

Effect of Sublingual Immunotherapy on Airway Inflammation and Airway Wall Thickness in Allergic Asthma



Makoto Hoshino, MD, PhD^a, Kenta Akitsu, MSc^b, and Kengo Kubota, MSc^b Atami, Shizuoka, Japan

What is already known about this topic? House dust mite (HDM) sublingual immunotherapy (SLIT) is indicated for the treatment allergic asthma, but knowledge of its effectiveness in airway inflammation or remodeling is little.

What does this article add to our knowledge? Adding 6 standardized quality HDM SLIT to the pharmacotherapy showed a reduction of eosinophilic airway inflammation, and its effect was correlated with the improvement of airflow limitation.

How does this study impact current management guidelines? These data suggest that adding SLIT to pharmacotherapy may lead to a beneficial effect not only on upper but also on lower allergic airway disease.

BACKGROUND: The efficacy of the standardized quality (SQ) house dust mite (HDM) sublingual immunotherapy (SLIT) has been demonstrated for respiratory allergic disease. However, the effects of SLIT on inflammation and structural changes of the airways are still unknown.

OBJECTIVE: The aim of this study was to assess the effects of the 6 SQ-HDM SLIT on airway inflammation and airway geometry in allergic asthma and rhinitis.

METHODS: One hundred two asthmatic patients with rhinitis sensitized to HDM were randomized to receive either SLIT plus pharmacotherapy or standard pharmacotherapy alone, for 48 weeks. Fractional exhaled nitric oxide (FeNO), pulmonary function, quantitative computed tomography, and clinical symptoms were performed at baseline and end of the study.

RESULTS: Compared with pharmacotherapy, SLIT demonstrated a significant reduction of FeNO ($P < .01$), airway wall area/body surface area (WA/BSA, $P < .001$), wall thickness ($T/\sqrt{BSA}$, $P < .001$), percentage wall area (WA/Ao, $P < .01$), increase in luminal area (Ai/BSA, $P < .05$), improvement of airflow limitation ($P < .001$), and clinical symptom scores ($P < .05$). The change in forced expiratory volume in 1 second

(FEV₁) was correlated with both changes in FeNO and airway dimensions. Multiple regression analysis showed that the change in FeNO was independently associated with an increase in FEV₁ in the SLIT group ($r^2 = 0.623$, $P = .037$).

CONCLUSIONS: Adding 6 SQ-HDM SLIT to standard asthma therapy provides a significant improvement in symptoms and pulmonary function compared with pharmacotherapy.

Improvement of airflow limitation with SLIT was associated with the decrease in eosinophilic airway inflammation. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:2804-11)

Key words: Airway inflammation; Airway wall thickness; Asthma; House dust mite; Remodeling; Rhinitis; Sublingual immunotherapy

Allergic asthma and rhinitis often coexist, with symptoms of rhinitis found in more than 70% of patients with asthma. Asthma and rhinitis are more common and severe with perennial allergies compared to seasonal allergies, tested for allergic causality, a prevalence of house dust mite (HDM) sensitization around 50% has been reported,¹ and exposure to HDM allergens has been related to asthma severity.² Allergen immunotherapy (AIT) is one of the cornerstones of the treatment of respiratory allergy, together with drug therapy and allergen avoidance.³ The efficacy of AIT in allergic rhinitis has been demonstrated in numerous clinical trials and confirmed by several meta-analysis.⁴ In contrast to Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines,⁵ the Global Initiative for Asthma (GINA) guidelines⁶ perceive the available limited evidence on AIT in allergic asthma to indicate a modest effect and recommend against its use for the treatment of this disease manifestation because the effect is not judged to outweigh the risks and inconveniences. To allow for convenient and reproducible at-home administration with no need for dose adjustment, a standardized quality (SQ)-HDM sublingual immunotherapy (SLIT) tablet is currently in development. Previously, the SQ-HDM SLIT has proven to be the

^aDivision of Clinical Allergy, Department of Internal Medicine, Atami Hospital, International University of Health and Welfare, Atami, Shizuoka, Japan

^bDepartment of Radiology, Atami Hospital, International University of Health and Welfare, Atami, Shizuoka, Japan

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication March 14, 2019; revised May 12, 2019; accepted for publication June 3, 2019.

Available online June 20, 2019.

Corresponding author: Makoto Hoshino, MD, PhD, Division of Clinical Allergy, Department of Internal Medicine, Atami Hospital, International University of Health and Welfare, 13-1 Higashikaigan-cho, Atami, Shizuoka, Japan. E-mail: hoshino@iuhw.ac.jp.

2213-2198

© 2019 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2019.06.003>

Abbreviations used

AE- Adverse event
Ai- Luminal area
AIT- Allergen immunotherapy
Ao- Total area of the airway
AQLQ- Asthma Quality of Life Questionnaire
ARIA- Allergic Rhinitis and its Impact on Asthma
BSA- Body surface area
CT- Computed tomography
FAS- Full analysis set
FeNO- Fractional exhaled nitric oxide
FEV ₁ - Forced expiratory volume in 1 second
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
HDM- House dust mite
ICH- International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use
ICS- Inhaled corticosteroid
JAU- Japanese allergy unit
LME- Linear mixed effect
MI- Multiple imputations
RQLQ- Rhinitis Quality of Life Questionnaire
SCIT- Subcutaneous immunotherapy
SD- Standard deviation
SLIT- Sublingual immunotherapy
SQ- Standardized quality
T- Wall thickness
WA- Airway wall area

reduction of the requirement of inhaled corticosteroid (ICS) dose and asthma exacerbations, and improve asthma control.⁷⁻¹⁰ However, there is little evidence for the effects of SLIT on airway inflammation or remodeling in asthma.

