Long-term efficacy of house dust mite sublingual immunotherapy on clinical and pulmonary function in patients with asthma and allergic rhinitis

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Background: A previous study reported that house dust mite (HDM) sublingual immunotherapy (SLIT) for 48 weeks was effective as add-on treatment for allergic asthma; however, data regarding its long-term efficacy are scarce.
Objective: We sought to evaluate the effect of HDM SLIT on asthma control, pulmonary function, and airway inflammation and remodeling throughout the 5-year treatment period.
Methods: A total of 140 patients with asthma and allergic rhinitis sensitized to HDM were randomized to receive either drugs alone or drugs plus SLIT for 5 years. The 5-item Asthma Control Questionnaire (ACQ-5), Asthma Quality of Life Questionnaire (AQLQ), Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), spirometry, quantitative computed tomography, and type 2 biomarkers were assessed.
Results: An improvement in the ACQ-5, AQLQ, and RQLQ scores was observed in the SLIT group compared with the control group. HDM SLIT increased lung function and reduced the percentage of airway wall area. The levels of fractional exhaled nitric oxide (FENO), blood eosinophil, serum specific IgE for HDM, and total IgE decreased and were sustained during the 5 years. The change in type 2 biomarkers correlated with change in the AQLQ score. On the basis of receiver-operating characteristic analysis for predicting responders, the area under the receiver-operating characteristic curve in FEV_1% predicted, airway wall area, FENO, and specific IgE was high. Multivariate regression analysis showed that the strongest predictor of responders was FENO.
Conclusions: HDM SLIT continued to provide sustained efficacy, improve lung function, and prevent progression of airway inflammation and remodeling in asthma throughout the 5-year treatment period. (J Allergy Clin Immunol Global 2024;3:100206.)

Key words: *Airway inflammation, allergic rhinitis, asthma, house dust mite sublingual immunotherapy, long-term efficacy, pulmonary function, quality of life, remodeling, symptom, type 2 biomarker*

Allergen immunotherapy (AIT) is the only causal treatment for allergy.[1] AIT can be administered as subcutaneous immunotherapy (SCIT) via injection or as sublingual immunotherapy (SLIT) in the form of a tablet or drop for a minimum treatment period of 3 years.[2] SLIT is more convenient and has less severe systemic reactions than SCIT.[3] The efficacy of SLIT for allergic rhinitis with comorbid asthma was demonstrated in house dust mite (HDM), grass, and tree pollen allergies.[4] HDM is the most common allergen associated with asthma, and more than 40% of adults with asthma were found to be atopic and tested positive in skin prick tests for HDM allergens.[5] In randomized controlled trials, treatment with standardized quality (SQ) HDM SLIT tablets in subjects with asthma with or without rhinitis reduced the use of inhaled corticosteroid (ICS) dose and asthma exacerbations.[6-8]

Although the efficacy and safety of HDM SLIT tablets for asthma have been demonstrated, uncertainty across longer follow-up periods of SLIT, in particular on asthma-related outcomes, remains.[9] Furthermore, there is little evidence for the effects of long-term HDM SLIT on airway inflammation or remodeling in patients with asthma.

We previously demonstrated that a 48-week HDM SLIT improved asthma symptoms, increased FEV_1, and reduced eosinophilic inflammation in allergic asthma.[10] In addition, we reported that an increased composite score of 2 type 2 inflammatory biomarkers (fractional exhaled nitric oxide [FENO] and serum periostin but not blood eosinophils or IgE) at baseline was independently associated with increased FEV_1.[11] In the present study, the treatment period with follow-up was extended from 1 year to 5 years to investigate the long-term and sustained efficacy of HDM SLIT.

METHODS

Study design

This was an open-label, parallel-group, randomized controlled study that evaluated 5-year HDM SLIT in patients with asthma and allergic rhinitis. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from all the subjects. The study protocol and extension were approved by the Ethics Committee of the International University of Health and Welfare, and it was registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry (UMIN000022390).

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Abbreviations used
ACQ-5: 5-item Asthma Control Questionnaire
AE: Adverse event
AIT: Allergen immunotherapy
AQLQ: Asthma Quality of Life Questionnaire
BSA: Body surface area
CT: Computed tomography
FENO: Fractional exhaled nitric oxide
HDM: House dust mite
ICS: Inhaled corticosteroid
JAU: Japanese allergy unit
LS: Least-squares
MCID: Minimal clinically important difference
QoL: Quality of life
ROC: Receiver-operating characteristic
RQLQ: Rhinoconjunctivitis Quality of Life Questionnaire
SCIT: Subcutaneous immunotherapy
s-IgE: Specific IgE
SLIT: Sublingual immunotherapy
SQ: Standardized quality
T: Wall thickness
t-IgE: Total IgE
WA/Ao: Wall area/total area of the airway

The trial consisted of a screening phase, a 4-week run-in period, and a 5-year treatment period. Participants who had already completed our previous studies[10,11] were eligible for enrollment in this study. The enrollment commenced in May 2016. Through computer-generated randomization, patients were randomly treated with 6 SQ-HDM SLIT tablets as add-on therapy to drug treatment (SLIT group) or pharmacotherapy alone (control group). The spirometry, computed tomography (CT) scans, clinical laboratory samples, 5-item Asthma Control Questionnaire (ACQ-5), Asthma Quality of Life Questionnaire (AQLQ), and Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) were conducted at baseline; years 1, 2, 3, and 4; and end of treatment (year 5). Adverse events (AEs) at all visits and once a month were reported.

