

Early Response of Specific IgE can Predict Satisfaction with Sublingual Immunotherapy

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Objective: To investigate predictive parameters at baseline and during the early response to sublingual immunotherapy (SLIT) for house dust mites in allergic rhinitis patients.

Study Design: Retrospective cohort study.

Methods: Patients were treated with SLIT for at least 3 years and serological tests performed at baseline and at 1-year follow-up to investigate predictive parameters. Satisfaction with SLIT, 4 nasal symptoms, and quality of life were evaluated before and after 3 years of SLIT. Sixty-one patients were enrolled and divided into two groups depending on their satisfaction after 3 years of SLIT: 43 were satisfied (70.5%) and 18 were not (29.5%).

Results: Immunological parameters at baseline did not differ significantly between the satisfactory and unsatisfactory groups. However, changes in both *Dermatophagoides pteronyssinus* (Dp)- and *D. farinae* (Df)-specific IgEs were significantly higher in the unsatisfactory group than in the satisfactory group during the early response to SLIT ($P = .006$ and $P = .045$, respectively).

Conclusion: The changes in both Dp- and Df-specific IgE levels during early response may be indicators for favorable long-term treatment outcomes with SLIT. These results suggest that clinicians could measure these immunological parameters 1 year after Dp and Df SLIT to indicate potential responders versus nonresponders.

Key Words: Allergic rhinitis, biomarkers, sublingual immunotherapy, house dust mites.

Level of Evidence: 2b

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INTRODUCTION

Allergic rhinitis is characterized by immunoglobulin E (IgE)-mediated inflammation induced by the exposure of specific allergens and its prevalence has increased over the past decades. Allergen-specific immunotherapy (AIT) has been used to treat IgE-mediated diseases, such as allergic rhinitis and asthma, for a century as it is the only treatment to modify the natural course of allergic diseases.¹ Subcutaneous immunotherapy has been prescribed as the conventional form of immunotherapy. Sublingual

immunotherapy (SLIT) is an alternative for subcutaneous immunotherapy.²⁻⁴

Efficacy of AIT ranges between 60% and 90%.⁵ At least 3 years of therapy is optimal to induce a clinical improvement which persists, therefore, selecting suitable subjects for SLIT is necessary because of its cost and duration of therapy.⁶⁻⁸ Immunological parameters, such as the baseline serum-specific IgE/total IgE ratio and serum-specific IgE, are suggested as predictors for treatment outcome, however, discordant results exist.⁹⁻¹⁵ Changes in immunological parameters during early treatment response to SLIT may be an alternative predictor to help clinicians decide its continuation beyond 1 year. Therefore, this study investigates predictive parameters with house dust mite (HDM) SLIT for allergic rhinitis at baseline and at 1 year of therapy.

METHODS

Study Design and Subjects

Subjects with a history of both dust mite allergy and positive skin prick test (SPT), a wheal diameter of 3 mm or greater to *Dermatophagoides pteronyssinus* (Dp) and/or *Dermatophagoides farinae* (Df) between 2009 and 2013 were enrolled in the study. All participants were requested to complete a questionnaire about their symptoms at baseline and after 3 years of Dp and Df SLIT. Serological tests were carried out at baseline and at 1-year follow-up to investigate predictive parameters for success. Sixty-one subjects who completed the questionnaire and the baseline and at 1 year follow-up serologic tests were selected. (Fig. 1). Informed

