Allergy, Asthma &
Immunology Research

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Efficacy and Safety of Sublingual Immunotherapy in Elderly Rhinitis Patients Sensitized to House Dust Mites

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ABSTRACT

Purpose: This study aims to determine the efficacy and safety of house dust mite (HDM)-sublingual immunotherapy (SLIT) in elderly patients with AR.
Methods: A total of 45 patients aged ≥ 60 years with HDM-induced AR who had ≥ 3 A/H ratio on skin prick test and/or ≥ 0.35 IU/L to both *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* by ImmunoCAP were enrolled in 4 university hospitals. To evaluate additional effects of HDM-SLIT, they were randomized to the SLIT-treated group (n = 30) or control group (n = 15). Rhinoconjunctivitis total symptom score (RTSS), rhinoscopy score, Korean rhinoconjunctivitis quality of life questionnaire, rhinitis control assessment test, asthma control test scores, and adverse reactions, were assessed at the first visit (V1) and after 1 year of treatment (V5); for immunological evaluation, serum levels of HDM-specific immunoglobulin A/IgE/IgG1/IgG4 antibodies and basophil response to HDMs were compared between V1 and V5 in both groups.
Results: There were no significant differences in demographics, RTSS, skin reactivity to HDMs, or serum total/specific IgE levels to HDMs ($P > 0.05$, respectively) between the 2 groups. Nasal symptom score and RTSS decreased significantly at year 1 in the 2 groups ($P < 0.05$). There were no significant differences in percent decrease in nasal symptom score and RTSS at year 1 between the 2 groups ($P > 0.05$); however, rhinoscopic nasal symptom score decreased significantly in the SLIT-treated group ($P < 0.05$). Immunological studies showed that serum specific IgA levels (not specific IgE/IgG) and CD203c expression on basophils decreased significantly at V5 in the SLIT-treated group ($P = 0.011$ and $P = 0.001$, respectively), not in the control group. The control group required more medications compared to the treatment group, but there were no differences in adverse reactions.
Conclusions: It is suggested that HDM-SLIT for 1 year could induce symptom improvement and may induce immunomodulation in elderly rhinitis patients.

Keywords: Allergic rhinitis; elderly; house dust mite; sublingual immunotherapy

INTROUDCTION

Chronic disease in the elderly has become a social problem worldwide along with increasing health care expenditure. Chronic respiratory disease is the third most common burden of disease in the elderly aged ≥ 60 years.[1] Although allergic rhinitis (AR) and asthma seem to decrease in the elderly, they are often underdiagnosed, undertreated and underestimated in the aspect of the current prevalence rate.[2] AR and asthma are common chronic diseases that affect quality of life and further alter mood or cognitive functions.[3]

House dust mites (HDMs) are the most common indoor inhalant allergen that can trigger AR and asthma. Allergen immunotherapy (AIT) is a therapeutic option for AR and asthma to alleviate nasal symptoms, induce immune modulation and prevent further sensitization to other allergens.[4] Guidelines regarding AIT rarely recommend and often ignore AIT in elderly rhinitis patients, since the immune system in elderly patients is down-regulated compared to younger population.[3] A few studies have reported that sublingual immunotherapy (SLIT) in elderly rhinitis patients shows no severe adverse reactions with only a few local side effects and fewer interactions with other comorbid conditions compared to subcutaneous immunotherapy (SCIT).[3,5,6] In a few trials, AIT for grass pollens and HDMs has been shown to be effective in elderly rhinitis patients.[4,5] However, AIT in elderly patients has not been actively conducted in clinical practice. The aim of this study is to determine the efficacy and safety of SLIT in patients aged ≥60 years with HDM-induced allergic rhinoconjunctivitis in comparison with standard pharmacotherapy on demand and to evaluate immunological responses by SLIT.