Population

Eligible patients (aged 20-65 years) were nonsmokers or ex-smokers with less than 5 pack years and who had stopped smoking at least 1 year before enrollment. Asthma was diagnosed on the basis of the American Thoracic Society criteria.[12] In brief, all patients had already been diagnosed with asthma on the basis of asthma-related symptoms, such as cough, dyspnea, chest tightness, and/or wheezing associated with a demonstrated reversible airflow limitation (12% and 200 mL variability in FEV_1 with a short-acting β_2-agonist). The inclusion criteria were a clinical history of HDM-related asthma, defined as positive HDM sensitization and asthma symptoms worsened by exposure to HDM (steps 2 and 3 in the Global INitiative for Asthma guideline)[13] with a duration of at least 1 year; use of an appropriate amount of ICS (200-800 μg/d of budesonide or equivalent); a clinical history consistent with HDM-induced allergic rhinitis (Allergic Rhinitis and its Impact on Asthma guidelines)[14] for at least 1 year; positive diagnostic test results to HDM (skin prick tests with a wheal size ≥3 mm to *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, or both); and serum specific IgE (s-IgE) for HDM greater than 0.7 kU/L. Patients continued their maintenance therapies throughout the study with no change in medications. Adherence to medication was checked by the amount of medication remaining at each visit. The patients were allowed to use a short-acting β_2-agonist as needed for symptom relief. Pharmacotherapy for rhinitis or conjunctivitis, that is, antihistamine tablets and eye drops or nasal steroids, was administered to subjects as needed to control their symptoms. The exclusion criteria were hospitalization due to asthma exacerbation within 3 months before screening, presence of uncontrolled asthma, FEV_1 less than 70% of the predicted value, relevant clinical history of perennial allergic asthma or rhinitis caused by other allergens, and presence of systemic immunologic diseases (eg, autoimmune disease, treatment with oral steroids, and malignancies).

Immunotherapy

The HDM SLIT tablets (Torii, Tokyo, Japan/ALK-Abelló, Hørsholm, Denmark) contained allergen extracts derived from *D farinae* and *D pteronyssinus* at a ratio of 1:1. Because of adjustment by correction value and titer of standardized HDM AIT vaccine, a nominal strength of 3.300 Japanese allergy units (JAUs) has the same potency as 2 SQ-HDM and 10.000 JAU as 6 SQ-HDM. On the basis of the safety profiles of European phase I trials,[15] 3.300 JAU (2 SQ-HDM) was chosen as the initial dose for 1 week, followed by upward titration of the dose to 10.000 JAU (6 SQ-HDM). The use of 6 SQ-HDM tablets is authorized in Japan.

Pulmonary function

Spirometry was conducted according to the American Thoracic Society/European Respiratory Society recommendation using a computerized spirometer (Fukuda Denshi, Tokyo, Japan).[16]

Computed tomography

Volumetric whole-lung scans were obtained using a 320-multislice scanner (Aquilion ONE, Canon Medical Systems, Tochigi, Japan) at full inspiration. Details of CT acquisition and quantitative airway morphometry were previously described.[17,18] The CT parameters were as follows: percentage of the wall area/total area of the airway (WA/Ao) and absolute wall thickness (T) at the right upper lobe apical segmental bronchus. Because the airway size may be affected by body size, T was normalized to the body surface area (BSA).

Type 2 inflammatory markers

FENO was measured using a portable nitric oxide analyzer (NIOX System; Aerocrine, Stockholm, Sweden). The levels of peripheral blood eosinophil, serum s-IgE (ImmunoCAP, Thermo Fisher/Phadia, Uppsala, Sweden), and total IgE (t-IgE) were determined.

Asthma control and quality of life

Asthma control was measured using the ACQ-5. The ACQ-5 score ranged from 0 to 6; uncontrolled was defined by a score greater than 1.5, and the minimum clinically important difference (MCID) was greater than 0.5.[19] Quality of life (QoL) was assessed using the AQLQ[20] and RQLQ.[21] The AQLQ contains 32