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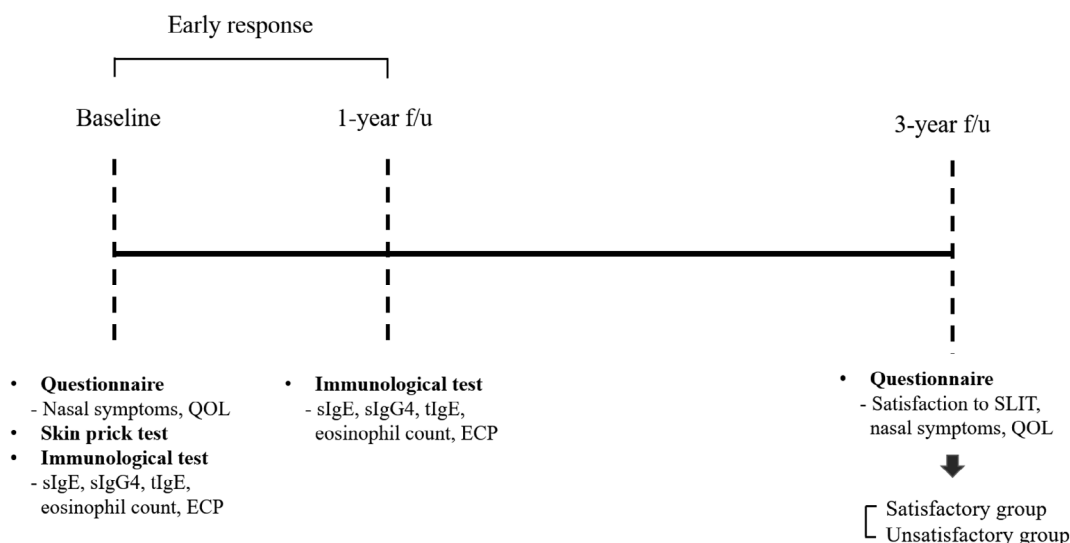


Fig. 1. The flowchart of the study design (n = 61).

	Satisfactory group (n = 43)	Unsatisfactory group (n = 18)	P
Age, mean $\pm$ SD, y	15.9 $\pm$ 11.1	11.6 $\pm$ 7.2	.080†
Sex (male: female)	28: 15	14: 4	.381‡
Duration of symptoms, mean $\pm$ SD, y	6.9 $\pm$ 6.1	4.7 $\pm$ 3.3	.078†
Baseline TNSS, mean $\pm$ SD	7.9 $\pm$ 2.9	8.2 $\pm$ 2.5	.681†
Monosensitized: Polysensitized	7: 36	1: 17	.417‡
Asthma history	4/43 (9.3%)	0/18 (0%)	.310‡

TNSS = total nasal symptom score.

†Two sample t-test.

‡Fisher's exact test.

consent was obtained from the patients or the patients' parents and the study approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1810-117-982).

Immunotherapy

SLITone (50% Dp and 50% Df, ALK-Abello, Madrid, Spain) was utilized for immunotherapy. Each package consists of 90 single-dose containers each containing 0.2-mL extractable volume of 1000-STU/mL solution. A prepared single-dose was taken in the morning, 30 minutes before breakfast. The patients were informed to maintain the SLIT allergen drops under their tongue for 2 to 3 minutes before swallowing.

Clinical Effects

All participants completed questionnaires about their symptoms, quality of life (QOL), and satisfaction with SLIT therapy before and after 3 years of treatment. The participants' subjective

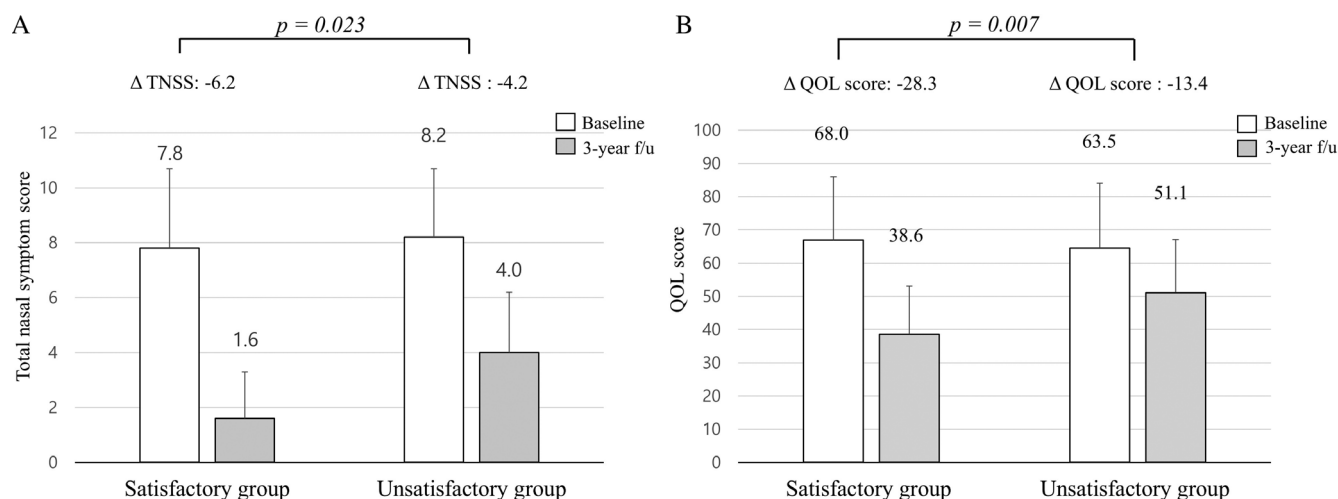


Fig. 2. Comparison of total nasal symptom score (A) and quality of life score (B) between the satisfactory and unsatisfactory groups.