MATERIALS AND METHODS

Patients and diagnostic methods

A total of 48 elderly rhinitis patients sensitized to HDMs were enrolled in 4 (Ajou, Yonsei, Korea, and Hallym University Hospitals) in South Korea, and the study flow is summarized in **Fig. 1**. Three patients who did not meet inclusion criteria were excluded. The patients had suffered from AR and/or bronchial asthma as defined by Allergic Rhinitis and its Impact on Asthma (ARIA) criteria and Global Initiative for Asthma (GINA), and had high serum specific IgE to *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* as confirmed by skin prick test and/or ImmunoCAP® (ThermoFisher Scientific, Waltham, MA, USA). At the time of enrollment, retrospective rhinoconjunctivitis total symptom score (RTSS) related to the previous winter season was at least 8 (out of a maximum of 18). RTSS is composed of 6 rhinoconjunctivitis symptoms, sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes during 24 hours, each symptoms assessed by 4-point-scale (0 = no symptoms to 3 = severe).[7] Patients with co-sensitization to other pollens or inhalant allergens were enrolled when: 1) typical symptoms due to co-allergens did not exist and 2) the reactions of the skin prick test for co-allergens were less than those for HDMs. We excluded the following patients who: 1) participated in other studies; 2) received immunotherapy with any allergens, SCIT with HDMs, and/or anti-IgE monoclonal antibody treatment; 3) had uncontrolled asthma, other active respiratory disease, and/or malignancy; and 4) were contraindicated to SLIT. This study was approved by the Institutional Review Board of Ajou University Hospital (Ajou IRB-MED-CT4-14-159) and each center. All the study patients gave informed consent. On the assumption that the mean change in reactivity is 0.2 in the control group and 0.3 in the optimal dose group and that the variance is 0.1 in both groups, sample
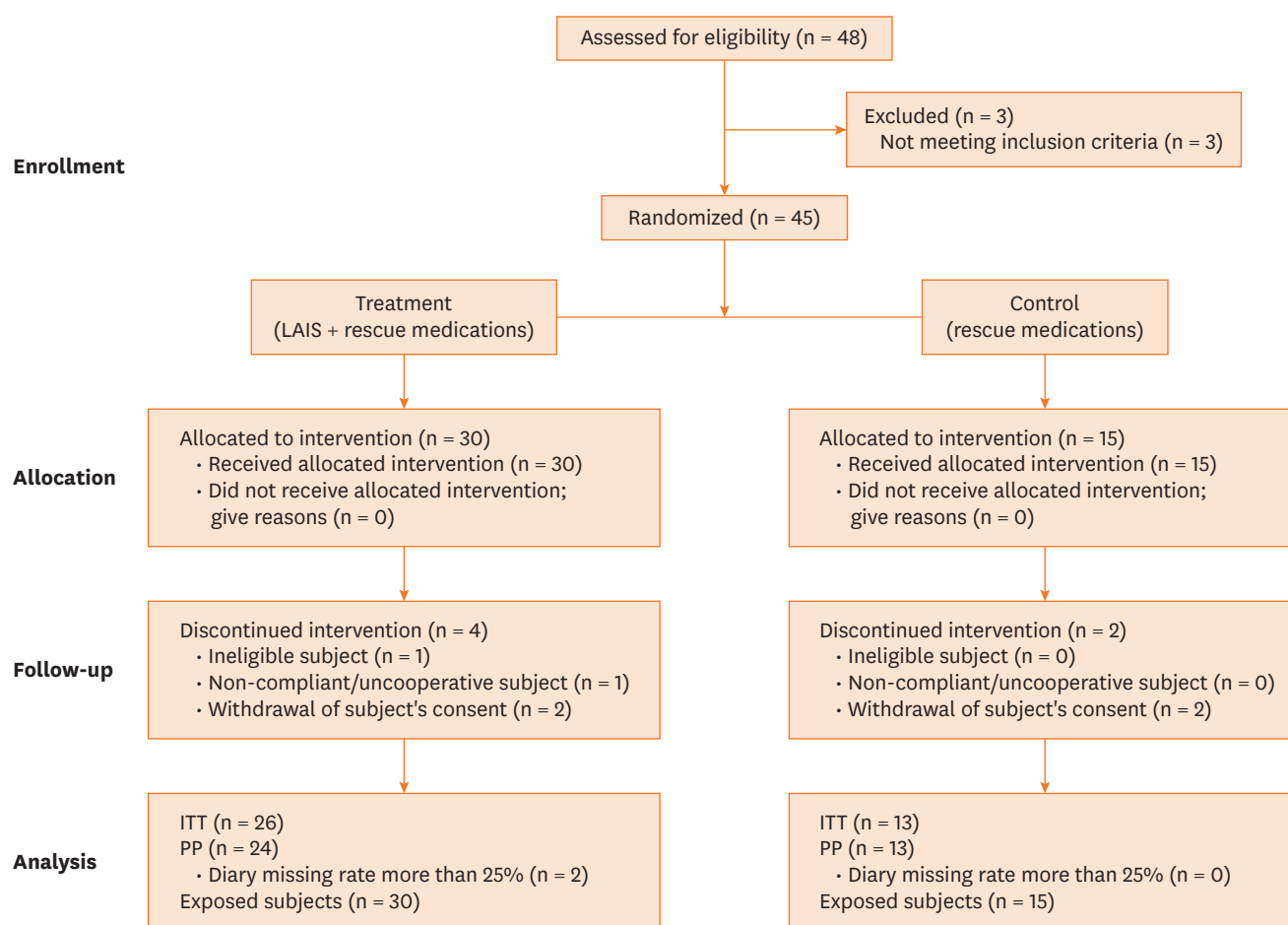
Assessed for eligibility (n = 48)

