

A randomized, double-blind, placebo controlled trial of sublingual immunotherapy with house-dust mite extract for allergic rhinitis

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ABSTRACT

Objective: This study was designed to evaluate the efficacy and safety of sublingual immunotherapy (SLIT) with house-dust mite (HDM) extract in Chinese patients with HDM-induced allergic rhinitis (AR).

Methods: A randomized, double-blind, placebo controlled trial was conducted with the outpatients of the Eye, Ear, Nose, and Throat Hospital, Fudan University. Forty-eight patients were eligible for randomization to SLIT with a mixture of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* extract or placebo for 1 year. The primary outcome measures for efficacy were the total nasal symptom score (TNSS) and the individual nasal symptom score. Secondary end points were allergic conjunctivitis scores (ACS) and medication scores (MS). Adverse events (AE) also were monitored.

Results: Intragroup analysis demonstrated a significant improvement in the active treatment group for individual nasal symptom score and TNSS ($p < 0.05$), although no improvement was observed in the placebo group of congestion, sneezing, and itching ($p > 0.05$). Furthermore, the ACS and MS in the active treatment group also statistically decreased ($p < 0.05$). In addition, the active treatment had significant effects on relieving nasal symptoms both in adults and children ($p < 0.05$), and no statistical difference was observed between these two subgroups ($p > 0.05$). AEs that occurred ranged from mild to moderate, and no severe systematic reactions were observed.

Conclusion: SLIT with a mixture of HDM extract significantly relieved allergy symptoms and reduced the need for antiallergic drugs, which indicated the superiority of active treatment over placebo for patients with HDM-induced AR. However, due to the limited sample size, the findings need to be further confirmed.

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Allergic rhinitis (AR) is a global health problem, and its incidence and prevalence are increasing in China and around the world.^{1–3} Although AR is not a serious illness, it is clinically relevant and affects quality of life and productivity at work or at school.^{4–7} In addition, AR implies elevated social costs and causes enormous socioeconomic burden.⁸ As is known, allergen-specific immunotherapy is a form of treatment that specifically aims at modifying the response to sensitizing allergens, hence preventing its exacerbation,⁹ and might halt progression from rhinitis to asthma.¹⁰ Allergen-specific immunotherapy has been used to treat allergic diseases for >100 years.¹¹ Among the methods of administering allergen, the sublingual route may offer a safe and effective alternative administration.^{12–15} Sublingual immunotherapy (SLIT) operations are relatively simple and well tolerated, and can be self-administered by patients in their home.^{14,16} There has been an increase in the use of SLIT over the past decade, especially in European countries.¹⁷ However, because the cost of SLIT treatment is considerable, it is not yet widely used in China.

Currently, SLIT products directed at *Dermatophagoides farinae* are the only standardized vaccine available for clinical use in China (Chanllergen, a vaccine made with a single extract of *D. farinae*, Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., HangZhou, China), and there is no standardized SLIT-drop mixture of *Dermatophagoides*

pteronyssinus and *D. farinae* extracts aimed at the two mites simultaneously available for patients with house-dust mite (HDM) induced AR. The efficacy and safety of the SLIT drop (*D. pteronyssinus* to *D. farinae*, 50:50, Pangramin SLIT; ALK-Abello, Madrid, Spain) have been proven by a number of clinical trials and it has been widely used in Europe for >20 years. However, the clinical trials of this sublingual drop have not been conducted in China, and the sublingual drop has not yet entered the Chinese market. Given that HDM (*D. pteronyssinus* and *D. farinae*) is the most common indoor allergen worldwide^{18–22} and that a large proportion of patients with AR are sensitized to both *D. pteronyssinus* and *D. farinae*, there is a need for a mixture of *D. pteronyssinus* and *D. farinae* extracts for SLIT. Therefore, we conducted this randomized, double-blind, placebo controlled study and investigated the efficacy and safety of SLIT by using a mixture of HDM extracts with the aim to explore safer and more-effective SLIT drops that could help patients with HDM-induced AR, particularly those who are sensitive to *D. pteronyssinus* and *D. farinae* simultaneously.