TABLE II.
Comparison of Immunological Parameters between Satisfactory and Unsatisfactory Groups.

	Satisfactory group (n = 43)	Unsatisfactory group (n = 18)	P
Dp-specific IgE, KU/L			
Baseline	54.3 ± 72.1	42.3 ± 38.1	.571
1-year f/u	72.8 ± 61.7	133.1 ± 133.4	.036
Early response	18.2 ± 65.7	90.8 ± 105.3	.006
Df-specific IgE, KU/L			
Baseline	115.2 ± 169.6	87.9 ± 110.8	.637
1-year f/u	130.4 ± 98.8	200.5 ± 206.6	.156
Early response	15.2 ± 130.1	112.7 ± 123.9	.045
Dp-specific IgG4, mg/L			
Baseline	0.27 ± 0.22	0.33 ± 0.21	.451
1-year f/u	0.40 ± 0.29	0.48 ± 0.41	.403
Early response	0.12 ± 0.20	0.15 ± 0.24	.616
Df-specific IgG4, mg/L			
Baseline	0.39 ± 0.34	0.46 ± 0.43	.595
1-year f/u	0.50 ± 0.37	0.59 ± 0.42	.498
Early response	0.11 ± 0.22	0.13 ± 0.14	.745
Total IgE, KU/L			
Baseline	483.1 ± 518.4	487.2 ± 360.7	.978
1-year f/u	542.8 ± 454.9	699.3 ± 602.5	.307
Early response	59.7 ± 372.8	212.2 ± 422.7	.200
Dp-specific IgE/Total IgE, ratio			
Baseline	0.13 ± 0.07	0.10 ± 0.05	.184
1-year f/u	0.18 ± 0.07	0.15 ± 0.08	.335
Early response	0.05 ± 0.06	0.05 ± 0.04	.800
Df-specific IgE/Total IgE, ratio			
Baseline	0.26 ± 0.12	0.21 ± 0.12	.331
1-year f/u	0.35 ± 0.13	0.24 ± 0.12	.041
Early response	0.09 ± 0.11	0.03 ± 0.06	.114
Dp-specific IgE/Dp-specific IgG4, ratio			
Baseline	231.3 ± 306.9	142.7 ± 133.5	.323
1-year f/u	255.5 ± 316.4	295.6 ± 284.1	.692
Early response	24.2 ± 326.8	152.8 ± 223.1	.199
Df-specific IgE/Df-specific IgG4, ratio			
Baseline	334.0 ± 398.8	213.6 ± 161.7	.362
1-year f/u	311.2 ± 254.3	395.9 ± 514.4	.493
Early response	-22.8 ± 252.8	182.4 ± 423.9	.071
Eosinophil count, /μL			
Baseline	395 ± 304	400 ± 208	.956
1-year f/u	278 ± 173	325 ± 180	.359
Early response	-117 ± 248	-74 ± 114	.373
ECP, μg/L			
Baseline	31.8 ± 31.2	18.6 ± 14.4	.100
1-year f/u	26.9 ± 29.1	17.6 ± 12.8	.212
Early response	-4.9 ± 23.4	-1.0 ± 10.4	.375

Values are demonstrated as mean ± SD.

Bold text indicates statistical significance ($P < .05$).

Early response: Change from baseline (1-year f/u - baseline).