Excluded (n = 3)
· Not meeting inclusion criteria (n = 3)

Enrollment

Randomized (n = 45)

Treatment
(LAIS + rescue medications)

Control
(rescue medications)

Allocation

Allocated to intervention (n = 30)
· Received allocated intervention (n = 30)
· Did not receive allocated intervention;
  give reasons (n = 0)

Allocated to intervention (n = 15)
· Received allocated intervention (n = 15)
· Did not receive allocated intervention;
  give reasons (n = 0)

Follow-up

Discontinued intervention (n = 4)
· Ineligible subject (n = 1)
· Non-compliant/uncooperative subject (n = 1)
· Withdrawal of subject's consent (n = 2)

Discontinued intervention (n = 2)
· Ineligible subject (n = 0)
· Non-compliant/uncooperative subject (n = 0)
· Withdrawal of subject's consent (n = 2)

Analysis

ITT (n = 26)
PP (n = 24)
· Diary missing rate more than 25% (n = 2)
Exposed subjects (n = 30)

ITT (n = 13)
PP (n = 13)
· Diary missing rate more than 25% (n = 0)
Exposed subjects (n = 15)

Fig. 1. Number of participating patients assessed for eligibility that completed the study.
ITT, intention to treat; PP, per protocol.

size was calculated to 30 patients in the treatment group and 15 patients in the control group to satisfy α = 0.05 and a power of 90%.

Treatment and follow-up schedules

The patients were randomized at the first visit (V1), and HDM-SLIT tablets (LAIS®; Lofarma SpA, Milano, Italy) with on-demand medications were given to the treatment group, while on-demand medications alone were given to the control group. From days 1 through 4, the treatment group received 300 allergenic unit (AU) of LAIS tablet; from day 5, they took 1,000 AU of LAIS twice a week for 48 weeks. The control group received standard medications on demand according to disease control status. The standard medications were defined as unexpected use of oral antihistamine, nasal corticosteroid, eye drops and inhaled corticosteroids with long acting-β2 agonists. All patients were scheduled to visit 1 week (visit 2, V2), 3 months (84 ± 7 days, visit 3, V3), 6 months (168 ± 7 days, visit 4, V4), and 1 year (336 ± 7 days, visit 5, V5) after the randomization. All patients filled out the rhinoconjunctivitis quality of life questionnaire (RQLQ), and received rhinitis control assessment test (RCAT) and asthma control test (ACT) at V1 and V5 as previously described.[7-9] Rhinoscopy was done by the investigators to evaluate symptoms scores. Blood samples were taken from each patient at V1 and V5 for immunological evaluation and were stored at −20°C for further immunological evaluation.

Symptom diary and efficacy variables

The diary was composed of questionnaire on nasal and eye symptom scores (sneezing, rhinorrhea, nasal obstruction, nasal itching sensation, tearing, eye itching and redness) ranging from 0 to 3 (0 = no symptom, 1 = mild symptom, 2 = moderate symptom and 3 = severe symptom) and medication scores (total number of antihistamine tablets, nasal sprays, and eye drops). The daily symptoms and medication scores were recorded daily on the distributed diary.

Each patient was asked to bring the diary at each visit to confirm records. The primary efficacy variable was RTSS, which is composed of 6 rhino-conjunctivitis symptoms (sneezing, rhinorrhea, nasal pruritus, nasal congestion, ocular pruritus and watery eyes). The secondary efficacy variables were medication requirements, rhinoscopy scores as evaluated by the investigators, which were composed of nasal symptoms, nasal congestion, nasal secretion and redness (ranging from 0 = none to 3 = severe), rhinoconjunctivitis quality of life by RQLQ and RCAT, and asthma control as assessed by ACT. RQLQ is composed of 7 domains (activity limitation, sleep, non-nose/eye symptoms, practical problems, nose symptoms, eye symptoms and emotional function) and 28 questions during the previous week. The RQLQ scale scores range from 1 = no impairment to 5=severe impairment. The RCAT of Korean version is composed of 6 questions regarding nasal and eye symptoms (nasal congestion, sneezing, watery eye, sleep disturbance and activity limitation; control status: 5 = never-controlled and 1 = well-controlled) during the previous week. ACT consists of 5 questions on a 5-point scale of 1 to 5 (higher scores reflecting better control state) to assess the effect of asthma on daily activities, asthma symptoms at daytime, asthma symptoms at night, use of rescue mediations and self-assessment of asthma control.