METHODS

Study Design

A randomized, double-blind, placebo controlled study was conducted in the Eye, Ear, Nose, and Throat Hospital, Fudan University, from May 2010 to January 2012. The patients diagnosed with moderate-to-severe AR (based on the criteria for diagnosis and the classification of AR from the documents of the Allergic Rhinitis and its Impact on Asthma guidelines)²³ and with or without mild intermittent asthma according to the Global Initiative for Asthma Management and Prevention guidelines²⁴ were included in this study. The preinclusion assessment comprised the clinical history, skin-prick tests, and serum HDM-specific immunoglobulin E assays (ImmunoCAP-radioallergosorbent test; Pharmacia-Diagnostics, Freiburg, Germany). After an initial screening examination, an 8-week baseline phase was carried out to determine whether the candidates met the criteria for inclusion in the study. The inclusion and exclusion criteria are presented in Table 1. Two months after the

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Table 1 Inclusion and exclusion criteria

Inclusion criteria
Male or female subjects ages 5–55 y
Submission of signed consent form
Diagnosis with at least 1 year of AR, sensitized to <i>Dermatophagoides pteronyssinus</i> and <i>Dermatophagoides farinae</i> (confirmed by clinical history, a positive skin-prick test, and a serum HDM-specific IgE level of >3.5 kU/L)
Average total nasal symptom score ≥ 2 and days of using rescue medication $\geq 25\%$ of baseline period at randomization
Exclusion criteria
Systemic immunologic disorders
Severe asthma with a FEV ₁ value of <70% of predicted value
Severe atopic dermatitis or food allergy
A history of chronic rhinosinusitis, angioedema, or anaphylactic shock
Treatment with an HDM extract in the past 5 y or any immunotherapy within 3 mo before the start of the study
Systematic treatment with immune suppressive drugs
Female subjects who were pregnant at the time of screening
Women of child-bearing age who were not using sufficient contraception
Severe acute or chronic concomitant disease that seriously affects the patient's general health
Concomitant disease that, according to current information, could affect the variables assessed in this study to such an extent that an objective judgment would not be possible
Reasonable doubts about patient cooperation or compliance
Dementia or any other serious intellectual impairment that would preclude correct history recording or impairing the patient's judgment

AR = Allergic rhinitis; HDM = house-dust mite; IgE = immunoglobulin E; FEV₁ = forced expiratory volume in 1 second.

baseline diaries were completed, a new visit was scheduled, and eligible patients were randomized to receive active treatment (a mixture of *D. pteronyssinus* and *D. farinae* extracts) and placebo (2:1) for 12 months by following a table of random numbers provided by the study sponsor. The study protocol was approved by the ethics committee of the Eye, Ear, Nose, and Throat Hospital, Fudan University, and written informed consent was obtained from each patient (or from a guardian if the patient was <18 years old) before his or her participation in the trial. Y. Guo and Y. Li contributed equally to this work.

The subjects were instructed to keep a diary throughout the trial, for making daily evaluations of symptoms according to a four-point scoring system: 0 to 3 (0, no symptoms; 1, weak symptoms; 2, moderate symptoms; 3, severe symptoms) for each rhinitis symptom (sneezing, rhinorrhea, itching, and nasal obstruction) and conjunctivitis symptom (itching, reddening, and tear flow), asthma symptoms (tightness of chest, wheezing, breathlessness, dyspnea, and cough, and symptoms induced by athletics). The use of symptomatic medications and the adverse events (AE) were also monitored. In addition, all the patients were asked to use a visual analog scale (VAS) at every hospital visit and to complete the rhinoconjunctivitis quality of life questionnaire (RQLQ)^{25–27} and the Asthma Quality of Life Questionnaire²⁸ before and after treatment. The outcome measures for efficacy were the total nasal symptom score (TNSS) and individual nasal symptom score. Secondary outcomes were the allergic conjunctivitis score (ACS) and the medication score (MS). AEs were also monitored.

Immunotherapy

The duration of treatment was 12 months. The 11th and 12th months were perceived as the evaluation period. The standard extract used during the study was a mixture of *D. pteronyssinus* and *D. farinae* administered as a glycerinated solution (*D. pteronyssinus* to *D. farinae*, 50:50, Pangramin SLIT; ALK-Abello, Madrid, Spain). Placebo vials that contained the Pangramin solution without the allergen and with the same appearance were supplied in the same packaging as the active substance. The patients were instructed for correct application of the products. The products were routinely self-administered at home and included a 1-month escalation phase, followed by a maintenance phase. During a 4-week up-dosing phase, the participants took daily increasing doses from one to five drops of dif-

ferent concentrations of the solution. After reaching the maintenance dose, the participants took the allergen three times a week during the maintenance phase. The protocol was recommended by the manufacturer.

