrated that AIT

induced an initial increase in serum HDM sIgE values after 1 year of treatment, which then declined to baseline value at 2–3 years. Significant decreases of Dp1 and Dp2 sIgE values during long-term immunotherapy was demonstrated by Mastrandrea *et al.*¹⁶ However, few studies have compared subjects who had positive versus negative clinical responses to AIT. It was found that, although sIgE values to Dp, Df, and major HDM allergens in the whole AIT group did not change significantly during 1 year of AIT, sIgE levels in the pAIT group and in the nAIT group were significantly different. In the pAIT group, Dp, Df, Dp1, and Df1 sIgE levels did not change much, whereas Dp2, Df, and Df2 sIgE levels decreased significantly after 1 year of AIT (median values of Δ Dp2, -10.09 kU/L; median values of Δ Df, -9.69 kU/L; median values of Δ Df2, -11.06 kU/L; $p < 0.05$). In the nAIT group, sIgE levels to Dp, Df, and their major allergens trended upward, although changes in sIgE levels within this group were not significant over time. When comparing the two groups, there were significant differences between the sIgE concentrations before and after 1 year of treatment, especially for Dp2 and Df2 sIgE (an increase in the nAIT group versus a decrease in the pAIT group).

During the AIT treatment, there was a robust increase in the levels of sIgG4 to both Dp and Df. The sIgG4 value in the AIT group was significantly higher than the sIgG4 value in the control group after 1 year. This result was consistent with most reports.^{9,10,19} However, there is no consensus regarding sIgG4 as a biomarker to predict clinical response to AIT.^{12,20} An increasing tendency was also found of sIgG4 levels to Dp, Df, and major allergens in both pAIT and nAIT groups. We could not state that there was no statistical significance of sIgG4 values between the two groups because of the limited portion of participants in each subgroup; this index was not sensitive enough to predict the clinical effect. Results of one recent study indicated a significant correlation between functional assays of inhibitory IgG4 and IgE-blocking factor with CSMS during AIT, but the relationship was weak (such as IgE-facilitated allergen binding [FAB], $r = 0.25$; IgE-blocking factor, $r = 0.28$ in the study by Shamji *et al.*⁹). The induction of sIgG4 during AIT might be more like an “epiphenomenon,” which reflects the development of tolerance, such as the appearance of interleukin 10 producing regulatory T cells.^{21,22}

There are some limitations to this study. First, the number of subjects was relatively small even though some of the changes in the

Table 3 Characteristics of patients in the nAIT and pAIT groups

	Before Treatment			After 1 Year of Treatment			Δ , 1 Year – before Treatment		
	nAIT (n = 6)	pAIT (n = 15)	p Value*	nAIT (n = 6)	pAIT (n = 15)	p Value*	nAIT (n = 6)	pAIT (n = 15)	p Value*
Male/female, no.	3/3	8/7							
Age, mean (range), y	16.98 (6–41)	18.76 (7–43)	0.76						
CSMS, mean $\pm$ standardization	1.63 $\pm$ 0.21	1.93 $\pm$ 0.36	0.07	1.5 $\pm$ 0.52	0.93 $\pm$ 0.43	0.018	0.13 $\pm$ 0.47	1.00 $\pm$ 0.33	<0.001
Immunoglobulin levels, median (range)									
Dp IgE	62.02 (4.59–200.78)	103.47 (4.82–644.33)	0.276	158.44 (4.15–449.98)	98.47 (8.29–802.68)	0.64	53.68 (–0.44 to 249.21)	1.65 (–68.74 to 158.35)	0.062
Dp1 IgE	16.04 (0.06–134.02)	28.41 (0.52–439.83)	0.243	37.41 (0.43–273.21)	27.68 (1.87–508.43)	0.938	21.37 (0.37–139.19)	1.84 (–33.72 to 68.59)	0.161
Dp2 IgE	68.68 (4.83–99.04)	42.15 (11.36–399.76)	0.815	74.57 (5–247.46)	32.14 (8.63–383.34)	0.586	5.89 (0.18–160.34)	–10.09 (–51.93 to 4.57)	0.001
Df IgE	68.32 (3.65–159.23)	83.25 (13.39–275.85)	0.876	128.31 (4.24–298.48)	64.29 (11.96–357.88)	0.533	17.54 (0.58–224.2)	–9.69 (–31.87 to 82.03)	0.004
Df1 IgE	27.16 (0.9–195.5)	46.13 (7.27–700.79)	0.484	102.14 (1.99–386.54)	57.88 (7.06–833.02)	0.697	46.27 (1.09–191.04)	9.03 (–41.93 to 132.23)	0.186
Df2 IgE	76.68 (7.61–125.1)	57.88 (19.18–356.6)	0.755	98.42 (8.88–309.99)	58.95 (15.56–348.17)	0.586	20.08 (–21.31 to 185.47)	–11.06 (–54.02 to 9.53)	0.013
Dp IgG4	0.68 (0.18–1.3)	0.34 (0.14–1.71)	0.276	4.98 (0.23–31.85)	2.52 (1.14–36.5)	0.276	4.4 (0.05–30.75)	1.87 (0.81–35.39)	0.35
Dp1 IgG4	0.31 (0.21–0.48)	0.24 (0.1–0.95)	0.258	3.2 (0.14–20.85)	1.71 (0.56–25.4)	0.312	2.9 (0–20.37)	1.44 (0.31–24.45)	0.312
Dp2 IgG4	0.18 (0.04–0.88)	0.07 (0.02–1.47)	0.172	1.83 (0.07–18.8)	1.24 (0.31–14.9)	0.243	1.68 (0.03–17.97)	0.69 (0.12–14.68)	0.392
Df IgG4	0.53 (0.21–1.44)	0.32 (0.14–1.85)	0.185	3.64 (0.24–25.5)	2.03 (0.77–30.9)	0.161	3.12 (0.03–24.06)	1.6 (0.26–30.06)	0.276
Df1 IgG4	0.28 (0.06–1.02)	0.18 (0.06–0.53)	0.227	3.05 (0.07–16.1)	0.93 (0.43–19.9)	0.139	2.79 (0.01–15.08)	0.82 (0.11–19.37)	0.119
Df2 IgG4	0.26 (0.05–1.23)	0.09 (0.01–1.66)	0.35	2.55 (0.07–21)	1.27 (0.24–15.5)	0.311	2.32 (0–19.77)	0.8 (0.23–15.3)	0.484