Immunological evaluation

Blood samples were obtained from each patient at V1 and V5, and immunological changes were compared before and after the start of treatment using the following 2 methods: 1) changes in serum specific IgA, IgE, and IgG1/IgG4 antibodies to *D. farinae* as measured by enzyme-linked immunosorbent assay (ELISA); and 2) changes in basophil responses to *D. farinae* as evaluated by basophil activation test (BAT). The levels of serum specific IgE, IgA, and IgG1/IgG4 antibodies to *D. farinae* were measured by ELISA as previously described.[10,11]

For BAT, peripheral blood samples were collected from each study patient at V1 and V5 as previously described.[12,13] Within 3 hours of blood sample collection in an ethylenediaminetetraacetic acid (EDTA) tube, ammonium chloride lysis buffer (0.154 M NH_4Cl, 10 mM $KHCO_3$, 0.1 mM EDTA, pH 7.2-7.4) was used to lyse red blood cells. Using anti-IgE antibody (1 μg/mL) and calcium inophore (1 μg/mL; Sigma-Aldrich Co., St. Louis, MO, USA), basophils were incubated as positive controls. After washing out with a phosphate-buffered saline, the resuspended cells were stained with phycoerythrin-conjugated antihuman CD203c antibody (Beckman Coulter, Marseille, France) on ice in the dark for 30 minutes. After another washing with phosphate-buffered saline, the cells were evaluated by using FACS Canto II flow cytometry (Becton Dickinson, San Jose, CA, USA) and were presented as % of cells expressing CD203c.

Statistical analysis

All statistical analyses were performed using SPSS ver. 20 (SPSS Inc., Chicago, IL, USA). The values are presented as mean ± standard deviation or median (minimal and maximal values). Student's *t* test was used to analyze differences between the 2 groups. Wilcoxon's signed rank test was done to compare changes in symptom/medication scores, RTSS, RQLQ, ACT,

RCAT and immunologic changes between V1 and V5 in both groups. A *P* value of < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

Total 45 patients were enrolled and randomized to the treatment group (n = 30), who received SLIT along with medications on demand, and the control group (n = 15) who were allowed to take medications, including antihistamines and intranasal steroids, on demand by using centralized, computer-generated randomization system. The mean age of the patients was 67.2 years (range, 60–81 years), and the male to female ratio was 22:17. Four patients in the treatment group and 2 in the control group were dropped out from the study, 1 patient was ineligible subject, 1 patient was uncooperative and 2 patients from each group withdrew informed consent. Among these 39 patients, 26 in the treatment group and 13 in the control group were analyzed. The mean age was 67.0 ± 5.8 years in the treatment group and 67.2 ± 6.5 years in the control group, with no significant difference. The baseline clinical characteristics, comorbid conditions, including asthma, skin reactivity or serum specific IgE to HDMs (as measured by ImmunoCAP), was not significantly different between the 2 groups (**Table 1**).

When rescue medications (including oral antihistamines, histamine eye drops, and intranasal steroids) were compared between the 2 groups, the dose of antihistamines (mg) tended to be more frequently used in the control group than in the treatment group, although there was no statistical significance (*P* = 0.054, **Table 2**).

Changes in RTSS, RQLQ, RCAT, and ACT scores

Nasal and eye symptoms decreased significantly between V1 and V5 in the treatment group (*P* = 0.001 and *P* = 0.036, respectively), while nasal symptoms and RTSS, except for eye symptoms, decreased in the control group (*P* < 0.001). However, RTSS decreased significantly both in the treatment and control groups (*P* = 0.001 for each). The RQLQ scores tended to