The drops were given before meals at the same time each day and held under the tongue for at least 3 minutes before swallowing. All the subjects were observed for at least 15 minute at the hospital after the first dose for possible AEs, and they returned every 2 months to be reviewed about AEs and to receive new supplies of the vaccine. A traffic subsidy was provided to the subjects, *i.e.*, a traffic subsidy of 50 yuan (7.25 dollars) per person for a follow-up visit to the hospital. Moreover, the entire study provided each patient with free symptomatic medication on demand. If the symptoms of AR and/or asthma, or conjunctivitis were aggravated during immunotherapy, then the patients were allowed to use rescue medications (intranasal steroid sprays, oral antihistamines, eye drops and β_2 -adrenoceptor agonist) in a stepwise fashion, depending on the persistence and severity of the symptoms, as recommended.²⁴

Statistical Analysis

We used a scoring system for symptoms (most frequently a daily quantification of nasal and eye symptoms entered on a diary card and subsequently totalled) and medication use (typically a daily score that reflected the use of nasal sprays and antihistamine tablets, and eye drops entered on a diary card and subsequently totalled). The comparison between pre- and posttreatment values was performed by using the Wilcoxon signed rank test. Differences between the groups were analyzed by using the Student's *t*-test or the Mann-Whitney *U* test. Categorical data were compared by using the χ^2 test. All analyses were performed with the Statistical Analysis Software (SAS version 9.1; SAS Institute, Inc., Cary, NC). A two-sided *p* value of <0.05 was considered statistically significant. For the power analysis, the group sample sizes of 14 and 28 to achieve 80% power to detect a difference of 0.5 between the null hypothesis that both group means are 1.0 and the alternative hypothesis that the mean of group 2 was 0.5 with an estimated group standard deviation of 0.5, and with a significance level (alpha) of 0.05000 when using a two-sided two-sample *t*-test.^{29,30} When considering a certain amount of dropout, 16 (placebo group) and 32 (treatment group) subjects were included.

Table 2 Comparison of population composition and symptom score between the SLIT and placebo groups at baseline

Characteristic	SLIT Group (n = 32)	Placebo Group (n = 16)	p Value*
Male/female subjects, no.	18/14	7/9	0.41
Age <18/≥18 y, no.	15/17	5/11	0.30
Age, mean ± SD, y	17.9 ± 9.4	25.3 ± 10.2	0.72
Duration of HDM-induced AR, mean ± SD, y	4.1 ± 1.9	4.0 ± 2.4	0.35
TNSS, mean ± SD	209.1 ± 72.2	198.3 ± 72.8	0.83
Rhinorrhea score, mean ± SD	54.9 ± 27.5	50.3 ± 23.5	0.51
Congestion score, mean ± SD	52.8 ± 35.9	56.8 ± 37.4	0.68
Itching score, mean ± SD	57.6 ± 26.0	50.4 ± 23.3	0.08
Sneezing score, mean ± SD	43.8 ± 25.3	40.8 ± 28.6	0.29
ACS, mean ± SD	26.8 ± 42.3	22.0 ± 34.6	0.56
MS, mean ± SD	75.4 ± 64.7	37.1 ± 37.6	0.12
RQLQ score, mean ± SD	83.9 ± 22.5	79.6 ± 23.4	0.61
VAS score, mean ± SD	6.0 ± 2.0	5.7 ± 1.7	0.61

SLIT = Sublingual immunotherapy; SD = standard deviation; HDM = house-dust mite; AR = allergic rhinitis; TNSS = total nasal symptom score; ACS = allergic conjunctivitis score; MS = medication score; RQLQ = rhinoconjunctivitis quality of life questionnaire; VAS = visual analog scale.

* $p > 0.05$.

Table 3 Course of symptom scores between active treatment group and placebo group during the study

Symptom	Group	$M_{11-12} - BL$, median (P_{25} to P_{75})*	p#
Rhinorrhea	Active treatment	-12.5 (-34 to 2)	0.01
	Placebo	-18 (-25 to -1)	
Congestion	Active treatment	-15.5 (-28 to 5)	0.01
	Placebo	-6 (-34 to 6)	
Sneezing	Active treatment	-15.5 (-23 to 0)	<0.01
	Placebo	-5.5 (-18 to 5)	
Itching	Active treatment	-15.5 (-29 to -6)	<0.01
	Placebo	-13 (-30 to -4)	
TNSS	Active treatment	-64 (-80 to -42)	<0.01
	Placebo	-55 (-82 to -35)	

M_{11-12} = Months 11 and 12; BL = baseline; $P_{25}-P_{75}$ = percentile 25 to percentile 75; TNSS = total nasal symptom score.