The measurement of fractional exhaled nitric oxide (FeNO) has been used to assess airway inflammation and is preferred over other tests because of its noninvasiveness, simplicity, and reproducibility.¹¹ Airway wall thickening is a prominent feature of airway remodeling, and it has been evaluated noninvasively using computed tomography (CT).¹² In this study, we addressed the disease-modifying effect (changes in pulmonary function, eosinophilic inflammation, and airway dimensions) of receiving SQ-HDM SLIT in allergic asthmatic patients with rhinitis sensitized to HDM.

METHODS

Study design

This was a randomized, open, parallel-group controlled study. The study consisted of a screening phase, a 4-week run-in period, and 48-week treatment phase (Figure 1). This trial was registered with the University Hospital Medical Information Network (<http://www.umin.ac.jp>; UMIN000022390). Using a computer-generated randomization method, patients were randomly assigned to the SLIT group (daily treatment with the SQ-HDM SLIT tablet at a dose of 10,000 Japanese allergy units [JAU] plus drug therapy) or to the control group (drug alone). Because there was limited AIT experience among Japanese patients, a 2-step dose escalation was chosen. Based on the safety profiles of the European phase I trials,¹³ 3300 JAU (2 SQ-HDM) were selected as the initial dose for a week, followed by upward titration of the dose to 10,000 JAU (6 SQ-HDM). Subsequent clinical

visits were scheduled once every 4 weeks during the treatment period. Spirometry, FeNO measurement, CT examination, blood tests, evaluation of the frequency of exacerbations, and assessment of a quality of life using a questionnaire were conducted during the run-in period and end of the trial. All patients provided written informed consent, and the study protocol was approved by our hospital ethics committee. This trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice.

Patients

Eligible patients (20-65 years) were non-smokers or ex-smokers with less than 5 pack-years and who had stopped smoking at least 1 year before enrolment. Asthma was diagnosed with forced expiratory volume in 1 second (FEV₁) reversibility of >12% after 400 µg of salbutamol. Inclusion criteria were as follows: a clinical history of HDM-related asthma (steps 2 and 3 in GINA 2002 guideline) of at least 1 year's duration; use of an appropriate amount of ICS (200-800 µg/day of budesonide or equivalent) for the control of mild-to-moderate persistent asthma; a clinical history consistent with HDM-induced allergic rhinitis (ARIA guideline) for at least 1 year; positive diagnostic test results to HDM (skin prick tests with a wheal size ≥3 mm to *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, or both and HDM-specific IgE ≥0.7 kU/L). Exclusion criteria were as follows: FEV₁ less than 70% of predicted value; hospitalization due to an asthma exacerbation within 3 months before screening; have a relevant clinical history of perennial allergic asthma or rhinitis caused by other allergens; systemic immunological diseases, malignancies, long-term treatment with oral steroids, or previous courses of immunotherapy.

Standardization

To standardize the SQ-HDM SLIT tablet (Torii, Tokyo, Japan/ ALK-Abello, Horsholm, Denmark), allergen contents of the standardize HDM AIT vaccine were first measured by using the manufacturer's methods to calculate the correction value. As a result of the adjustment by correction value and titer of standardized HDM AIT vaccine, a nominal strength of 3300 JAU has the same potency as 2 SQ-HDM, and 10,000 JAU has the same potency as 6 SQ-HDM.

Pulmonary function

Spirometry was performed using a computed spirometry (Fukuda Denshi, Tokyo, Japan). The predicted values for FEV₁ and forced vital capacity (FVC) for a Japanese population were calculated using the formula proposed by the Japanese Respiratory Society.¹⁴

FeNO

FeNO was measured using a portable nitric oxide analyzer (NioxMino; Aerocrine, Solna, Sweden), which provides measurements at an exhalation flow rate of 50 mL/s.¹⁵

CT measurements

Scans were performed at full inspiration by using a 64-multislice scanner (Aquilion-64; Toshiba Medical, Tokyo, Japan) as described previously.^{16,17} The scan parameters were as follows: 120 kV, 200 mA, and a slice thickness of 1 mm. The full-width at half-maximum principle was applied to determine the following airway parameters: luminal area (Ai), total area of the airway (Ao), wall area (WA = Ao - Ai), absolute wall thickness (T), and percentage wall area

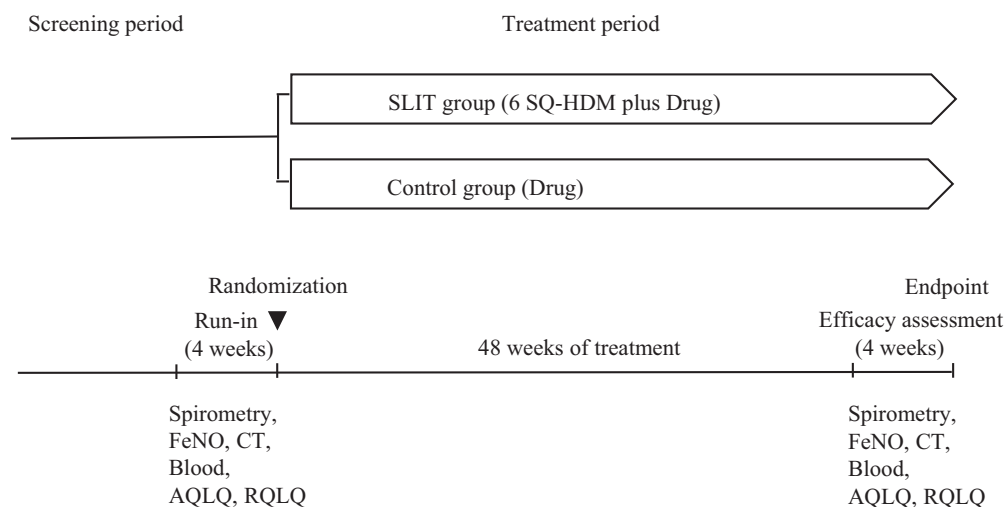


FIGURE 1. Study design. *AQLQ*, Asthma quality of life questionnaire; *CT*, computed tomography; *FeNO*, fractional exhaled nitric oxide; *HDM*, house dust mite; *RQLQ*, Rhinitis Quality of Life Questionnaire; *SLIT*, sublingual immunotherapy; *SQ*, standardized quality.