TABLE I. Baseline characteristics

Characteristics	SLIT (n = 66)	Control (n = 74)	*P* value
Age (y)	51 ± 11	53 ± 11	.222
Sex, male/female	24/42	20/54	.501
Body mass index (kg/m^2)	23.7 ± 3.6	24.8 ± 4.3	.434
Asthma duration (y)	18.0 ± 15.8	17.5 ± 15.4	.440
Prebronchodilator FEV_1 (L)	2.14 ± 0.25	2.24 ± 0.28	.256
Prebronchodilator FEV_1 (% predicted)	93.7 ± 23.6	94.8 ± 20.5	.416
WA/Ao (%)	71.1 ± 6.2	72.3 ± 6.4	.179
T/√BSA(mm/m)	0.95 ± 0.24	1.04 ± 0.38	.061
FENO (ppb)	33.8 ± 40.0	29.3 ± 33.7	.294
Blood eosinophil (/μL)	281.6 ± 211.2	377.6 ± 450.4	.073
s-IgE HDM (kUL)	11.5 (3.6-22.2)	7.7 (3.2-19.8)	.208
t-IgE (IU/mL)	262.0 (77.2-746.0)	118.0 (46.6-430.7)	.140
ACQ-5 score	0.85 ± 0.22	0.87 ± 0.17	.314
Overall AQLQ score	5.74 ± 1.06	5.75 ± 1.05	.553
Overall RQLQ score	2.93 ± 0.84	3.20 ± 0.97	.648
Medication			
ICS, n (μg/d)*	66 (493.3 ± 169.7)	74 (548.4 ± 187.3)	.131
LABA, n (%)	55 ± 83.3	57 ± 77.0	.324
LTRA, n (%)	29 ± 43.9	27 ± 36.4	.791

Data are presented as mean ± SD or median (IQR).
IQR, Interquartile range; *LABA*, long-acting β_2-agonist; *LTRA*, leukotriene receptor antagonist.
*Dose of stable maintenance treatment (budesonide or equivalent dose).

items covering 4 domains scored on a 7-point scale. The RQLQ contains 28 items covering 7 domains scored on a 7-point scale. Overall, the mean AQLQ and RQLQ scores with each domain weighted equally were calculated for each patient. A change of greater than 0.5 points in the score represents a clinically meaningful improvement in QoL.

SLIT responder

HDM SLIT responders were those who exhibited improvement in the AQLQ score from baseline that reached or exceeded the MCID threshold of 0.5.

Outcomes

The primary end points were the AQLQ score, ACQ-5 score, and change from baseline up to year 5. The secondary end points were the effect of HDM SLIT on the RQLQ, pulmonary function, airway dimensions, and type 2 inflammatory biomarkers during the 5-year treatment period. Safety profile was assessed using AEs, vital sign, physical examination, and laboratory investigations.

Statistical analysis

Efficacy analyses were conducted in the intent-to-treat population, consisting of patients who underwent randomization. Data were analyzed according to the assigned intervention, whether or not it was received. Changes from baseline in the ACQ-5 score, AQLQ score, RQLQ score, FEV_1, airway dimensions, and type 2 biomarkers were reported as least-squares (LS) mean values and analyzed using mixed-effects model with repeated measures, including assigned intervention, age, sex, baseline eosinophil level, baseline ICS dose, visit, Treatment × Visit interaction, corresponding baseline value, and Baseline × Visit interaction as covariates. Linear regression models were used to describe the relationship between changes (Δ: at year 5 − baseline) in type 2 biomarkers and changes in the AQLQ score and WA/Ao.

To determine the use of clinical index in detecting response to SLIT, receiver-operating characteristic (ROC) analysis was conducted. Response to SLIT was assessed as effective or ineffective using the area under the ROC curve. Univariate analysis followed by multivariate logistic regression analysis was to evaluate which one predicted ΔAQLQ. All statistical tests were conducted using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Participants

A total of 168 subjects were enrolled. However, 140 subjects (SLIT group, 66; control group, 74) were included in the final analysis, of whom 118 completed the 5-year treatment period (see Fig E1 in this article's Online Repository at www.jaci-global.org). Across the treatment groups, the numbers of dropouts were comparable (SLIT group, 12; control group, 10), with the reasons being consent withdrawal, noncompliance, AEs, and lost to follow-up. The patients' baseline demographic and clinical characteristics are presented in Table I. The overall demographic characteristics were similar between the 2 groups.

Asthma control and QoL

At 1 year, the SLIT group exhibited improved ACQ-5 score. In this group, the LS mean change from baseline at 1 year was −0.56 (SE, 0.18; difference vs control [95% CI], −0.55 [−0.88 to −0.22]; $P = .007$). Overall, improvement was sustained through year 5 by −0.59 (SE, 0.13; difference vs control [95% CI], −0.48 [−1.10 to 0.13]; $P = .031$) (Fig 1, *A*; see Table E1 in this article's Online Repository at www.jaci-global.org). HDM SLIT significantly improved the AQLQ score compared with the control during the treatment period. In the SLIT group, the LS mean change from baseline at 1 year improved by 0.57 (SE, 0.08;