Table 1. Baseline clinical characteristics of the study subjects

Variables	Treatment group (n = 26)	Control group (n = 13)	P value
Age (yr)	67.0 ± 5.8	67.2 ± 6.5	0.956
Height (cm)	163.6 ± 7.3	161.6 ± 6.7	0.436
Sex (male)	15 (57.7)	7 (53.8)	1.000
Weight (kg)	64.9 ± 9.9	63.8 ± 9.9	0.746
Current smoker	6 (23.1)	1 (7.7)	0.388
Atopic dermatitis	5 (19.2)	1 (7.7)	0.643
Food allergy	3 (11.5)	0 (0.0)	0.538
Diagnosis of rhinitis (yr)			
20 ‹ age › 40	1 (3.8)	1 (7.7)	1.000
› 40	25 (96.2)	12 (92.3)	1.000
Asthma	17 (65.4)	12 (92.3)	0.119
Baseline FEV1 (mL)	2,419.6 ± 664.2	2,243.3 ± 527.1	0.425
Total IgE (IU/L)	611.82 ± 923.14	581.09 ± 786.78	0.599
Specific IgE to Dp (IU/L)	5.07 ± 9.29	5.06 ± 8.22	0.998
Specific IgE to Df (IU/L)	12.41 ± 21.77	8.07 ± 9.64	0.541
Wheal size of Dp (mm)	5.03 ± 4.79	6.667 ± 3.77	0.225
Wheal size of Df (mm)	5.27 ± 3.92	5.500 ± 3.31	0.883

Data are expressed as mean ± standard deviation or number (%).
FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E; Dp, *Dermatophagoides pteronyssinus*; Df, *Dermatophagoides farinae*.

Table 2. Changes in rhinitis/eye symptoms and clinical scores in the study period between the treatment and control groups

Variables	Treatment group				P value*	Control group				P value*
	V1	V3	V4	V5		V1	V3	V4	V5	
Nasal symptoms	8 (5–10)	2 (0–7)	2 (0–8)	2.5 (0–7)	< 0.001	8 (6–10)	1 (0–8)	3 (0–6)	2 (0–5)	< 0.001
Eye symptoms	2 (0–4)	0.5 (0–4)	0.5 (0–5)	1 (0–5)	0.036	1 (0–4)	1 (0–4)	1 (0–5)	0 (0–5)	0.363
RTSS	10 (8–12)	3 (0–8)	3 (0–12)	4 (0–9)	< 0.001	9 (8–13)	2 (0–12)	3 (0–10)	3 (0–10)	< 0.001
RQLQ	54.5 (32–95)	48 (34–76)	53.5 (30–87)	50 (33–75)	0.053	59 (31–84)	38 (28–84)	45 (28–78)	42 (28–94)	0.077
RCAT	21.5 (14–27)	23 (16–30)	22 (19–30)	22.5 (16–28)	0.105	22 (17–29)	25 (16–30)	22 (13–30)	23 (17–30)	0.528
ACT	21 (13–24)	20.5 (9–24)	19.5 (14–25)	21 (13–24)	0.841	19.5 (14–25)	22.5 (11–25)	21 (12–25)	22 (14–25)	0.469

All values were presented as median (minimum–maximum values).
RTSS, rhinoconjunctivitis total symptom score; RQLQ, rhinoconjunctivitis quality of life questionnaire; ACT, asthma control test; RCAT, rhinitis control assessment test, V, visit.
*Wilcoxon-signed rank test comparing scores between V1 and V5.

decrease in the treatment group without statistical significance ($P > 0.05$). No significant change was noted in RCAT or ACT scores between V1 and V5 in both groups (**Table 2**).

Rhinoscopy score

Rhinoscopy scores as measured by the investigators at each visit were compared between V1 and V5 in the treatment and control groups. A significant difference was noted only in changes in nasal symptom scores ($P = 0.038$), although nasal congestion, secretion, and redness scores were not significantly different in the 2 groups ($P > 0.05$, **Fig. 2**).

Changes in immunological parameters

Serum specific IgE to *D. farinae* tended to decrease between V1 and V5 in the treatment and control groups, but no statistical significance was reached. However, the serum specific IgA levels to *D. farinae* decreased significantly in the treatment group ($P = 0.011$), while they were not in the control group. There were no significant changes in serum specific IgG1 and G4 antibodies to *D. farinae* between V1 and V5 in the 2 groups (**Fig. 3**).