nAIT = Negative allergen immunotherapy; pNIT = positive allergen immunotherapy; CSMS = Combined Symptom and Medication Score; Dp = Dermatophagoides pteronyssinus; IgE = immunoglobulin E; Df = Dermatophagoides farinae.

*The Mann-Whitney test, except the CSMS values.

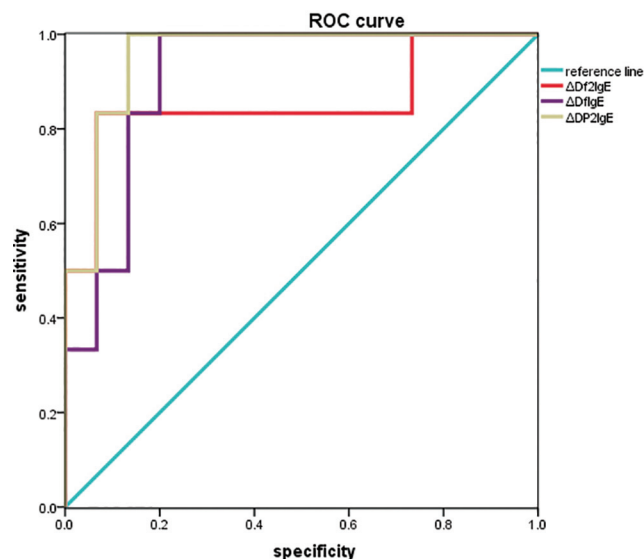


Figure 1. ROC analysis with critical biomarkers to predict success of AIT. ROC = Receiver operating characteristic; AIT = allergen immunotherapy.

Table 4 AUC analysis of different biomarkers

Biomarkers	AUC	SD*	Asymp Sig.	Asymp 95% CI	
				Minimum	Maximum
ΔDp IgE	0.767	0.114	0.062	0.543	0.990
ΔDp1 IgE	0.700	0.132	0.161	0.442	0.958
ΔDp2 IgE	0.956	0.042	0.001	0.873	1.000
ΔDf IgE	0.911	0.063	0.004	0.787	1.000
ΔDf1 IgE	0.689	0.139	0.186	0.417	0.960

ROC = Receiver operating characteristic; AUC = area under ROC curve; SD = standard deviation; Asymp Sig = asymptotic significance; CI = confidence interval; Dp = *Dermatophagoides pteronyssinus*; IgE = immunoglobulin E; Df = *Dermatophagoides farinae*.

*Nonparametric hypothesis.

sIgE and sIgG4 values were significant. Second, this study was not a randomized controlled clinical trial. Third, it would be interesting to see the changes in IgE or IgG4 values in a longer follow-up study, such as 3–5 years. Our study results indicated that sIgE at 1 year of AIT could be an important marker for clinical response and could be used as an objective tool to make a decision about either continuing or stopping AIT. A future study to investigate the levels of sIgE and sIgG4 to HDM at 3 or 5 years after AIT and their correlation with clinical responses would provide valuable information in allergy clinical practice.