*The total score of months 11 and 12 minus the baseline.

$p < 0.05$.

RESULTS

Patients

Forty-eight patients were included and randomized to active treatment ($n = 32$) or placebo ($n = 16$). The sample was composed of 25 male and 23 female patients ($p > 0.05$). The composition of patients is presented in Table 2. There was no significant difference between the two groups in terms of demographics, TNSS, RQLQ score, VAS score, and MS at baseline ($p > 0.05$). Because only two subjects were diagnosed with mild intermittent asthma, the score of Asthma Quality of Life Questionnaire between the two groups was almost the same. In addition to *D. farinae* and *D. pteronyssinus*, some frequent causative allergens, such as animal dander and pollen, were also tested. Based on the percentage of allergens, all the subjects ($n = 48$) were mainly sensitive to *D. farinae* and *D. pteronyssinus*, 19 to animal danders (39.6%), and 8 to pollen (16.7%). Furthermore, four patients (two in the active treatment group and two in the placebo group) discontinued treatment for a variety of reasons: two dropped out because they thought the effect of treatment was not satisfactory, and the other two just simply did not want to join the study. Overall, the percentage of patients who dropped out of the study was not significantly different ($p = 0.85$) between the two groups.

Nasal Symptom Scores

All data were analyzed according to the intention-to-treat principle, and the patients with poor adherence and the four dropouts were

excluded from analysis. Intragroup analysis performed on rhinitis symptom scores demonstrated a significant improvement in the active treatment group for all parameters: rhinorrhea, congestion, sneezing, itching, and TNSS during month₁₁₋₁₂ (Months 11 and 12) compared with baseline ($p < 0.05$), whereas no improvement was observed in the placebo group in terms of congestion, sneezing, and itching ($p > 0.05$). Although some parameters also decreased in the placebo group (rhinorrhea and TNSS), the decrease of symptom scores in the active treatment group was higher than in the placebo group, and indicated that the SLIT was significantly more effective than placebo in relieving allergy symptoms (Table 3).

Efficacy in Adults and Children in the Active Treatment Group

Because the sample in the active treatment group was composed of 17 adults and 15 children, the efficacy between the subgroups was further analyzed. As shown in Table 4, there were significant improvements in the adults in terms of congestion, sneezing, itching, and TNSS during month₁₁₋₁₂ compared with baseline ($p < 0.05$). The other symptom scores in children had significantly improved after 1 year of treatment ($p < 0.05$), except for the symptom score for congestion. In addition, except that the symptom scores of congestion in children were lower than in adults, there was no significant difference in other symptom scores at baseline ($p > 0.05$, independent *t*-test). At the end of treatment, no statistical difference was observed both for individual nasal symptom and TNSS among children and adults ($p > 0.05$), which indi-

Table 4 Course of symptom scores between adults and children during the study

Symptom	Group	M ₁₁₋₁₂ – BL, median (P ₂₅ to P ₇₅)*	p
Rhinorrhea	Adults	–2 (–23 to 9)	0.29
	Children	–25 (–41 to –9)	0.03#
Congestion	Adults	–24.5 (–34 to –2)	0.02#
	Children	–8 (–24 to 8)	0.18
Sneezing	Adults	–11 (–22 to 1.5)	0.04#
	Children	–17.5 (–23 to 0)	0.02#
Itching	Adults	–20.5 (–35 to –6)	<0.01#
	Children	–9.5 (–28 to –3)	0.01#
TNSS	Adults	–58.5 (–80 to –35.5)	<0.01#
	Children	–68 (–80 to –47)	0.01#

M₁₁₋₁₂ = months 11 and 12; BL = baseline; P₂₅–P₇₅ = percentile 25 to percentile 75; TNSS = total nasal symptom score.

*The total score of months 11 and 12 minus the baseline.

#p < 0.05.

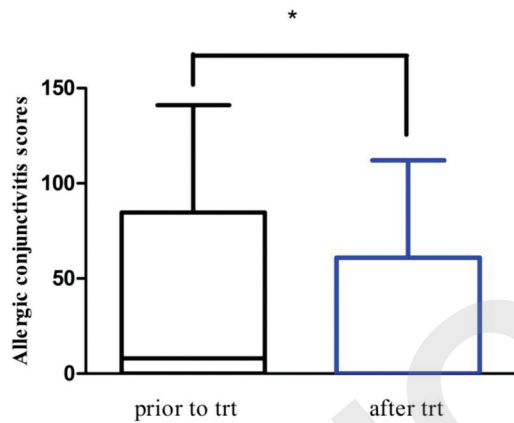


Figure 1. The change of allergic conjunctivitis scores (ACS) in the active treatment group. *p < 0.05, Wilcoxon signed rank test.