($WA/Ao = WA/Ao \times 100$) at the right upper lobe apical segmental bronchus (RB1). Because airway size may be affected by body size, *Ai*, *WA*, and *T* were normalized to the body surface area (*BSA*).

Eosinophils count and IgE measurements

Blood eosinophil count was measured using hemocytometry. Total and allergen-specific serum IgE levels were measured using a radioallergosorbent fluoroenzyme immunoassay test (Phadia, Uppsala, Sweden).

Quality of life

The Asthma Quality of Life Questionnaire (AQLQ) contains 32 items covering 4 domains (symptoms, activities, emotions, and environment) using a 7-point scale.¹⁸ The Rhinitis Quality of Life Questionnaire (RQLQ) consists of 28 items in 7 domains, with each score on a 7-point scale. The 7 domains were activities, sleep, non-nose and non-eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional.¹⁹ A change of >0.5 point represents a clinically meaningful improvement in quality of life.

Outcome measurements

Overall measurements were calculated for each subject at randomization and/or initiation of treatment and at the end of the trial visit. The primary end point was to evaluate the effect of 6 SQ-HDM on airway inflammation and dimensions as an add-on to drug therapy compared with drug therapy alone. The secondary objectives were pulmonary function, asthma, and rhinitis score. The safety profile was assessed by adverse events (AEs), vital sign, physical examination, and laboratory investigations.

Statistical analysis

All statistical tests were performed with SAS version 9.1 software (SAS Institute, Cary, NC) with a 5% significance level, and all tests and 95% CIs were 2-sided. Nonparametric and parametric data were presented as medians (interquartile ranges) or means (standard deviations [SDs]), respectively. The primary analysis was a linear mixed effects (LME) model adopting the FeNO and airway dimensions at baseline and the treatment group. The primary outcome was pairwise comparison between treatment groups by using a *t* test in the LME model. The full analysis set (FAS) included all randomized subjects in accordance

with the ICH intent-to-treat principle. The primary analysis was the FAS with multiple imputations for missing data (FAS-MI), which conservatively treated all subjects with missing data as having no treatment effect. The key secondary efficacy analysis was based on LME models and performed on the FAS-MI. Multiplicity for the primary and secondary analyses was controlled for by using the Fisher least significant difference procedure. Statistical significance was set at a *P* value of less than .05. The change in the each variable during treatment (Δ) was calculated as after treatment minus before treatment (baseline). Univariate correlations were assessed by using the Pearson correlation coefficient. Variables that had a *P* < .10 in the univariate analysis were included in the multivariate regression analysis to evaluate which one predicts ΔFEV_1 .

RESULTS

Population

A total of 122 patients were evaluated. Of the enrolled population, 102 (83.6%) patients fulfilling the inclusion criteria were assessed at baseline, and 88 (86.2%) completed the 1-year evaluation (Figure 2). At the end of the observation period, there were 8 dropouts in the SLIT group, and 6 in the control group, with no statistically significant difference. The reasons for the 14 patients who prematurely discontinued the study medication were as follows: AEs (*n* = 6), noncompliance (*n* = 4), and lost to follow-up (*n* = 4). The characteristics of the patients are shown in Table I. Patient demographic and baseline characteristics were similar between the 2 groups.

Primary endpoints

The level of FeNO significantly decreased from baseline to the end of treatment in the SLIT group (*P* < .01). No significant changes in FeNO were observed in patients in the control group (*P* = .488). There was a significant difference in the change of FeNO between patients with SLIT plus drug and those treated with drug alone (*P* < .01, Table II). Compared with the control group, blood eosinophil count in the SLIT therapy showed a trend of decreasing but did not reach statistical significance (*P* = .283). In the SLIT group, there was a significant reduction in WA/BSA , $T/\sqrt{BSA}$, and WA/Ao (*P* < .001, respectively), and a