In BAT, CD203 expression levels decreased significantly after incubation with 0.1 and 10 ug/mL of *D. farinae* at V5 compared to V1($P = 0.001$ and $P = 0.046$, respectively, **Fig. 4**), while no significant changes were noted in the control group.
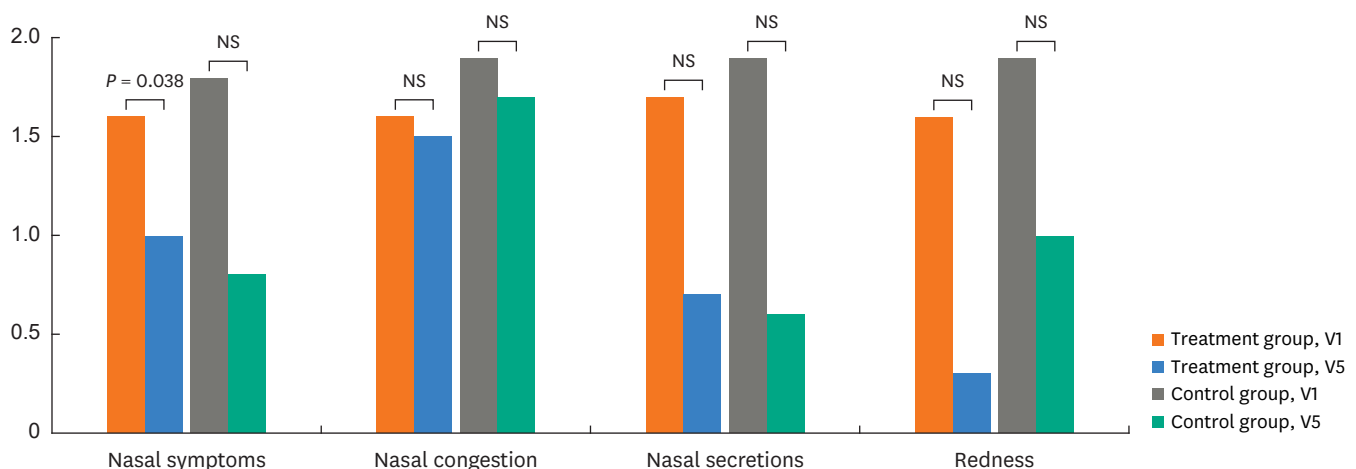

Fig. 2. Changes in nasal symptoms, nasal congestion, nasal secretions and redness before (visit 1, V1) and after treatment (visit 5, V5) in the treatment and control groups. All scores were analyzed by Wilcoxon's signed rank test.
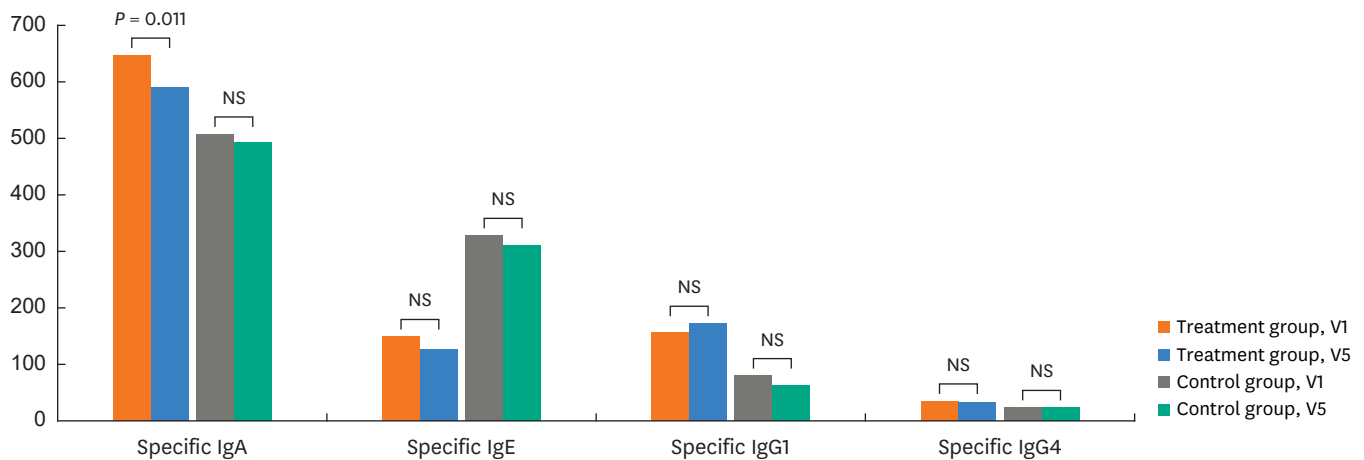NS, not significant.