CONCLUSION

The patients with a pAIT showed significantly different sIgE values to HDM allergens compared with those with an nAIT. The sIgE values to group 2 HDM allergens after 1 year of AIT decreased significantly and were the most sensitive marker that reflected AIT clinical efficacy. The sIgG4 levels to Dp, Df, and their major allergens increased significantly after 1 year of AIT treatment, but no correlation was found between the sIgG4 levels and clinical responses. This was a novel finding that sIgE to HDM group 2 allergens can be used as a biologic marker for clinical efficacy of HDM AIT, even though this needs to be confirmed in larger randomized controlled clinical trials.

ACKNOWLEDGMENTS

We thank Liu Tiantian and Zhong Haifeng for the skilled IgE and IgG4 tests.

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.
- Thomas WR, Smith WA, Hales BJ, et al. Characterization and immunobiology of house dust mite allergens. *Int Arch Allergy Immunol* 129:1–18, 2002.
- Thomas WR, Smith WA, and Hales BJ. The allergenic specificities of the house dust mite. *Chang Gung Med J* 27:563–569, 2004.
- Heymann PW, Chapman MD, Aalberse RC, et al. Antigenic and structural analysis of group II allergens (Der f II and Der p II) from house dust mites (*Dermatophagoides* spp.). *J Allergy Clin Immunol* 83:1055–1067, 1989.
- Xiaoxiong X, Dongming H, Biyun C, et al. Influence of Dp specific immunotherapy on Df specific IgG4 in mite allergic patients [in Chinese]. *Chinese J Allergy Clin Immunol* 3:34–38, 2009.
- Cox L. The role of allergen immunotherapy in the management of allergic rhinitis. *Am J Rhinol Allergy* 30:48–53, 2016.
- Oktemer T, Altıntoprak N, Muluk NB, et al. Clinical efficacy of immunotherapy in allergic rhinitis. *Am J Rhinol Allergy* 30(suppl. 1):4–7, 2016.
- Blumberga G, Groes L, and Dahl R. SQ-standardized house dust mite immunotherapy as an immunomodulatory treatment in patients with asthma. *Allergy* 66:178–185, 2011.
- Shamji MH, Ljørring C, Francis JN, et al. Functional rather than immunoreactive levels of IgG4 correlate closely with clinical response to grass pollen immunotherapy. *Allergy* 67:217–226, 2012.
- Lai X, Li J, Xiao X, et al. Specific IgG4 production during house dust mite immunotherapy among age, gender and allergic disease populations. *Int Arch Allergy Immunol* 160:37–46, 2013.
- Şahin E, Bafaqeeh SA, Güven SG, et al. Mechanism of action of allergen immunotherapy. *Am J Rhinol Allergy* 30(suppl. 1):1–3, 2016.
- Shamji MH, James LK, and Durham SR. Serum immunologic markers for monitoring allergen-specific immunotherapy. *Immunol Allergy Clin North Am* 31:311–323, x, 2011.
- Aalberse RC, Stapel SO, Schuurman J, and Rispens T. Immunoglobulin G4: An odd antibody. *Clin Exp Allergy* 39:469–477, 2009.
- Wang HY, Gao ZS, Zhou X, et al. Evaluation of the role of IgE responses to Der p 1 and Der p 2 in Chinese house dust mite-allergic patients. *Int Arch Allergy Immunol* 167:203–210, 2015.
- Yang X, Fan G, and Li J. Diagnostic value of Der p 1 and Der p 2 specific IgE in *Dermatophagoides pteronyssinus* IgE sensitization. *Ann Allergy Asthma Immunol* 116:295–301, 2016.
- Mastrandrea F, Serio G, Minardi A, et al. IgE responses to *Dermatophagoides pteronyssinus* native major allergens Der p 1 and Der p 2 during long-term specific immunotherapy. *Allergy* 52:1115–1119, 1997.
- Brożek 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.
- Pfaar O, Demoly P, Gerth van Wijk R, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: An EAACI Position Paper. *Allergy* 69:854–867, 2014.
- Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: A practice parameter third update. *J Allergy Clin Immunol* 127(suppl.): S1–S55, 2011.
- Ewan PW, Deighton J, Wilson AB, and Lachmann PJ. Venom-specific IgG antibodies in bee and wasp allergy: Lack of correlation with protection from stings. *Clin Exp Allergy* 23:647–660, 1993.
- Jutel M, Jaeger L, Suck R, et al. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 116:608–613, 2005.
- Möbs C, Slotosch C, Löffler H, et al. Cellular and humoral mechanisms of immune tolerance in immediate-type allergy induced by specific immunotherapy. *Int Arch Allergy Immunol* 147:171–178, 2008. □

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