ECP = eosinophil cationic protein; f/u = follow-up.

satisfaction after the completion of 3 years of SLIT was categorized as “satisfied, fair, or dissatisfied” (Fig. 1). After 3 years of SLIT, the satisfactory group was defined as patients who selected “satisfied” whereas those who selected “fair” or “dissatisfied” were categorized into the unsatisfactory group. Four nasal symptoms assessed include sneezing, itching, rhinorrhea, and nasal congestion. Each symptom was graded from 0 to 3 points: 0 for no, 1 for mild, 2 for moderate, and 3 for severe symptoms. The total nasal symptom score (TNSS) was calculated using the sum of each symptom score. QOL was measured by the Korean version of the modified Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ),^{16,17} consisting of seven domains: practical problems, sleep problems, nasal symptoms, generalized symptoms, activities, emotions, and ocular symptoms. Responses were scored on a scale of 1 to 5 points: 1 for not, 2 for rarely, 3 for mildly, 4 for moderately, and 5 points for severely affected.

Immunological Parameters

SPTs (Allergo-Pharma, Reinbek, Germany) were performed initially on all participants. A wheal diameter of at least 3 mm was considered positive. Sensitization to HDM is defined as having a positive reaction to Dp and/or Df at baseline. Histamine (1% histamine phosphate) and 0.9% saline are positive and negative controls, respectively. A venous sample was obtained from the participants at baseline and 1-year follow-up. Specific IgE (sIgE) and IgG4 (sIgG4) for Dp and Df, total IgE (tIgE), and eosinophil cationic protein (ECP) were measured using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) and peripheral blood eosinophils were counted. The following formula was used to calculate ratios: sIgE/tIgE ratio = sIgE/tIgE and sIgE/sIgG4 ratio = sIgE/sIgG4.

Statistical Analysis

Continuous values of demographic, immunological parameters, TNSS, and QOL scores are presented as mean ± SD and analyzed using the two-sample t-test. Fisher's exact test was carried out to evaluate categorical variables. Changes from baseline were calculated (1-year follow-up vs baseline) to evaluate changes. Adjusting confounding factors, multiple logistic regression was performed to validate the potential predictors in univariate analysis. A receiver operating characteristic (ROC) curve of the changes in both Dp and Df sIgE was generated to find the best cutoff to predict “satisfaction” with SLIT. The area under the curve (AUC) for each potential predictor was determined. Hence, an AUC with a value close to 1 indicates a high accuracy of prediction. Among several cutoff points, the lowest $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ value was selected as the best optimal cutoff value. All statistical analyses were performed using R for Windows, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria). A P value of $< .05$ was considered significant.

RESULTS

Sixty-one patients are enrolled in the study and divided into 2 groups: 43 in the satisfactory group (70.5%) and 18 in the unsatisfactory group (29.5%). The demographic and clinical features are presented in Table I. The mean age of the satisfactory and unsatisfactory groups was 15.9 ± 11.1 and 11.6 ± 7.2 , respectively ($P = .080$). There is no significant difference in the male-female ratio, symptom duration, the ratio of mono- and poly-sensitized subjects, or baseline TNSS. Four subjects in the satisfactory versus none in the unsatisfactory