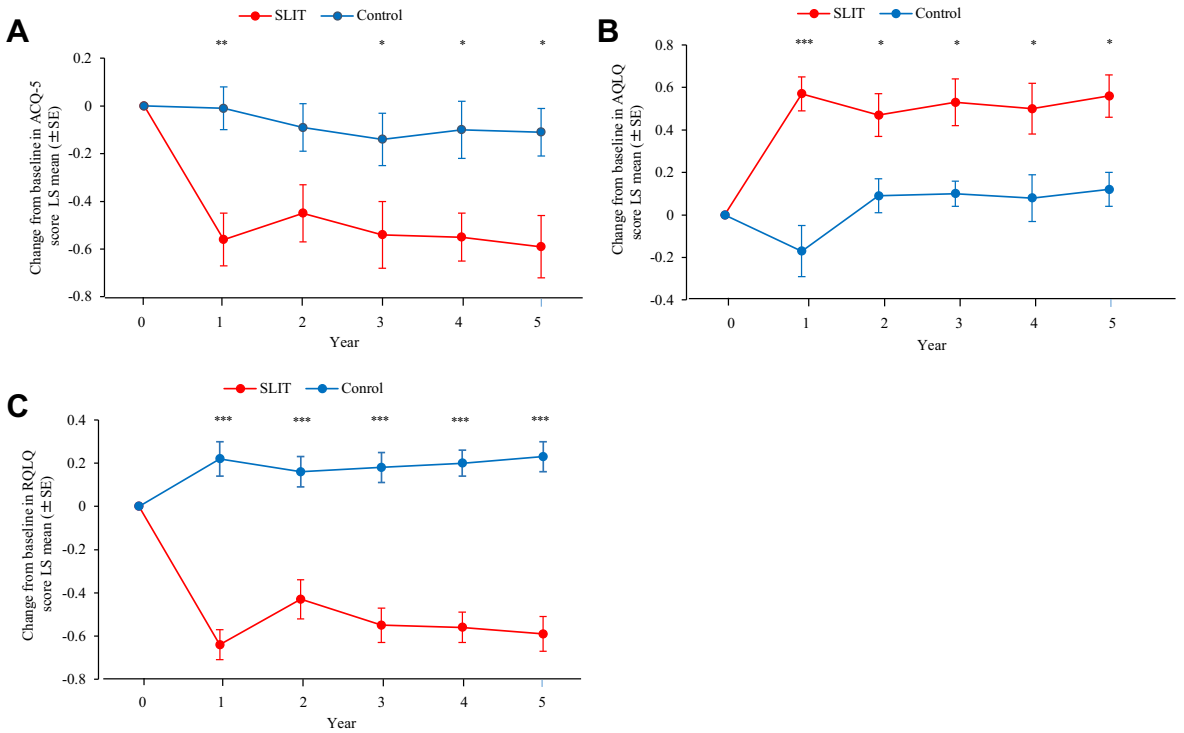

FIG 1. Effect of HDM SLIT on asthma control (**A**) and QoL (**B** and **C**) during the 5-year treatment in patient with asthma and allergic rhinitis. *$P < .05$; **$P < .01$; ***$P < .001$ vs matched control.

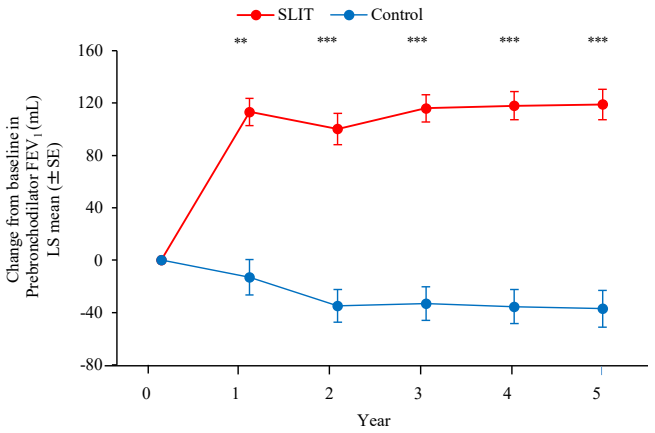

FIG 2. Effect of HDM SLIT on pulmonary function during the 5-year treatment in patient with asthma and allergic rhinitis. **$P < .01$; ***$P < .001$ vs matched control.

difference vs control [95% CI], 0.74 [0.01 to 1.49]; $P < .001$). Improvement was sustained through year 5 by 0.56 (SE, 0.10; difference vs control [95% CI], 0.44 [0.01 to 0.88]; $P = .014$) (Fig 1, *B*; see Table E2 in this article's Online Repository at www.jaci-global.org). Similarly, the LS mean change from baseline at 1 year in the RQLQ score improved by −0.64 (SE, 0.07; difference vs control [95% CI], −0.86 [−1.10 to −0.63]; $P < .001$) (Fig 1, *C*; see Table E3 in this article's Online Repository at www.jaci-global.org), and it was maintained throughout the 5-year treatment period.

Lung function

The use of HDM SLIT tablets was associated with a significant increase in prebronchodilator FEV_1 from baseline at 1 year. In the SLIT group, the LS mean change from baseline at 1 year in prebronchodilator FEV_1 was greater by 113.2 mL (SE, 10.9; difference vs control [95% CI], 126.2 mL [−3.31 to 255.74]; $P = .003$). Improvement was sustained throughout the 5-year treatment period by 118.9 mL (SE, 11.5; difference vs control [95% CI], 196.0 mL [64.59 to 327.53]; $P < .001$) (Fig 2; see Table E4 in this article's Online Repository at www.jaci-global.org).

Airway dimension

Patients treated with SLIT versus control exhibited a significant decrease in WA/Ao and T/$\sqrt{}$BSA, as assessed via CT during the treatment period (Fig 3, *A* and *B*; see Tables E5 and E6 in this article's Online Repository at www.jaci-global.org). The LS mean change from baseline at 1 year decreased by −2.26% (SE, 2.05; difference vs control [95% CI], −2.70% [−5.75 to 0.33]; $P = .003$) and −0.08 mm/m (SE, 0.039; difference vs control [95% CI], −0.12 mm/m [−0.27 to –0.04]; $P = .001$) in WA/Ao and T/$\sqrt{}$BSA, respectively. A numerical decrease in airway dimensions in SLIT versus control was observed throughout the 5-year treatment period.