Fig. 3. Changes in serum specific antibodies to *Dermatophagoides farinae* by ELISA before (visit 1, V1) and after the treatment (visit 5, V5) in the treatment and control groups. All values are presented as absorbance value x 1,000 and compared by using Wilcoxon's signed rank test.
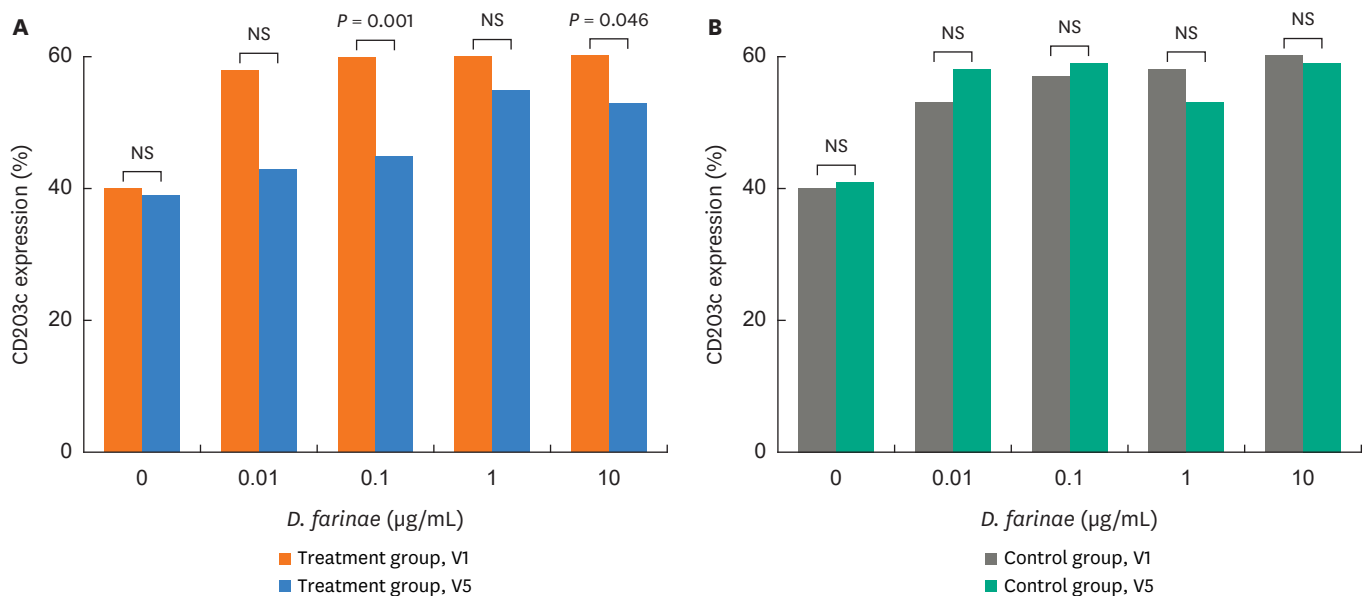ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; NS, not significant.

Fig. 4. Changes in basophil CD203c expression with additions of *Dermatophagoides farinae* before (visit 1, V1) and after the treatment (visit 5, V5) in the treatment (A) and control groups (B). Wilcoxon's signed rank test was applied to compare the results between the 2 groups.
NS, not significant.

Safety assessment

There was no significant difference in adverse reactions between the 2 groups. Most of the reactions were mild, recovered completely without any reported complications. Rhinitis and conjunctivitis exacerbations were reported from the treatment and control groups. The most frequent adverse reaction was upper respiratory infection in the 2 groups (10 events from 6 patients in the treatment group, 17 events from 4 patients in the control group). No systemic or severe adverse reaction was reported.

DISCUSSION

Recent epidemiological studies have often underestimated elderly rhinitis patients and excluded elderly subjects aged ≥60 years in the analysis of rhinitis prevalence and outcomes.[14] There have been few publications on the efficacy and safety of AIT in elderly patients sensitized to HDMs, and especially no published data on immunological responses during AIT in elderly rhinitis patients. In addition, elderly subjects are known to show decreased immune regulations compared to younger subjects; therefore, AIT has not been actively recommended in such subjects.[15] A few studies have reported the favorable efficacy of SLIT in the elderly. SLIT with grass pollens and HDMs significantly reduced medication scores in elderly rhinitis patients. Furthermore, SLIT in elderly rhinitis patients was well tolerated without any severe adverse events.[5,16] The present study is a randomized controlled trial of HDM-SLIT for 1 year in elderly rhinitis patients sensitive to HDM. During the 1-year study period, both rhinoscopy scores (an objective parameter) observed by the investigators and subjective symptom scores (RTSS) evaluated by the patients were significantly improved in the treatment group, with minimal adverse reactions. These findings can provide evidence for the favorable efficacy of HDM-SLIT in elderly rhinitis patients sensitized to HDMs, although further studies with longer study periods are needed to confirm our results.

HDMs are the most common inhalant allergen in both elderly and non-elderly patients with rhinitis in Korea.[17] Moreover, the effect of SLIT with HDM can decrease medication scores and improve quality of life in adult patients with AR and in asthmatic children. Moreover, SLIT induces symptom relief and decreases medication requirements, which may lead to remission.[18] Since concomitant medications can affect not only rhinitis and asthma control status, but also general conditions in elderly patients, a decrease in medication requirements is an issue in such patients.[19] Antihistamines are effective in reducing rhinitis symptoms in the elderly, but cause adverse effects, such as urinary retention, dry mouth, constipation, arrhythmia and postural hypertension.[20,21] In the present study, total use of antihistamines tended to be lower in the treatment group than in the control group; therefore, SLIT may be beneficial for elderly rhinitis patients to reduce total medication use.

