Efficacy and safety of sublingual immunotherapy in children aged 3–13 years with allergic rhinitis

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ABSTRACT

Background: *Sublingual immunotherapy (SLIT) is recommended for allergic diseases. However, clinical studies containing evidence-based data of this treatment in young children, which is rarely reported in the literature, are needed. This study was designed to assess the efficacy and safety of SLIT in children, including very young children.*

Methods: *Two hundred sixty-four children aged 3–13 years old (133 children, 3–5 years old) with* Dermatophagoides farinae*–induced allergic rhinitis with or without asthma treated by standard pharmacotherapy had randomly received either SLIT (SLIT group) or no SLIT (control group) for 12 months. Symptoms, medications, visual analog scale (VAS) and presence of adverse events (AEs) were assessed at monthly visits. Skin-prick test and* Dermatophagoides farinae*-specific IgE and IgG4 were measured before and after treatment.*

Results: *Both treatments were effective in the global clinical scores during the first seven visits when compared with baseline (all, $p < 0.01$), and SLIT showed lower symptoms scores and VAS scores throughout this period (all, $p < 0.01$). These improvements continued until the later visits only in the SLIT group. Also, the asthma medication consumption was decreased by SLIT treatment only at the end of study ($p < 0.01$). The specific IgG4 was significantly increased after SLIT treatment when compared with the control group, but no significant change of specific IgE was observed in either groups. In the SLIT group, there was no significant difference between children less than or more than 5 years old in terms of clinical efficacy, onset of action, immunologic parameters, and safety. No severe systemic AEs were reported.*

Conclusion: *SLIT is effective and well-tolerated in children with allergic rhinitis 3–13 years old.*

(Am J Rhinol Allergy 28, 131–139, 2014; doi: 10.2500/ajra.2014.28.4006)

An increased prevalence of allergic rhinitis (AR) has been found worldwide and the onset age has decreased in pediatric patients.[1,2] In China, the prevalence of AR in children has increased from 9.1% in 2001[3] to 15.4% in 2010,[4] and house-dust mites (HDMs) have been documented to be the most prevalent allergens.[5] Once AR develops in childhood, it rarely naturally remits in childhood and may impair quality of life and school performance for many years. Additionally, AR is also closely related with the onset of asthma, rhinoconjunctivitis, and other diseases.[1]

The only treatment targeting the underlying immune response of IgE-mediated hypersensitivity is immunotherapy.[6,7] Sublingual immunotherapy (SLIT), with better safety, tolerability, cost-effectiveness, and compliance, is currently accepted as an effective administration route of immunotherapy.[8–10] Moreover, in addition to proven clinical efficacy, the long-term efficacy and preventive effects on onset of asthma and new sensitization in AR patients has been documented.[11,12] SLIT is believed to involve a similar mechanism to subcutaneous immunotherapy with altered T-cell responses and changes in circulating antibody expression levels, particularly allergen-specific IgG4.

The efficacy of SLIT in children has been established,[13,14] but many unmet aspects including the minimal age of starting SLIT, risk–benefit ratio in very young children, the effectiveness of AR in real-life, and preventive potency[15] still need to be better addressed. Otherwise, although it is accepted that the immune system can be modulated from infancy to old age as indicated by vaccination,[16] SLIT has been only recommended to children >5 years old (which is the age cutoff for subcutaneous immunotherapy) in real-life clinical practice. The minimum age of children with AR in research on the efficacy of SLIT with pollen extracts is 3 years old,[14] but the efficacy of SLIT with HDMs extracts in children <5 years is not reported. There are only a few studies reporting the safety of SLIT with HDMs extracts in children aged 3–5 years old,[17,18] but none of them has focused on the efficacy. Therefore, the safety and efficacy of SLIT in children sensitized to HDMs, especially young children, still need more and better clinical evidence in real life. This study aimed to evaluate the efficacy and safety of SLIT in AR children aged 3–13 years old.