Type 2–associated biomarkers

The LS mean change from baseline at 1 year in FENO significantly decreased in the SLIT group compared with the control

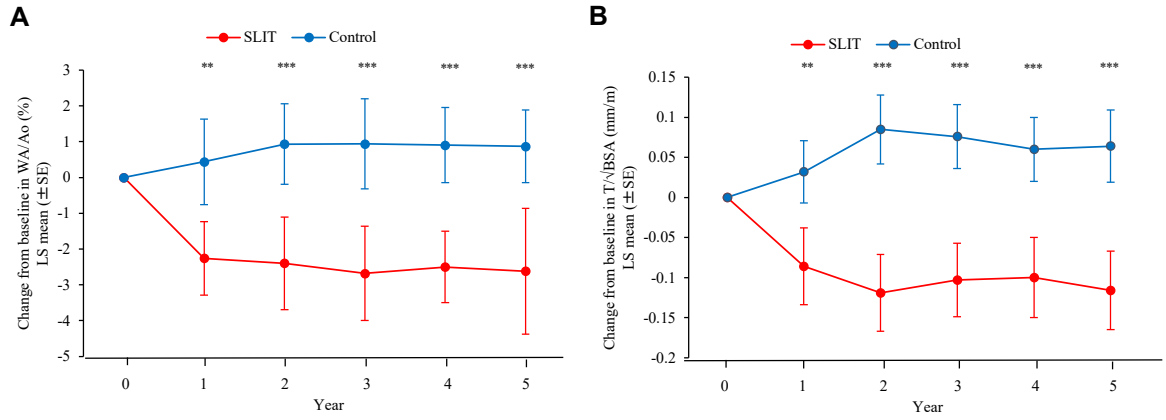

FIG 3. Effect of HDM SLIT on airway dimension during the 5-year treatment in patient with asthma and allergic rhinitis. $^{**}P < .01$; $^{***}P < .001$ vs matched control.

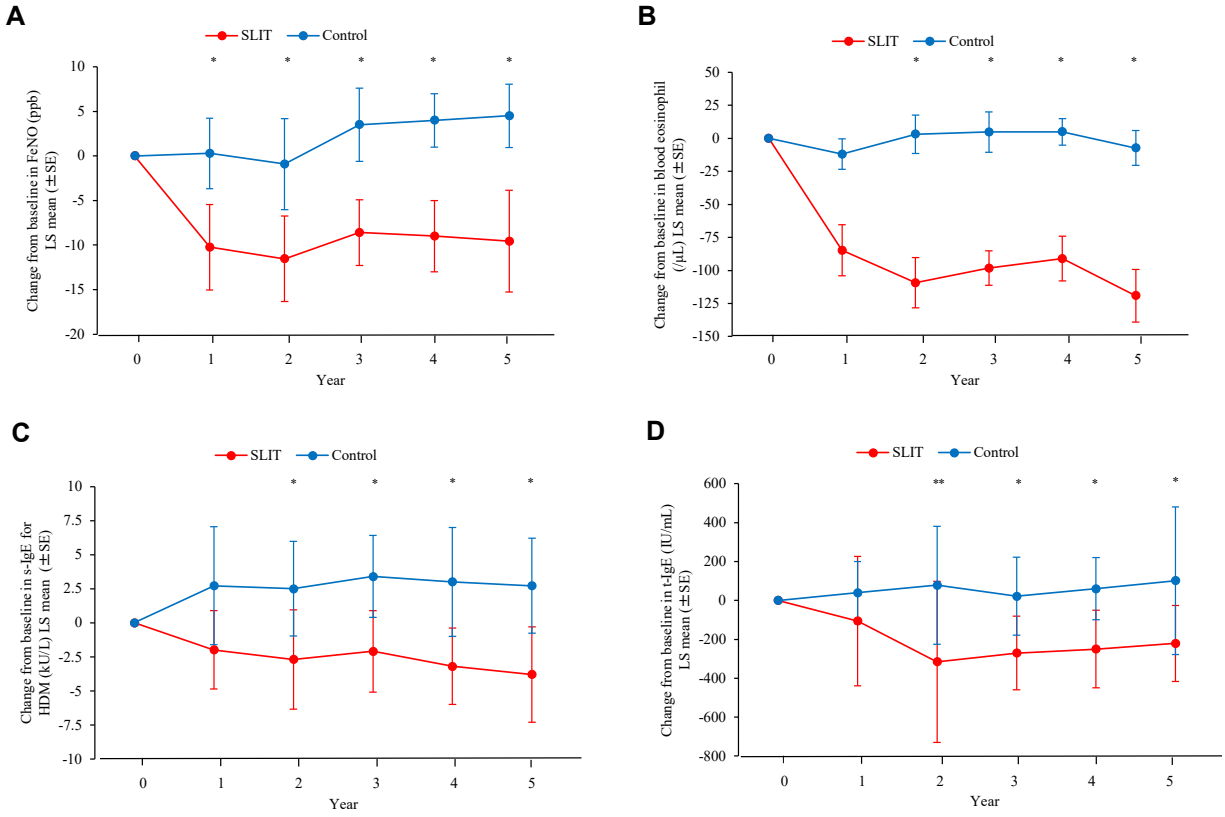

FIG 4. Effect of HDM SLIT on FENO (**A**), blood eosinophils (**B**), s-IgE for HDM (**C**), and t-IgE (**D**) during the 5-year treatment in patient with asthma and allergic rhinitis. $^{*}P < .05$; $^{**}P < .01$ vs matched control.