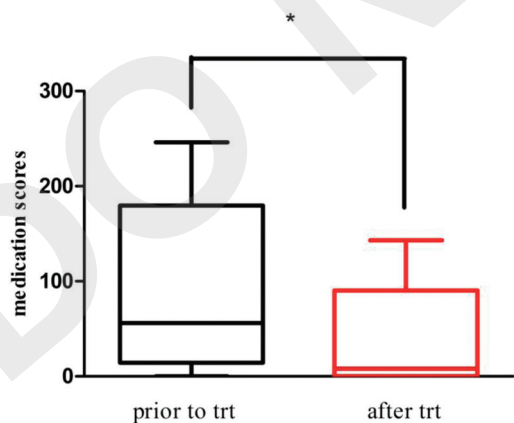


Figure 2. The change of medication scores (MS) in the active treatment group. *p < 0.05, Wilcoxon signed rank test.

cated that the active treatment had great efficacy on alleviating the symptom of congestion in adults.

ACS and MS

After 12 months of treatment, the median ACS in the active treatment group decreased from 8 to 0 points (Fig. 1), and the MS decreased from 56 to 8 points (Fig. 2). The decreases both in ACS and MS

were highly significant in comparison with the baseline ($p < 0.05$). However, the median ACS in the placebo group decreased from 7.5 to 0 points, and the MS decreased from 32.5 to 30 points. No significant difference was observed in the placebo group compared with the baseline ($p > 0.05$).

VAS and RQLQ scores

VAS and RQLQ scores in the active treatment group had statistically decreased after treatment ($p < 0.05$). However, no significant difference was observed in the placebo group ($p > 0.05$).

AEs

AEs were classified according to the European Academy of Allergy and Clinical Immunology grading system.³¹ Fourteen subjects underwent mild-to-moderate AEs (29.2%): 11 in the active treatment group (34.4%) and 3 in the placebo group (18.9%). There was no significant difference in the incidence of AEs between the two groups ($p = 0.26$). Regarding the AEs, urticaria and/or eczema and various eczematous skin diseases were the most commonly reported (28.6%); second was pain in the stomach (21.4%); and mouth and throat irritation, headache, and diarrhea also occurred. In addition, one subject who experienced increased asthma symptoms of moderate severity did not require treatment other than occasional use of an albuterol metered-dose inhaler, and one subject had an attack of asthma and was treated in the hospital. Half of these events occurred during the dose-escalation phase. Although, in most instances, the AEs resolved within 1 to 22 days, one subject had mild and occasional abdominal cramps. The AE occurred in the third month and persisted to the sixth month of treatment; the symptoms resolved with continued therapy, and the subject required oral antihistamine on an as-needed basis. No severe systemic reactions were observed.

Adherence

In our study, adherence was calculated from the amount of allergen left in the returned vials on follow-up visits. The volume of extract used by each patient was recorded on a scale from insufficient to excellent. It was considered as excellent, good, and insufficient when the amount used accounted for was 80%, 60–80%, and <40% of the total amount, respectively. As far as adherence concerned, there were 21 patients who could be considered as excellent, and 20 patients as good adherence. Given that the total number of patients was 48, 85.5% of the patients were either excellent or good. Therefore, we think the adherence with SLIT regimens was satisfactory.

DISCUSSION

Since the first report of a successful trial of SLIT in the treatment of AR caused by HDM sensitivity in 1986,³² several meta-analyses based

on studies mainly conducted in Europe examined the role of SLIT in the management of allergic respiratory disease.^{33–38} These studies generally support the use of SLIT regimens as being relatively safe and effective.^{14,15,39} Currently, SLIT is marketed and used in routine clinical practice in many European countries, and standardized vaccines are available. With different allergen immunotherapy products beginning to be used in China, more and more attention is being paid to SLIT. In 2006, a vaccine made with a single extract of *D. farinae* (Chanllergen) was introduced for clinical use and was approved by the Chinese State Food and Drug Administration. Until now, the SLIT products sold on the current Chinese market were directed at a single kind of dust mite and there was no standardized SLIT mixture that aimed at two mites simultaneously available for patients. Because a large proportion of patients with AR is sensitized to both *D. pteronyssinus* and *D. farinae*,⁴⁰ there is a need for a mixture of *D. pteronyssinus* and *D. farinae* extracts for SLIT. Therefore, we conducted the randomized, double-blind, placebo controlled study, and evaluated the efficacy and safety of SLIT drops mixture of *D. pteronyssinus* and *D. farinae* or placebo.