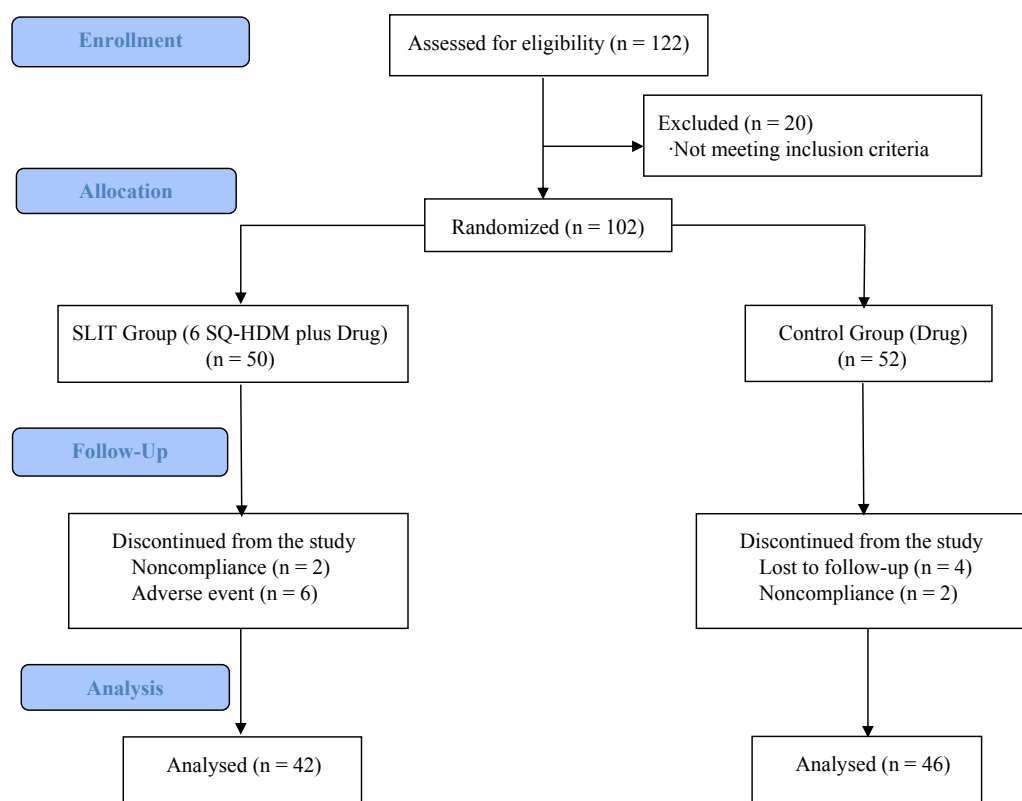


FIGURE 2. Patient deposition. *HDM*, house dust mite; *SLIT*, sublingual immunotherapy; *SQ*, standardized quality.

significant increase in Ai/BSA ($P < .001$), whereas no significant changes in these airway dimension were observed in the control group ($P = .068, .134, .215$, and $.203$, respectively). The difference in the changes in WA/BSA , $T/\sqrt{BSA}$, WA/Ao , and Ai/BSA between patients treated with SLIT plus drug and those treated with drug was statistically significant (Table II).

Secondary endpoints

Overall, pulmonary function treatment with SLIT resulted in significant increases in FEV_1 ($P < .01$) and FVC ($P < .01$). However, no significant differences were observed in pulmonary function indices in the patients treated with drug only ($P = .277$ and $.307$, respectively). Differences in spirometric parameters between patients treated with the SLIT group and those treated with the control group were significant (Table II). In the SLIT group, there was a significant reduction of the serum IgE level from baseline to the end of the study ($P < .05$), whereas no significant change was observed in the control group ($P = .073$). The difference between the SLIT and control group was significant ($P < .05$, Table II). Domain analysis of AQLQ revealed significantly better scores for symptoms and emotions in the SLIT group (mean [SD] differences in symptoms 0.52 ± 1.09 , $P < .01$, and emotions 0.54 ± 0.93 , $P < .01$). However, no improvement in AQLQ scores was observed in the control group. Terms of symptom and emotion domain are a significant difference between the SLIT and the control ($P < .05$, respectively, Table II). For the SLIT group, the differences from the control group are also statistically significant for nasal symptoms (0.55 ± 0.77 , $P < .01$) and eye symptoms

(0.69 ± 1.09 , $P < .01$) in the RQLQ domains ($P < .001$, respectively, Table II).

SLIT analysis

Correlations between the changes in pulmonary function, FeNO, airway dimensions, and clinical indices in the SLIT treatment are shown in Table III. The improvement of airflow limitation was strongly inversely associated with the changes in FeNO and the changes of CT parameters. Figure 3 shows the relationship between the change in FEV_1 and the change in FeNO, and the change in FVC and the change in WA/Wo . There was a weak but significant correlation between the change in FEV_1 and the change in blood eosinophil count. Multivariate regression analysis showed that only the change in FeNO was independently associated with an increase in FEV_1 ($r^2 = 0.623$, $P = .037$, Table IV).

Safety

The 6 dropouts because of AEs in the SLIT groups were 3 oral itching, 1 ear pruritus, and 2 gastroenteritis. The most frequent AEs of the HDM tablet were oral pruritus, nasopharyngitis, mouth edema, and throat irritation. Most of these AEs were mild, no systemic allergic reactions were reported, and no subjects required treatment with epinephrine. After an interruption of several days, most of the affected subjects resumed and continued treatment until the end of the trial.

DISCUSSION

In the current study, we found: (1) a significant decrease of eosinophilic inflammation of airways after add-on treatment with