group (LS mean difference vs control [95% CI], −10.5 ppb [−25.0 to –4.0]; $P = .011$). Reduction was sustained through to year 5 by −9.5 ppb (SE, 5.7; difference vs control [95% CI], −14.0 ppb [−21.1 to −12.9]; $P = .012$) (Fig 4, *A*; see Table E7 in this article's Online Repository at www.jaci-global.org). The LS mean change from baseline at 1 year in blood eosinophil level decreased in the SLIT group compared with the control group, but did not reach significant difference (LS mean difference vs control [95% CI], 72.7/μL [−412.6 to 558.0]; $P = .054$) (Fig 4, *B*). Similar results were obtained for s-IgE for HDM (LS mean difference vs control [95% CI], 4.71 kU/L [2.03 to 7.11]; $P = .051$) (Fig 4, *C*) and t-IgE (LS mean difference vs control [95% CI], −140.3 IU/mL [−799.8 to −579.2]; $P = .172$) (Fig 4, *D*) at 1 year. However, the LS mean change from baseline after 2 years in blood eosinophil, s-IgE for HDM, and t-IgE levels significantly decreased in the SLIT group compared with the control group (Fig 4, *B-D*; see Tables E8-E10 in this article's Online Repository at www.jaci-global.org).

TABLE II. Correlations between the changes in type 2 biomarkers and clinical response or airway remodeling

	ΔAQLQ		ΔWA/Ao (%)	
Variables*	r	*P* value	r	*P* value
ΔFeno (ppb)	−0.846	<.001	0.766	<.001
ΔBlood eosinophil (/μL)	−0.330	.037	−0.120	.725
Δs-IgE HDM (kU/L)	−0.616	<.001	0.563	.002
Δt-IgE (IU/mL)	−0.497	.024	0.326	.041

*Variables refer to the absolute change (Δ: year 5 − baseline).

TABLE III. Multivariate regression models for prediction of improvement in the AQLQ score with HDM SLIT

Characteristics	Model r^2	β	95% CI	*P* value
Prebronchodilator FEV_1 (% predicted)	0.604	0.043	0.006 to 0.079	.023
WA/Ao (%)		0.001	−0.006 to 0.011	.743
Feno (ppb)		0.015	0.009 to 0.021	1.81×10^{-5}
Blood eosinophil (/μL)		-6.90×10^{-6}	−0.001 to 0.001	.988
s-IgE HDM (kU/L)		0.018	0.002 to 0.034	.036

Relationship between type 2 biomarkers and clinical response or airway remodeling

The changes in AQLQ score after SLIT (ΔAQLQ) correlated with ΔFeno, Δblood eosinophil, Δs-IgE for HDM, and Δt-IgE. Similar significant correlations were observed between ΔWA/Ao and ΔFeno, Δs-IgE for HDM, and Δt-IgE (Table II).

Prediction of SLIT responders

Of the 66 patients in the SLIT group, 43 (63%) were identified as responders on the basis of clinical improvement in the AQLQ score. ROC curves were generated to determine the use of baseline characteristics and biomarkers for assessing the responder analysis (see Table E11 in this article's Online Repository at www.jaci-global.org). The ROC analysis revealed that prebronchodilator FEV_1% predicted distinguished responders from nonresponders with a cutoff value of 88.3%, sensitivity of 75.0%, specificity of 75.0%, and area under the ROC curve of 0.76 (95% CI, 0.59-0.92; $P = .004$) (Fig 5, *A*). Furthermore, WA/Ao, Feno, and s-IgE for HDM distinguished responders from nonresponders with a cutoff value of 71.7% and area under the ROC curve of 0.83 (95% CI, 0.69-0.97; $P = .002$) (Fig 5, *B*), 19.0 ppb and 0.89 (95% CI, 0.81-0.98; $P < .001$) (Fig 5, *C*), and 7.4 kU/L and 0.84 (95% CI, 0.71-0.96; $P < .001$) (Fig 5, *D*), respectively. Multivariate analysis revealed that FEV_1% predicted, Feno, and s-IgE for HDM were independently associated with an improvement in the AQLQ score, with Feno making the strongest unique contribution (Table III).

Safety

Long-term HDM SLIT tablet exposure was well tolerated with an acceptable safety profile. The most common AEs related to the HDM tablet were mild or moderate application-site reactions typically associated with SLIT. Four subjects dropped out from the study because of the following reasons: 2 oral itching and edema, 1 ear pruritus, and 1 gastroenteritis. No treatment-related serious AEs or events of severe systemic allergic reactions were reported during the 5-year treatment period.