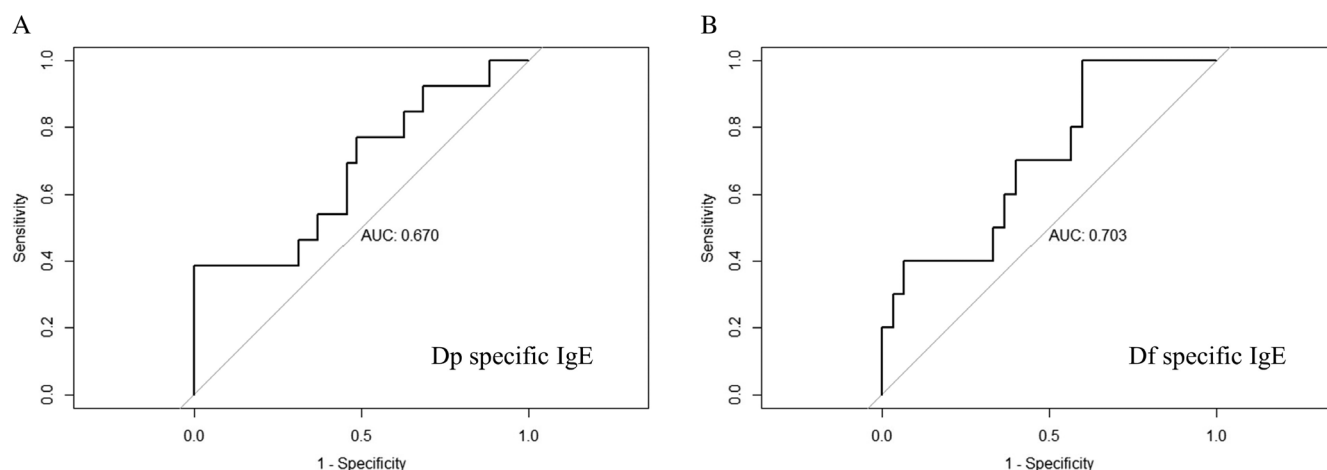


Fig. 3. Receiver operating characteristic (ROC) curves of the early response (1-year follow-up vs baseline) in Dp- and Df-specific IgE for predicting subjects' satisfaction at 3-year follow-up. (A) ROC curve for the early response in Dp specific IgE. (B) ROC curve for the early response in Df-specific IgE. Predictive ability was calculated based on the area under the curve (AUC).

group had a history of asthma ($P = .310$). The changes in TNSS 3 years after beginning SLIT was compared between the two groups. The decrease in TNSS was larger in the satisfactory versus the unsatisfactory group ($P = .023$; Fig. 2A). Also, the changes in QOL scores are significantly higher in the satisfactory group ($P = .007$; Fig. 2B).

Immunological parameters at baseline and 1-year follow-up were obtained to investigate predictors of satisfaction after 3 years in both groups (Table II). An early response of these immunological parameters was defined as changes between baseline and the 1-year follow-up. The satisfactory versus the unsatisfactory group did not differ in baseline immunological parameters: sIgE, sIgG4, tIgE, eosinophil count, and ECP. However, the changes in both Dp and Df sIgE are significantly higher in the unsatisfactory versus the satisfactory group. Furthermore, the unsatisfactory group versus the satisfactory group have higher Dp sIgE at the 1-year follow-up ($P = .036$). However, the changes in Dp and Df sIgG4 are not significantly different between the two groups ($P = .616$ and $P = .745$, respectively). The satisfactory group does not differ from the unsatisfactory group in the early changes in tIgE, eosinophil counts, and the level of ECP. In the comparison of the ratio of immunological parameters, Df sIgE/tIgE at 1-year follow-up is significantly higher in the satisfactory versus unsatisfactory group ($P = .041$); however, the changes in Df sIgE/tIgE are not significantly different ($P = .114$). Otherwise, there are no significant differences in the ratio of immunological parameters between the groups. Adjusting age, sex, duration of symptom, history of asthma, ratio of monosensitized and polysensitized patients, baseline total IgE, eosinophil count, and ECP, there was significant difference in the early changes in Dp and Df sIgE (Adjusted OR for satisfaction, 0.982 and 0.984; $P = .024$ and $.039$, respectively).

Receiver operating characteristic (ROC) curves of early response of Dp and Df sIgE were analyzed to predict subject satisfaction at 3-year follow-up (Fig. 3). The areas under the curve (AUCs) are 0.670 and 0.703 for

early response of Dp and Df sIgE, respectively. The best threshold value with optimal sensitivity and specificity yielded a value of ≤ 13.2 KU/L for the increase in Dp sIgE, demonstrating a sensitivity of 76.9% and a specificity of 51.4% (Fig. 3A) and a value of ≤ 28.1 KU/L for the increase in Df sIgE, demonstrating a sensitivity of 70.0% and a specificity of 60.0% (Fig. 3B).

DISCUSSION

Many studies demonstrate efficacy of SLIT.^{2-4,18-22} However, some subjects do not improve with such therapy. Therefore immunological parameters to demonstrate future efficacy are important. A predictive parameter in previous studies is the baseline serum sIgE/tIgE ratio; however, discordant values exist among studies.⁹⁻¹¹ The high serum sIgE/tIgE ratio ($>16.2\%$) in the Lorenzo et al. study¹⁰ is associated with an effective clinical response. However, a low serum sIgE/tIgE ratio (≤ 0.19) is correlated to a better outcome in a study by Fujimura et al.¹¹ Serum sIgE is considered a potential biomarker also to predict response to allergen immunotherapy in several studies.¹²⁻¹⁵ In the studies by Ciprandi et al. and Lee et al.,^{13,14} subjects with high sIgE levels (>9.74 kU/L and >17.5 kU/L, respectively) versus lower levels are more likely to achieve a better response. However, two additional studies do not show these same results.^{12,15} Therefore, additional studies are necessary to determine immunological parameters which predict a clinical response to SLIT.