According to the World Allergy Organization Task Force, the ideal efficacy study of a specific allergen immunotherapy should be performed in patients who are monosensitized or in patients concomitantly sensitized to non-cross-reacting allergens.⁴¹ In our study, although some patients had multiple allergies, their main allergens were *D. pteronyssinus* and *D. farinae*. Moreover, they were asked to avoid exposure to other allergens during the treatment period. The results demonstrated that there were no significant differences between patients who were only sensitive to HDMs and those who had multiple allergies in terms of efficacy and AEs. Also, we observed that the efficacy of the active treatment was higher than placebo, which manifested both in nasal symptoms scores, ACS, and MS. Furthermore, the VAS and RQLQ scores in the active treatment group also statistically decreased after treatment ($p < 0.05$).

Some evidence for the efficacy of SLIT in children remains inconclusive.⁴² In a Cochrane review, Wilson *et al.*³⁴ concluded that SLIT was an accepted treatment for adults; studies with children revealed no significant reduction in symptoms and MS. Another study⁴³ considered that SLIT was superior to subcutaneous therapy, especially in childhood. The results indicated that SLIT had a positive effect on the reduction of a multiple symptom MS, mainly by significantly reducing rescue medication use, but had no significant effect on symptoms alone in children.⁴³ In addition, there is evidence that the results of SLIT are less obvious in adult patients compared with patients <18 years old.⁴⁴ Yonekura *et al.*⁴⁵ demonstrated that SLIT with house dust extract for >30 weeks was safe and effective for HDM AR in children. In our study, overall, the results demonstrated that the active treatment had significant effects on relieving allergy symptoms both in adults and children, and no statistical difference was observed between these two subgroups. Although we further analyzed the efficacy in children and adults, these data must be interpreted with caution because the number of study patients was small.

It is well known that a strong placebo effect has been observed in allergic diseases. In our study, we also observed the similar placebo effect as presented by Tonnel *et al.*⁴⁶: there also was a decrease in rhinorrhea and TNSS in the placebo group. Nowadays the placebo effect is viewed as a psychobiological event that results from the interaction between individual patient factors and factors that relate to the physician and the therapeutic environment.⁴⁷ In addition, the efficacy in our study was mainly evaluated by subjective parameters. It is necessary for future investigators to conduct more studies by using objective or biochemical parameters to determine the efficacy of the product tested here or placebo.

Compared with subcutaneous immunotherapy, SLIT seems to offer practical advantages for treatment and adherence because injections can be avoided, the treatment is generally well tolerated, and the risk of severe allergic reactions seems to be negligible.^{34,48,49} In this trial, AEs that occurred ranged from mild to moderate and that were

possibly caused by the study product were common, *e.g.*, oral itching and mucosal swelling, gastrointestinal upset, neurodermatitis. No severe systemic reactions were observed. AEs mostly resolved during continued application of SLIT, and termination of treatment due to AEs was not registered. Allergic AEs were reported in both children and adults; children had the majority of AEs (12/14 [85.7%]); therefore, it is necessary to pay more attention to children who accept SLIT treatment.

SLIT is often acclaimed to be more acceptable for patient adherence because frequent outpatient visits are not required.⁴⁹ Compared with subcutaneous immunotherapy, patients on SLIT need to take the medication while at home, which requires that the patients take the medication by themselves without being reminded. In our study, there were 21 patients who could be considered as having had excellent adherence, and 20 patients had good adherence. Of the total number of patients (48), 85.5% of the patients (41) had either excellent or good adherence. Therefore, we believed that the adherence with SLIT regimens was satisfactory. However, for various reasons, there were seven patients (14.5%) with poor adherence who once stopped treatment without informing the researchers. Although they have not been excluded from the trial according to the study protocol, inadequate control of drug use might be a drawback of SLIT because SLIT is self-administered.

CONCLUSION

In this randomized, double-blind, placebo controlled study that evaluated the efficacy and safety of SLIT with a mixture of *D. pteronyssinus* and *D. farinae* extracts in patients with HDM-induced AR, we demonstrated that the sublingual drops could significantly relieve allergy symptoms and reduce the need for antiallergic drugs, which indicated the superiority of active treatment over placebo. However, due to the limited sample size, the findings need to be further confirmed.

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