DISCUSSION

To our knowledge, this is the first comprehensive assessment of the long-term efficacy and disease modification of HDM SLIT in patients with asthma and allergic rhinitis. The important distinguishing feature between pharmacotherapy and SLIT is that the latter can profoundly modify immune response to allergens. In fact, it has been demonstrated that the mechanism of action involves a shift from a classical type 2 immune response to induce allergen-specific IgE production to a modified type 2 response characterized by the induction of regulatory T and B cells[22] and an increase in specific IgG4 "blocking" antibodies.[23] AIT possesses special properties, such as long-lasting efficacy after discontinuation and ability to modify the natural course of the disease. Because immunotherapy is a causal therapy, long-term follow-up data are important. Nevertheless, several of HDM SLIT regimens feature treatment periods of just a few months.[24] In the present study, the efficacy of SLIT was confirmed by significant improvement in asthma control and QoL across 5 years of follow-up, demonstrating long-term and sustained effects beyond the observation period that was reported previously. Our data, in accordance with previous literature,[7,25,26] validate the efficacy of HDM SLIT in treating asthma and allergic rhinitis.

Although the degree of changes in FEV_1 by the addition of HDM SLIT was small, the improvement in FEV_1 for SLIT- versus control-treated patients was significant. The impact of AIT on lung function was inconclusive because the eligible patients had mild to moderate asthma and spirometry was almost normal at the time of enrollment. Despite normal FEV_1 at baseline, most patients still demonstrated FEV_1 improvement, which exceeded the MCID of 100 mL,[27] suggesting that these patients may show more increase in FEV_1 for SLIT.

Airway remodeling is a cardinal feature of asthma and is responsible for structural alterations of the airways and lung parenchyma. Furthermore, it leads to the development of fixed airflow limitation.[28] In the last decade, high-resolution CT has gained attention as a noninvasive technique for examining different aspects of airway remodeling in asthma.[29] Airway wall thickness contributes to the degree of airflow obstruction in asthma.[17,30] Interestingly, HDM SLIT reduced the WA/Ao