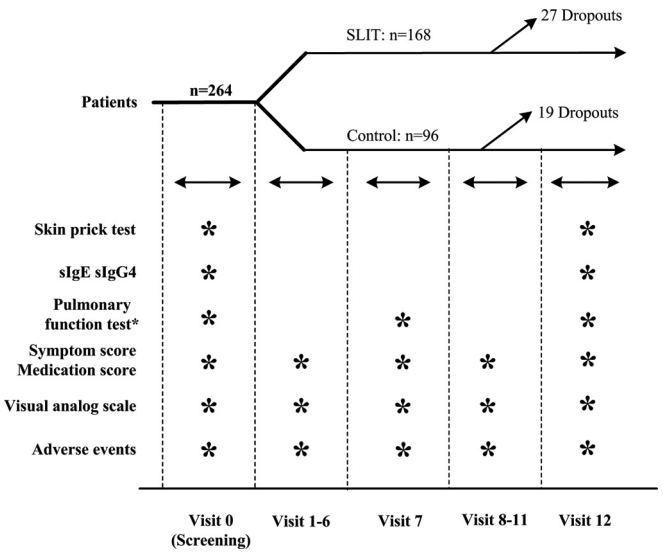

Figure 1. *Study design. *Only performed in children with asthma.*

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Funded by Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China

The authors have no conflicts of interest to declare pertaining to this article

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Table 1 **SLIT schedule**

	Weeks	No. Vial*	Volume (mL)						
			Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Induction phase	1	1	0.05	0.10	0.15	0.20	0.30	0.40	0.50
	2	2	0.05	0.10	0.15	0.20	0.30	0.40	0.50
	3	3	0.05	0.10	0.15	0.20	0.30	0.40	0.50
Duration phase	4–52	4				0.15			

**The concentration of major allergens extracts in vials 1, 2 ,3, and 4 is 1,10, 100, and 333 μg/mL, respectively.*
SLIT = sublingual immunotherapy.

MATERIALS AND METHODS

Study Design

This multicenter, controlled, randomized, open-label study was approved by the Ethics Committee and is in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice (2003 revision, China). Guardians of each child fully understood and signed the patient informed consent. A total of 264 AR children were recruited from six centers located in four provinces in China (from October 2008 to August 2009) and were randomized to receive either SLIT or no SLIT for 12 months. Children in both groups had also received standard pharmacotherapy as needed according to Allergic Rhinitis and Its Impact on Asthma[1] and the Global Initiative for Asthma[19] throughout the study period. All of the children had been evaluated at visit 0 as baseline and then evaluated monthly (visits 1–12) as described in Fig. 1. During the study, the guardians were required to record symptoms, medication consumption, and adverse events (AEs) on a diary card and give it to physicians every month. AEs were monitored at each visit and physicians were present for questions on AEs. Jie Shao, Yu-xia Cui, and Yu-fei Zheng contributed equally to this work.

Study Subjects

Two hundred sixty-four children with AR (163 girls, aged 3–13 years) were recruited. The inclusion criteria were (1) diagnosed with moderate-to-severe/persistent AR without severe/uncontrolled asthma according to Allergic Rhinitis and Its Impact on Asthma[1] and the Global Initiative for Asthma[19], (2) have a clinical history of mite allergy and sensitization to *Dermatophagoides farinae* as confirmed by a positive skin-prick test (SPT) and serum-specific IgE of ≥0.7 kU/L, and/or (3) a forced expiratory volume in 1 second of ≥70% of predicted volume.

Skin-Prick Test

SPT including eight aeroallergen (*D. farinae*, *Dermatophagoides pteronyssinus*, cat, dog, German cockroach, *Artemisia* pollen, humulus pollen, and platan pollen) were performed on the forearm according to standard protocol, using histamine phosphate (positive control) and normal saline (negative control) for comparison. A wheal size of ≥3 mm in diameter for allergen extracts (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China) was deemed as positive.

Sublingual Immunotherapy

The standardized *D. farinae* drops (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd.) approved by the China Food and Drug Administration was offered (Table 1*)*. The first dose was taken under medical supervision. Children were instructed to self-administer at home daily and keep the drops under the tongue for 1–3 minutes, and then swallow and not to drink within 15 minutes. The young children were administered the SLIT extracts under the supervision of their guardians. In case of AEs, the dose up was delayed or reduced under the guidance of physicians.