TABLE I. Baseline characteristics and demography

	SLIT (n = 50)	Control (n = 52)	P value
Age (y)	42 (11)	43 (12)	.430
Male/female	23/27	19/33	.223
Body mass index (kg/m ²)	23.5 (3.2)	23.1 (3.7)	.271
Asthma duration (y)	16 (15)	14 (13)	.299
Serum IgE (IU/mL)	1116.7 (239.8)	1247.5 (471.5)	.146
Blood eosinophil (/μL)	264.9 (209.7)	329.5 (316.9)	.124
Pulmonary function			
FEV ₁ (% predicted)	94.0 (24.8)	95.1 (20.3)	.414
FVC (% predicted)	106.0 (21.2)	104.5 (16.9)	.354
FEV ₁ /FVC (%)	72.8 (13.9)	75.0 (11.1)	.210
FeNO (ppb)	31.9 (6.2)	28.4 (5.5)	.328
CT scan measurement			
WA/BSA (mm ² /m ²)	15.3 (11.9-18.2)	16.3 (14.0-18.4)	.137
T ₁ /BSA (mm/m)	0.97 (0.80-1.09)	0.96 (0.80-1.08)	.359
WA/Ao (%)	68.9 (66.0-75.2)	65.4 (62.7-70.1)	.278
Ai/BSA (mm ² /m ²)	6.9 (4.7-9.9)	7.2 (5.3-10.7)	.431
AQLQ score			
Symptoms	5.5 (1.3)	5.7 (1.1)	.291
Activities	5.6 (1.2)	5.6 (1.1)	.461
Emotions	5.6 (1.2)	5.7 (1.1)	.320
Environment	5.7 (1.0)	5.7 (1.0)	.498
RQLQ score			
Nasal	3.0 (0.9)	3.3 (1.1)	.106
Eye	2.5 (1.0)	2.5 (1.1)	.497
Medication			
ICS (μg/day)*	487.5 (169.7)	530.7 (219.2)	.144

Ai, Luminal area; Ao, total area of the airway; AQLQ, asthma quality of life questionnaire; BSA, body surface area; CT, computed tomography; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; IQR, interquartile range; RQLQ, Rhinitis Quality of Life Questionnaire; SD, standard deviation; SLIT, sublingual immunotherapy; T, absolute wall thickness; WA, airway wall area.

Data are presented as mean (SD) or median (IQR).

*Dose of stable maintenance treatment (budesonide or equivalent dose).

6 SQ-HDM SLIT compared with pharmacotherapy alone; (2) a significant reduction in airway wall thickness and an increase in airway caliber; (3) a significant improvement in pulmonary function; and (4) a significant improvement in asthma and rhinitis symptom scores. Furthermore, the changes in FeNO and the airway wall thickness were significantly correlated with the improvements in airflow limitation, and the independent predictor for improvement of FEV₁ was the change in FeNO. To the best of our knowledge, this is the first study evaluating the clinical efficacy of airway inflammation and airway geometry in patients with asthma with rhinitis undergoing SLIT.

Specific AIT is the only treatment modality with the capacity of changing the natural course of the allergic disease,^{20,21} prevents progression of rhinitis to asthma in children, and also reduces the sensitization of at-risk infants to HDM allergy.²²⁻²⁴ ICS is the mainstream of asthma therapy because it targets the airway inflammation. However, ICS does not alter the disease progression, and some patients fail to achieve adequate control. Currently, both subcutaneous immunotherapy (SCIT) and SLIT routes are validated and accepted for clinical trials. In recent years, SLIT has gained increasing credibility, and is now included in guidelines²⁵ and used in many European countries. SLIT is

more convenient because of home administration and is associated with fewer and less AEs than SCIT.²⁶ SLIT has been progressively applied for treatment to allergic asthma in combination with pharmacological treatment, and moreover appears to be resulted in the reduction of ICS dose.^{7,8}

FeNO measurement is the currently validated noninvasive method and has been shown to serve as a surrogate marker of eosinophilic airway inflammation. FeNO is higher in patients with asthma than in healthy subjects,²⁷ and previous report²⁸ has already shown that treatment with inhaled or oral corticosteroids is able to decrease the level of FeNO. In the present study, the addition of SLIT to standard pharmacotherapy resulted in a significant reduction in FeNO. Concerning the effect on local allergic inflammation, our result supported that nasal smear for eosinophil count decreased after SLIT in birch pollens.²⁹ Furthermore, the reduction of FeNO was associated with significant increases in FEV₁. The inconclusiveness of AIT's impact on lung function has been reported, because eligible asthmatic patients were mild-to-moderate severity and spirometry was almost normal.³⁰ Recently, Marogna et al¹⁰ showed that add-on SLIT treatment maintained intact the pulmonary function, in contrast to the decline of FEV₁ in drug treatment alone. Our result is in accordance with Djuric-Filipovic et al,³¹ who demonstrated not only the reduction of FeNO concentration but also the improvement of pulmonary function in asthmatic children treated with SLIT. This suggests that SLIT may have additional benefits in asthma through targeting an inflammatory pathway distinct from that of steroids.

Several cytokines, including IL-4, IL-5, IL-13, and IL-33, play important roles in the regulation of type 2 immunity and contribute to not only allergic airway inflammation but also remodeling. The mechanisms underlying airway remodeling include the bronchial subepithelial fibrosis, increased smooth muscle mass, and submucosal edema. CT scan is unable to evaluate each component but does allow evaluation of remodeling as increased airway wall thickness and enlarged wall area. Airway wall thickness contributes to the degree of airflow obstruction in asthma.^{12,16,32} An interesting result obtained in the present study is the modification of the airway thickness in SLIT, and the change of airway dimensions was correlated with the improvement of airflow limitation. When the change in WA/Ao was included in adjusted multivariate models, however, only the change in FeNO remained associated with the increase in FEV₁. The lack of a correlation between indices of airway dimensions and pulmonary function might be related to the treatment period, and it is possible that the duration of disease was longer in patients with asthma, which may have made their airways less responsive to SLIT.