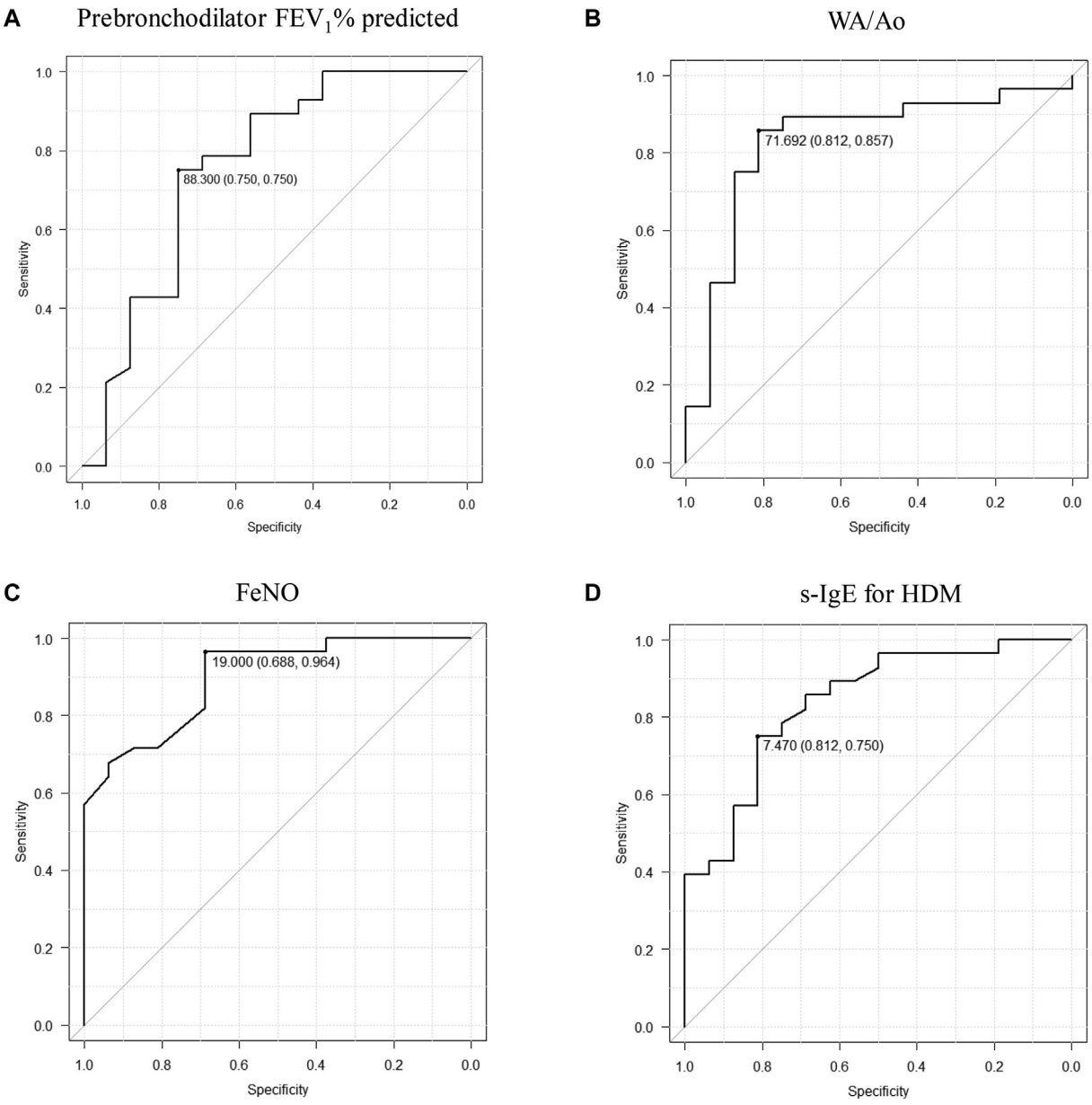

FIG 5. ROC curves for prebronchodilator FEV_1% predicted (**A**), WA/Ao (**B**), FENO (**C**), and s-IgE for HDM (**D**) distinguishing responder from nonresponder in asthmatic patients with SLIT. The optimal cutoff values (sensitivity, specificity): prebronchodilator FEV_1% predicted of 88.3%, WA/Ao of 71.7%, FENO of 19.0 ppb, and s-IgE for HDM of 7.47 kU/L.

and $T/\sqrt{BSA}$, and the degree of WA/Ao was correlated with the changes in FENO, s-IgE, and t-IgE. This may have delayed effects on immune and structural cells in addition to early effects on airway inflammation because SLIT decreases the levels of T_H2 cytokines, such as IL-4, IL-9, and IL-13, which are involved in airway remodeling.[31,32] Recent data obtained using experimental murine models of allergic asthma indicated that HDM SLIT can also affect bronchial remodeling, thus reducing goblet cell metaplasia, collagen deposition, and smooth muscle hypertrophy.[33]

On the basis of airway inflammation, asthma has been divided into T2-high and T2-low asthma, although the presence of the latter is still not certain in clinical practice.[34,35] T2-high asthma, characterized by type 2 biomarkers, included increased serum IgE and high levels of blood eosinophil and FENO. Importantly, the reduction in type 2 biomarkers parallels the improvement in symptoms in the SLIT group. The result of this study is consistent with that of a previous study that observed not only a decrease in FENO level but also an increase in FEV_1 in children with asthma treated with SLIT.[36] Besides the reduction in blood eosinophil level, there was continued reduction in both serum t-IgE and s-IgE concentrations. These findings support the concept that immunotherapy suppresses B-cell class switching and IgE production. In grass pollen immunotherapy, symptomatic improvements were found to be correlated with the reduction in eosinophil level and IL-5 mRNA expression in the nasal mucosa during the pollen season.[37] This finding could be explained by the fact that in patients with residual airway inflammation, HDM was present and contributed to the current disease.

Although SLIT is effective in treating respiratory allergic diseases, not all patients respond to this treatment. Thus, the availability of a biomarker for predicting response to SLIT would be useful in clinical practice and is a topic of growing interest. On the basis of ROC analysis, prebronchodilator FEV_1% predicted, WA/Ao, FENO, and s-IgE for HDM detected clinical response to SLIT. However, multivariate analysis showed FENO to be better associated with ΔAOLQ than FEV_1% predicted or s-IgE. These results suggest that FENO may serve as a biomarker for responders in HDM SLIT in asthma. The trial population had prebronchodilator FEV_1 greater than 70% of the predicted value. According to the European Academy of Allergy and Clinical Immunology guideline, the HDM SLIT tablet is recommended as add-on to regular controllers for adults with fully or partially controlled HDM-driven allergic asthma and FEV_1 of 70% or more of the predicted value.[38] The result of this study is consistent with those of previous studies reporting that serum s-IgE could be an effective biomarker for predicting response to SLIT.[39,40] High levels of serum allergen s-IgE along with a history of exposure to allergens may be the major indications for immunotherapy. Furthermore, Di Lorenzo et al[41] demonstrated that high serum s-IgE/t-IgE ratio is associated with an effective clinical response.

This study had several limitations. First, it did not include a placebo arm because the ethics committee did not allow it because of the long study duration. The problem is that a rigorous head-to-head comparison would require a double-blind, placebo-controlled design, which is difficult to apply in a study with a long duration. However, the open-label design allowed us to increase the number of enrolled patients in trials. To avoid observer bias after removing the patient's name and date of examination, the blood samples were coded and analyzed randomly. Second, the sample size may have been small in each arm. This could result in a type 2 error. However, we used strict criteria to define the patients in this study; all the subjects were carefully followed up, and the final follow-up rate at the end of the study was high. Third, some results crossed 0 with 95% CI. A CI with a value of 0 does not guarantee the absence of treatment effect, but it weakens the results, possibly because of subject heterogeneity.

HDM SLIT continued to provide sustained efficacy, increase pulmonary function, prevent airway remodeling, and reduce airway inflammation in patients with asthma and allergic rhinitis throughout the 5-year treatment period.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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Clinical implications: HDM SLIT continued to provide sustained efficacy in patients with asthma and allergic rhinitis throughout the 5-year treatment period.

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