Symptoms and Medication Scoring System

The guardians were instructed to keep a diary card and record all symptoms and medication consumption during the study period. Each nasal symptom (nasal discharge, nasal obstruction, itching, and sneezing) was evaluated according to a 0- to 3-point scoring system as follows: sneezing (successive numbers per time), 0 points = none, 1 point = 3–5, 2 points = 6–10, and 3 points = ≥11; nasal discharge (times per day), 0 points = none, 1 point = ≤5, 2 points = 5–9, and 3 points = ≥10; itching, 0 point = none, 1 point = intermittent itching, 2 points = tolerable itching, and 3 points = intolerable itching; nasal obstruction, 0 points = none, 1 point = congestion but no mouth breathing, 2 points = severe congestion with occasional mouth breathing, and 3 points = severe congestion with mouth breathing during the whole day. The total rhinitis symptoms score (TRSS) was the sum of four nasal symptoms scores. The asthmatic symptoms in children with asthma were also recorded. The daytime asthma symptoms were scored from 0 to 5 points according to the general severity of wheeze, shortness of breath, dyspnea, and cough and its impact on daily life. The nocturnal symptoms were scored from 0 to 4 points according to the frequency of nocturnal and early morning awakening by asthma.[20] The total asthma symptoms score (TASS) was the sum of daytime and nocturnal asthma symptoms scores. The TRSS and TASS were evaluated monthly.

The following medications were allowed: oral antihistamines and intranasal corticosteroid. In regard to children with asthma, inhaled corticosteroid, antileukotrienes, and β_2-agonists were also permitted. The scoring system was established according to references[1,19,21,22] and the type and daily recommended dosage of medications. The rhinitis medications score (RMS) was calculated as follows (per day): 1 point for each 40 mg of loratadine, 20 mg of cetirizine hydrochloride, or 200 μg of levocabastine hydrochloride; 2 points for each recommended daily dosage of intranasal corticosteroid according to directions. The asthma medications score (AMS) was calculated as follows (per day): 1 point for each 10 mg of antileukotrienes, 100 μg of salbutamol sulfate aerosol or 50 μg of salmeterol; 2 points for each 200 μg of budesonide aerosol, 250 μg of beclomethasone dipropionate, 100 μg of fluticasone propionate, 10 mg of bambuterol (oral), or 1 mg of procaterol (oral); 9 points for each 1 mg of budesonide suspension for inhalation.

Visual Analog Scale

Patients were asked to record the overall severity of rhinitis symptoms on a 10-cm visual analog scale where 0 indicated "no symptom" and 10 indicated "maximal symptoms" at each visit.

Immunoglobulins

Serum *D. farinae*–specific IgE and IgG4 (sIgE and sIgG4) were measured by ELISA kits (Dr. Fooke Laboratorien GmbH, Neuss,

Germany) at visits 0 and 12. The results were expressed as kilounit per liter for sIgE and milligrams per liter for sIgG4.

Pulmonary Function Test

Children with asthma and their guardians were instructed to record peak expiratory flow (PEF) with a Mini-Wright peak flow meter (Shanghai Wanbo Technology Co., Ltd, Shanghai, China) in the morning and evening. The PEF (percent predicted) provided by medical records before treatment were deemed as baseline. During the study, the PEF (percent predicted) was recorded at visits 7 and 12.

Adverse Events

All of the AEs reported during the study period were recorded on diary card and were promptly addressed under the instruction of the physician based on the following principles[23]: mild local reactions, none; aggravating local reactions/moderate reactions, drug therapy or other treatments as needs and/or proper delay or reducing of SLIT dose. AEs were rated on five levels (0–4 scale) according to grading system proposed by European Academy of Allergy and Clinical Immunology,[23] which is based on the rate of onset and severity of the reactions.

Statistical Analysis

Statistical analysis was performed using SAS Version 9.2 (SAS Institute, Inc., Cary, NC). All tests were two tailed, and the level of significance was set at 0.05. ANOVA or χ^2-test was used in the screening visit and tested the values intragroup (baseline versus each visit). The *t*-test or Wilcoxon test were used to examine the difference between SLIT and control group. Unordered categorical variable used Fisher test and ordinal categorical variable used Cochran-Mantel-Haenzel χ^2-test. Values were shown as mean ± SE.