AR results from an IgE-mediated chronic inflammation of nasal mucosa triggered by allergens and various environmental factors, provoking intermittent or persistent symptoms such as rhinorrhea, nasal congestion, nasal/ocular pruritus, sneezing and postnasal drips. These nasal symptoms are not life-threatening, but they negatively affect quality of life as it is a chronic inflammatory disease.[20] Moreover, rhinitis symptoms may lead to sleep disturbance and alterations in physiological processes among geriatric patients such as endocrine function, cognitive function, glucose metabolism and appetite control.[21] Rhinitis significantly affects quality of life in elderly patients compared to younger adults.[22,23] In the present study, Korean versions of RQLQ and RCAT were used to assess quality of life in the study patients, and ACT was also included in the questionnaire on asthma control status in the study patients with asthma. RQLQ tended to decrease and RCAT tended to increase in the treatment group, implying that quality of life and clinical symptoms can be improved after 1-year HDM-SLIT in elderly rhinitis patients sensitized to HDMs.

Alterations in immune function due to aging, environmental factors and lifestyle cause immunosenescence, resulting in increased CD4^{+} T memory cells, reduced naïve T lymphocytes and decreased B-lymphocyte activity, which suppress humoral immune responses in elderly patients.[24,25] Therefore, AIT has not been actively recommended for

elderly rhinitis patients due to its low efficacy. To the best of our knowledge, the present study is the first trial to evaluate changes in immunological responses to HDM during 1-year HDM-SLIT in the elderly rhinitis patients. Allergen-specific IgA is known to play a critical role in the regulation of the oral mucosa immune system by repeated exposure to allergens during SLIT.[26] Specific IgA in saliva and serum are increased in patients with food allergy (induced by peanuts and eggs) during allergen-specific SLIT, suggesting that specific IgA may be a useful biomarker for the efficacy and immunomodulating effect of SLIT.[27,28] In the present study, serum specific IgA to *D. farinae* decreased; serum specific IgG4 to *D. farinae* tended to increase after 1-year SLIT in the treatment group, while these findings were not found in the control group. These results suggest that HDM-SLIT for 1 year may induce immune modulation as well as clinical improvement in elderly rhinitis patients, although long-term studies are needed to confirm these effects.

BAT has been widely used in the diagnosis of drug allergy as well as other allergic diseases such as chronic urticaria, food allergy and insect venom allergy.[29,30] It has been applied to the assessment of AIT or anti-IgE treatment outcomes.[31] The CD63 expression levels significantly decreased after 6 months of AIT in patients treated with venom immunotherapy,[32] while they did not in those treated with AIT using grass pollens.[33] In the present study, CD203c-expressing cells (%) decreased after 1-year SLIT, suggesting that HDM-SLIT could reduce basophil responsiveness to HDMs even in elderly rhinitis patients. Further long-term studies are needed to evaluate BAT changes as a biomarker for evaluating the efficacy of SLIT.

SLIT has several advantages over SCIT: noninvasiveness, self-administration and less frequent/severe adverse reactions.[34] Common adverse events of SLIT are oral itching sensation and throat irritations.[18] In the present study, no difference in the incidence or severity of adverse reactions were noted between the 2 groups, suggesting that SLIT is a safe and effective treatment modality in elderly rhinitis patients, although long-term safety studies are needed.

There are several limitations in this study. First, this study was not a placebo-controlled trial, and the patients in both groups took medications on-demand which results in symptom improvement in the control group. Drug compliance is lower in chronic diseases, such as diabetes, osteoporosis, and hypertension respiratory disease, as compared to respiratory diseases, such as chronic obstructive pulmonary disease.[35] Although all patients were asked to record medications and symptoms on a daily basis, they took medications as symptoms appeared and a few patients belonging to the treatment group did not take any medication when symptoms were aggravated, because they regarded SLIT tablets as investigational products. Secondly, the patients were enrolled, irrespective of seasons. Since the questionnaires were filled out in different seasons, the patients may have reported different symptoms, affecting the questionnaire results.

In conclusion, the results of this study suggest that SLIT with HDMs can be beneficial in improving rhinitis symptoms and inducing immunomodulation in elderly rhinitis patients.

ACKNOWLDEGMENTS

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