Although many mechanisms are not fully elucidated, AIT-induced immune tolerance depends on suppression of the functions of allergen-specific T and B cells, on modulation of allergen-specific IgE- and IgG-mediated responses.³³ In addition, AIT reduces airway eosinophilic infiltration, and induces changes that skew Th2- to Th1-type response related to an increased IFN-γ and IL-2 production, with a reduction in Th2 activity, through a mechanism of anergy or tolerance, the latter being related to the generation of allergen-specific T regulatory cells, which produce cytokines such as IL-10 and TGF-β.³⁴ Pollen immunotherapy was associated with decreases in the ratio of IL-5/IFN-γ mRNA⁺ cells in the nasal mucosa and increases in IFN-γ protein levels in nasal fluid during natural seasonal

TABLE II. Changes in parameters from baseline and analysis of efficacy at week 48

Variables	Change from baseline		SLIT – control difference	95% CI	P value
	SLIT	Control			
Pulmonary function					
FEV ₁ (mL)	119.3 (10.3)	−33.7 (12.0)	103.02	(29.16 to 176.88)	<.001
FEV ₁ (% predicted)	5.5 (2.2)	−0.1 (2.6)	3.58	(−0.64 to 7.81)	.010
FVC (mL)	132.4 (12.8)	−34.8 (12.7)	117.27	(110.85 to 123.68)	.002
FVC (% predicted)	5.3 (2.4)	−0.1 (2.4)	3.41	(2.78 to 4.05)	.014
FEV ₁ /FVC (%)	1.2 (1.8)	−2.4 (4.0)	3.65	(−22.85 to 30.16)	.105
CT scan measurement					
WA/BSA (mm ² /m ²)	−0.89 (−1.78 to −0.31)	0.74 (−0.60 to 1.88)	−1.78	(−3.11 to −0.39)	<.001
T/√BSA (mm/m)	−0.10 (−0.16 to 0.00)	0.07 (0.00 to 0.17)	−0.17	(−0.26 to −0.08)	<.001
WA/Ao (%)	−3.58 (−6.77 to −1.40)	1.24 (−1.35 to 5.08)	−4.24	(−14.41 to 5.94)	.005
Ai/BSA (mm ² /m ²)	0.71 (−0.05 to 1.16)	0.06 (−0.91 to 0.80)	0.65	(−0.31 to 1.61)	.023
FeNO (ppb)	−8.4 (3.8)	3.6 (4.1)	−12.12	(−16.38 to −7.85)	.003
Blood eosinophil (/ μ L)	−29.4 (13.0)	1.8 (15.2)	28.61	(−97.08 to 154.31)	.283
Serum IgE (IU/mL)	−270.3 (32.9)	214.1 (27.1)	484.4	(−208.48 to 1177.45)	.017
AQLQ score					
Symptoms	0.52 (1.09)	0.10 (0.66)	0.42	(−0.42 to 1.27)	.025
Activities	0.43 (1.01)	0.07 (0.75)	0.36	(−0.16 to 0.88)	.043
Emotions	0.54 (0.93)	0.12 (0.80)	0.42	(0.15 to 0.69)	.019
Environment	0.32 (0.78)	0.01 (0.62)	0.22	(−0.09 to 0.55)	.087
RQLQ score					
Nasal	−0.55 (0.77)	0.18 (0.60)	−0.73	(−1.08 to −0.38)	<.001
Eye	−0.69 (1.09)	0.41 (0.84)	−1.11	(−1.59 to −0.62)	<.001

Ai, Luminal area; Ao, total area of the airway; AQLQ, asthma quality of life questionnaire; BSA, body surface area; CT, computed tomography; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IQR, interquartile range; RQLQ, Rhinitis Quality of Life Questionnaire; SD, standard deviation; SLIT, sublingual immunotherapy; T, absolute wall thickness; WA, airway wall area.

Data are presented as mean (SD) or median (IQR).

TABLE III. Correlations between the changes in pulmonary function and clinical indices in treatment of patients with asthma with SLIT

Variables*	FEV ₁ (mL)		FVC (mL)	
	r	P value	r	P value
FeNO (ppb)	–0.832	<.001	–0.702	<.001
WA/BSA (mm ² /m ²)	–0.788	<.001	–0.727	<.001
T/√BSA (mm/m)	–0.733	<.001	–0.690	<.001
WA/Ao (%)	–0.685	<.001	–0.711	<.001
Ai/BSA (mm ² /m ²)	0.746	<.001	0.704	<.001
Blood eosinophil (μL)	–0.326	.045	–0.305	.068
Serum IgE (IU/mL)	–0.027	.498	–0.043	.418

Ai, Luminal area; Ao, total area of the airway; BSA, body surface area; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; SLIT, sublingual immunotherapy; T, absolute wall thickness; WA, airway wall area.

*Variables refer to the absolute change (after treatment minus before treatment).

allergen exposure.³⁵ As for SLIT, some reports demonstrated an increase in Th1 cytokines³⁶ and IL-10 after HDM SLIT treatment.³⁷ A recently published paper by Hagner et al³⁸ showed preventive efficacy of HDM SLIT in the mouse model of allergic inflammation due to the reduction of eosinophil infiltration in bronchoalveolar lavage, IL-5 and IL-10 levels in supernatants of lymph node cells, and peribronchial cellular infiltrate paralleled by a trend to lower numbers of mucous producing goblet cells.

AIT has been robustly demonstrated clinically effective in reducing symptoms in respiratory allergy.³⁹ Data from literature

suggested overall clinical effectiveness of SLIT in patients with allergic asthma and rhinitis.²⁶ Our data are in accordance with previous reports; improvements in both asthma and rhinitis symptoms were statistically significant for adding SLIT compared with pharmacotherapy alone.