Patients in this study were divided into two groups depending on their satisfaction after 3 years of SLIT. Satisfaction was utilized to decide outcomes instead of reduction of nasal symptoms because such results are associated not only with a reduction in symptoms but also improvement in QOL, as demonstrated in this study. When comparing demographic and clinical characteristics between the two groups, there is no statistical difference. Baseline TNSS was not different between the two groups in contrast to a previous study in which the severity of rhinitis is associated with an effective response.¹³

Immunological parameters at baseline and 1-year follow-up were compared between the two groups to assess predictors for satisfaction after 3 years of SLIT. There is no significant difference in immunological parameters at baseline between the two groups.

However, when comparing the early response to SLIT the changes in both Dp and Df sIgE levels are higher in the unsatisfactory versus satisfactory group. Likewise, the unsatisfactory versus the satisfactory group have higher Dp sIgE levels at 1-year follow-up. The Stylianou et al. study indicates that sIgE increases initially in subjects treated with birch and/or timothy subcutaneous immunotherapy, however, thereafter it decreases.²³ This decrease in sIgE levels determined before and after subcutaneous immunotherapy (22–41 months) could be associated with favorable outcomes.²⁴ However, this issue was not addressed by the authors. Therefore, in contrast to the satisfactory group in our study, sIgE in the unsatisfactory group does not decrease after several months, ultimately predicting unfavorable outcomes. To be specific, we believe that a small increase in the satisfactory group may mean a large decrease after the surge. To confirm our theory, further investigation to measure sIgE at earlier time points (eg, at 1-month, 3-month, and 6-month follow-up) should be conducted.

The changes in sIgG4 as a blocking antibody, the increase of which is regarded as a positive indicator for successful immunotherapy outcome,^{25,26} are not different between the two groups. Some studies demonstrate a lack of correlation between changes in IgG4 levels and treatment outcomes.^{27,28} To explain this discrepancy, role of the functional blocking IgG antibody was suggested.²⁹ Blocking IgG competes with IgE for the binding to the epitopes for the allergen molecule, thus inhibits activation of mast cells and basophils.³⁰ However, non-blocking IgG that recognize different epitopes than IgE specific for the same allergen molecule does not prevent binding of IgE, and both IgE and IgG can bind simultaneously to the same allergen molecule.³⁰ For this reason, functional rather than quantitative IgG4 was emphasized in the previous study, in which the changes in functional specific antibodies accounted for about 40% of the clinical outcomes, and quantitative changes in specific IgG4 levels accounted for only 13%.³¹

There are no significant differences in both Dp and Df sIgE/tIgE ratio between satisfactory and unsatisfactory groups at baseline in contrast to a previous study.¹⁰ Instead, the Df sIgE/tIgE ratio is significantly higher in the satisfactory versus the unsatisfactory group at 1-year follow-up. However, the satisfactory does not differ from the unsatisfactory group in the change in the Df sIgE/tIgE ratio. Furthermore, there is no significant difference in Dp sIgE/tIgE ratio between the two groups at 1-year follow-up.

Limitations of the study include: First, the treatment outcomes of subjects followed for 3 years can be biased. Due to the economic burden for SLIT and the long duration for treatment, there is a possible bias in that only subjects who had clinical improvement maintained SLIT. Second, treatment outcomes were evaluated by satisfaction, not a typical parameter to decide a successful

SLIT treatment in previous studies. However, satisfaction is advantageous in that it theoretically is associated not only with a decrease in nasal symptoms but also with improvement of QOL. Hence, we believe that satisfaction of individual patients is a useful parameter to assess treatment outcomes. Lastly, the number of subjects is relatively small, because the design for this study required 3-year follow-up and serological tests at baseline and 1 year. Therefore, further investigation with a larger population is necessary to confirm the results of this study.

CONCLUSION

The present study is advantageous in its novel design. Previous studies focused on the immunological parameters at baseline to investigate predictive outcomes.⁹⁻¹⁵ Because of the discrepancy among these studies, the authors assessed both baseline immunological parameters and the changes at 1 year. The changes in both Dp and Df sIgE levels during the early response to Dp and Df SLIT, as illustrated in this paper, are positive indicators for favorable treatment outcomes.

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