In the current trial, an up dosing scheme was chosen according to Japanese traditions. The safety data from the Japanese populations in the present trial are consistent with what has previously been observed with the SQ-HDM SLIT tablet^{9,40} and confirm a safety and tolerability profile compatible with at-home administration. For the development of the SQ-HDM SLIT tablet, the optimal dose was needed to be established as the dose that provides the optimal balance between therapeutic effect and tolerability. In Europe, 12 SQ-HDM (20,000 JAU) were chosen as the marketed dose, as a more robust response with regard to key secondary end points was observed. In the current study with the 6 SQ-HDM (10,000 JAU) and 12 SQ-HDM in a Japanese population, modest differences in the primary and secondary end points were observed between the 2 doses. Consequently, 6 SQ-HDM were chosen as the marketed dose in Japan.⁴¹ Population-specific differences in the response to treatment cannot be ruled out, but similarity with regard to inclusion criteria and demographic characteristics of the European and Japanese trial together with comparable clinical responses indicates that 6 SQ-HDM might be effective and tolerated in both populations. Neither severe systematic adverse reactions nor any life-threatening adverse reactions (including anaphylactic shock) were observed. Our results would suggest that SLIT may be used with a favorable safety profile and well tolerated.

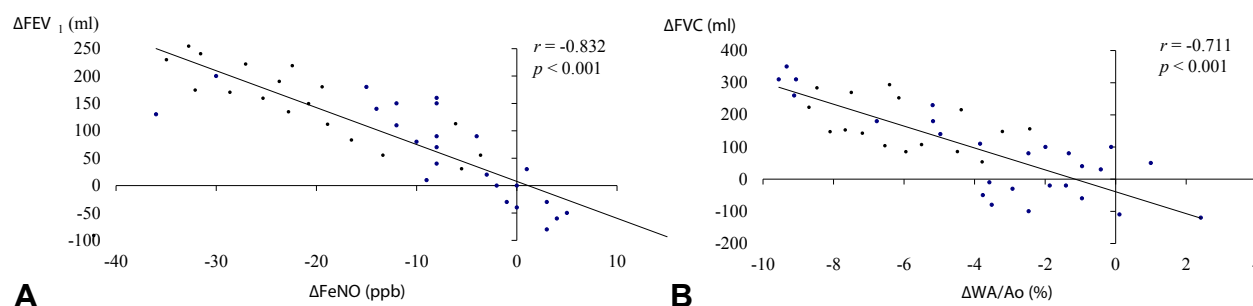


FIGURE 3. Relationship between changes in (A) fractional exhaled nitric oxide (FeNO) and forced expiratory volume in 1 second (FEV₁) and (B) percentage of the wall area (WA/Ao) and forced vital capacity (FVC) before and after treatment with 6 SQ-HDM SLIT. *HDM*, House dust mite; *SLIT*, sublingual immunotherapy; *SQ*, standardized quality.

TABLE IV. Multivariate regression models for prediction of FEV₁ in SLIT treatment

	Model r^2	β	95% CI	P value
FeNO (ppb)	0.623	-2.879	(-5.577 to -0.180)	.037
WA/Ao (%)		-12.864	(-26.601 to 0.872)	.054
Blood eosinophil (/ μL)		0.099	(-0.054 to 0.252)	.192

Ao, Total area of the airway; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; SLIT, sublingual immunotherapy; WA, airway wall area.

There were some limitations in the present study. First, this study did not include a placebo arm, which was not allowed by the ethics committee because of the long duration of the study. In fact, the problem is that a rigorous head-to-head comparison would require double-blind, double-dummy design, which is difficult to do for long period. Second, this trial had a shorter duration than a standard immunotherapy (often over 3-year period), which limits the conclusions on the sustained effect. The comparison between immunotherapy and pharmacotherapy is still a matter of debate. The main problem in comparison agents is that the clinical benefits of SLIT can be appreciated only in the long term, whereas pharmacotherapy can act immediately. On the other hand, the small number of patients lost to follow-up after 1 year indirectly testifies for the persistence of subjects with the prescribed care. Third, we evaluated a low number of patients included in each arm, which increased the risk of a statistical error II. Nevertheless, the strength was the application of the randomization method, selecting monosensitized patients and including the positive control group. Despite the limitations inherent to a real-life setting, the results of this study evidenced that SLIT had a beneficial effect of respiratory allergy.

In conclusion, adding SLIT to standard asthma therapy provides a significant improvement in symptoms and pulmonary function compared with pharmacotherapy in patients with asthma and rhinitis sensitized to HDM. Improvement of airflow limitation with SLIT was associated with the decrease in eosinophilic airway inflammation independently.

REFERENCES

- Zureik M, Neukirch C, Leynaert B, Liard R, Bousquet J, Neukirch F, European Community Respiratory Health Survey. Sensitisation to airborne moulds and severity of asthma: cross sectional study from European Community respiratory health survey. *BMJ* 2002;325:411-4.
- Kupeczyk M, Kupryś I, Górski P, Kuna P. Aspirin intolerance and allergy to house dust mites: important factors associated with development of severe asthma. *Ann Allergy Asthma Immunol* 2004;92:453-8.
- Bousquet J, Lockett R, Malling HJ, Alvarez-Cuesta E, Canonica GW, Chapman MD, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 1998;81:401-5.
- Canonica GW, Bousquet J, Casale T, Lockett RF, Baena-Cagnani CE, Pawankar R, et al. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;64(Suppl 91):1-59.
- Bousquet J, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126:466-76.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention 2011. Available from: <http://www.ginasthma.org>. Accessed January 10, 2013.
- Mosbech H, Deckelmann R, Blay F, Canonica GW. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2014;134:568-75.
- de Blay F, Kuna P, Prieto L, Ginko T, Seitzberg D, Riis B, et al. SQ HDM SLIT-tablet (ALK) in treatment of asthma—*post hoc* results from a randomised trial. *Respir Med* 2014;108:1430-7.
- Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a house dust mite sublingual allergen immunotherapy tablet in adults with allergic asthma. *JAMA* 2016;315:1715-25.
- Marogna M, Massolo A, Passalacqua G. Effect of adjuvanted and standard sublingual immunotherapy on respiratory function in pure rhinitis due to house dust mite over a 5-year period. *World Allergy Organ J* 2017;10:7.
- Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FENO) for Clinical Applications. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602-15.
- Niimi A, Matsumoto H, Amitani R, Nakano Y, Mishima M, Minakuchi M, et al. Airway wall thickness in asthma assessed by computed tomography. Relation to clinical indices. *Am J Respir Crit Care Med* 2000;62:1518-23.
- Corzo JL, Carrillo T, Pedemonte C, Plaza Martín AM, Martín Hurtado S, Dige E, et al. Tolerability during double-blind randomized phase I trials with the house dust mite allergy immunotherapy tablet in adults and children. *J Investig Allergol Clin Immunol* 2014;24:154-61.
- The Committee of Pulmonary Physiology, Japanese Respiratory Society. Guidelines for pulmonary function tests. Spirometry, flow volume curve, diffusion capacity of the lung. Tokyo: The Japanese Respiratory Society; 2004 (in Japanese).
- American Thoracic Society, European Respiratory Society. ATS/ERS Recommendations for Standardized Procedures for the Online and Offline Measurement of Exhaled Lower Respiratory Nitric Oxide and Nasal Nitric Oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912-30.

16. Hoshino M, Matsuoka S, Handa H, Miyazawa T, Yagihashi K. Correlation between airflow limitation and airway dimensions assessed by multidetector CT in asthma. *Respir Med* 2010;104:794-800.
17. Hoshino M, Ohtawa J. Effects of budesonide/formoterol combination versus budesonide on airway dimensions in asthma. *Respirology* 2012;7:639-46.
18. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76-83.
19. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol* 1999;104:364-9.
20. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. *J Allergy Clin Immunol* 2012;129:717-25.
21. Pfaar O, Bonini S, Cardona V, Demoly P, Jakob T, Jutel M, et al. Perspectives in allergen immunotherapy: 2017 and beyond. *Allergy* 2018;73(Suppl 104):5-23.
22. Schmitt J, Schwarz K, Stadler E, Wüstenberg EG. Allergy immunotherapy for allergic rhinitis effectively prevents asthma: results from a large retrospective cohort study. *J Allergy Clin Immunol* 2015;136:1511-6.
23. Zielen S, Devillier P, Heinrich J, Richter H, Wahn U. Sublingual immunotherapy provides long-term relief in allergic rhinitis and reduces the risk of asthma: a retrospective, real-world database analysis. *Allergy* 2018;73:165-77.
24. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sørensen HF, et al. GAP investigators. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol* 2018;141:529-38.
25. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *Aria Workshop Group; World Health Organization. J Allergy Clin Immunol* 2001;108:S147-334.
26. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J* 2014;7:6.
27. Kharitonov SA, Barnes PJ. Exhaled markers of pulmonary disease. *Am J Respir Crit Care Med* 2001;163:1693-722.
28. Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med* 2001;164:1376-81.
29. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: a 3-year randomized controlled study. *J Allergy Clin Immunol* 2005;115:1184-8.
30. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: a systematic review and meta-analysis. *Allergy* 2017;72:1825-48.
31. Djuric-Filipovic I, Caminati M, Filipovic D, Salvottini C, Zivkovic Z. Effects of specific allergen immunotherapy on biological markers and clinical parameters in asthmatic children: a controlled-real life study. *Clin Mol Allergy* 2017;15:7.
32. Kasahara K, Shiba K, Ozawa T, Okuda K, Adachi M. Correlation between the bronchial subepithelial layer and whole airway wall thickness in patients with asthma. *Thorax* 2002;57:242-6.
33. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clinical Immunol* 2014;133:621-6.
34. Larché M, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. *Nat Rev Immunol* 2006;6:761-71.
35. Durham SR, Ying S, Varney VA, Jacobson MR, Sudderick RM, Mackay IS, et al. Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. *J Allergy Clin Immunol* 1996;97:1356-65.
36. Arikian C, Bahceciler NN, Deniz G, Akdis M, Akkoc T, Akdis CA, et al. Bacillus Calmette-Guérin-induced interleukin-12 did not additionally improve clinical and immunologic parameters in asthmatic children treated with sublingual immunotherapy. *Clin Exp Allergy* 2004;34:398-405.
37. Cosmi L, Santarlasci V, Angeli R, Liotta F, Maggi L, Frosali F, et al. Sublingual immunotherapy with Dermatophagoides monomeric allergoid down-regulates allergen-specific immunoglobulin E and increases both interferon-gamma- and interleukin-10-production. *Clin Exp Allergy* 2006;36:261-72.
38. Hagner S, Rask C, Brimnes J, Andersen PS, Raifer H, Renz H, et al. House dust mite-specific sublingual immunotherapy prevents the development of allergic inflammation in a mouse model of experimental asthma. *Int Arch Allergy Immunol* 2016;170:22-34.
39. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol* 2015;136:556-68.
40. Demoly P, Emminger W, Rehm D, Backer V, Tommerup L, Kleine-Tebbe J. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clinical Immunol* 2016;137:444-51.
41. Okubo K, Masuyama K, Imai T, Okamiya K, Stage BS, Seitzberg D, et al. Efficacy and safety of the SQ house dust mite sublingual immunotherapy tablet in Japanese adults and adolescents with house dust mite-induced allergic rhinitis. *J Allergy Clin Immunol* 2017;139:1840-8.