RESULTS

Study Subjects

Two hundred sixty-four children with AR (133 children were 3–5 years old) were enrolled into the study. There were no significant differences between the two groups in age, sex ratio, type of diseases, RMS, TRSS, TASS, and four individual rhinitis symptoms scores at baseline (all $p > 0.05$; Table 2); 83.93% of the children (141/168) in the SLIT group and 80.21% of the children (77/96) in the control group had completed the study ($\chi^2 = 0.3575$; $p > 0.05$). No child withdrew from the study because of an AE (Fig. 2).

Table 2 **Demographic and clinical characteristics**

	SLIT Group $n = 168$	Control Group $n = 96$	p Value
Demographic characteristics			
Age (years, mean±SE)	6.37 ± 0.20	5.92 ± 0.31	>0.05
Gender (male/female)	104/64	59/37	>0.05
Age			
3–5 yr old	80	53	>0.05
6–13 yr old	88	43	
Diseases			
AR	29	17	>0.05
AR with asthma	139	79	
Other allergic disorders	19	1	<0.05
Conjunctivitis	4	1	
Atopic dermatitis	3	0	
Food allergy	17	1	
Severity of AR			
Moderate–severe intermittent	1	0	>0.05
Mild persistent	154	94	
Moderate–severe persistent	13	2	
Severity of allergic asthma			
Intermittent	1	0	<0.05
Mild	127	62	
Moderate	11	17	
Positive allergens			
D. farinae only	7	1	>0.05
D. farinae and *D. pteronyssinus* with/without others	152	94	
D. farinae and others (except *D. pteronyssinus*)	9	1	
Skin index* of SPT (*D. farinae*)			
0.5–1.0	20	1	>0.05
1.0–2.0	51	44	
>2.0	97	51	
Clinical data (scores, mean ± SE)			
TRSS	5.20 ± 0.14	5.40 ± 0.15	>0.05
Sneezing	1.23 ± 0.04	1.23 ± 0.06	>0.05
Nasal discharge	1.29 ± 0.05	1.39 ± 0.06	>0.05
Nasal obstruction	1.33 ± 0.05	1.40 ± 0.06	>0.05
Itching	1.35 ± 0.05	1.39 ± 0.06	>0.05
RMS	0.40 ± 0.04	0.38 ± 0.04	>0.05
AMS	4.02 ± 0.16	3.62 ± 0.19	>0.05
TASS	1.72 ± 0.11	2.92 ± 0.13	<0.01

**Skin index: the area of* D. farinae *tested wheel divided by the area of standard positive control solution.*

RMS = rhinitis medications score; TRSS = total rhinitis symptoms score; AMS = asthma medications score; TASS = total asthma symptoms score; SLIT = sublingual immunotherapy; AR = allergic rhinitis; SPT = skin-prick test.

Effects on AR

The TRSS in both groups significantly improved from visit 1 and this improvement was maintained throughout the study period ($p < 0.01$, respectively), where the SLIT group showed much lower scores (Fig. 3 *a*; all, $p < 0.01$). Interestingly, a continuous decrease of TRSS was only observed in the SLIT group after visit 7, and a greater reduction over the control group was achieved at the end of study ($p < 0.01$). There were also significant reductions of the four individual rhinitis symptoms scores in both groups after visit 1 or 2, with significant differences between groups (Fig. 3, *c–f*). Especially, the significant difference in nasal discharge symptom was found since visit 1, which was 1 month earlier than in the control group.

After treatment, a significant reduction of RMS was first found at visit 2 in the SLIT group ($p < 0.05$) and visit 3 in the control group ($p < 0.05$) and this effect was maintained throughout the study period (Fig. 3 *b*). The significant differences of RMS were found at visits 4 ($p < 0.05$), 10, 11 and 12 ($p < 0.01$, respectively) between the two groups, and the SLIT group had achieved more reduction of RMS over the control group at the end of study ($p < 0.01$). The RMS in the two groups began to diverge after visit 7, where continuous reductions were only shown in the SLIT group. The decline of visual analog scale scores was consistent with that of allergic symptoms and medication in both groups ($p < 0.01$; Fig. 4).

Immunologic Parameters

As shown in Table 3, sIgG4 had significantly increased in both groups after treatment ($p < 0.01$ respectively), but sIgE remained

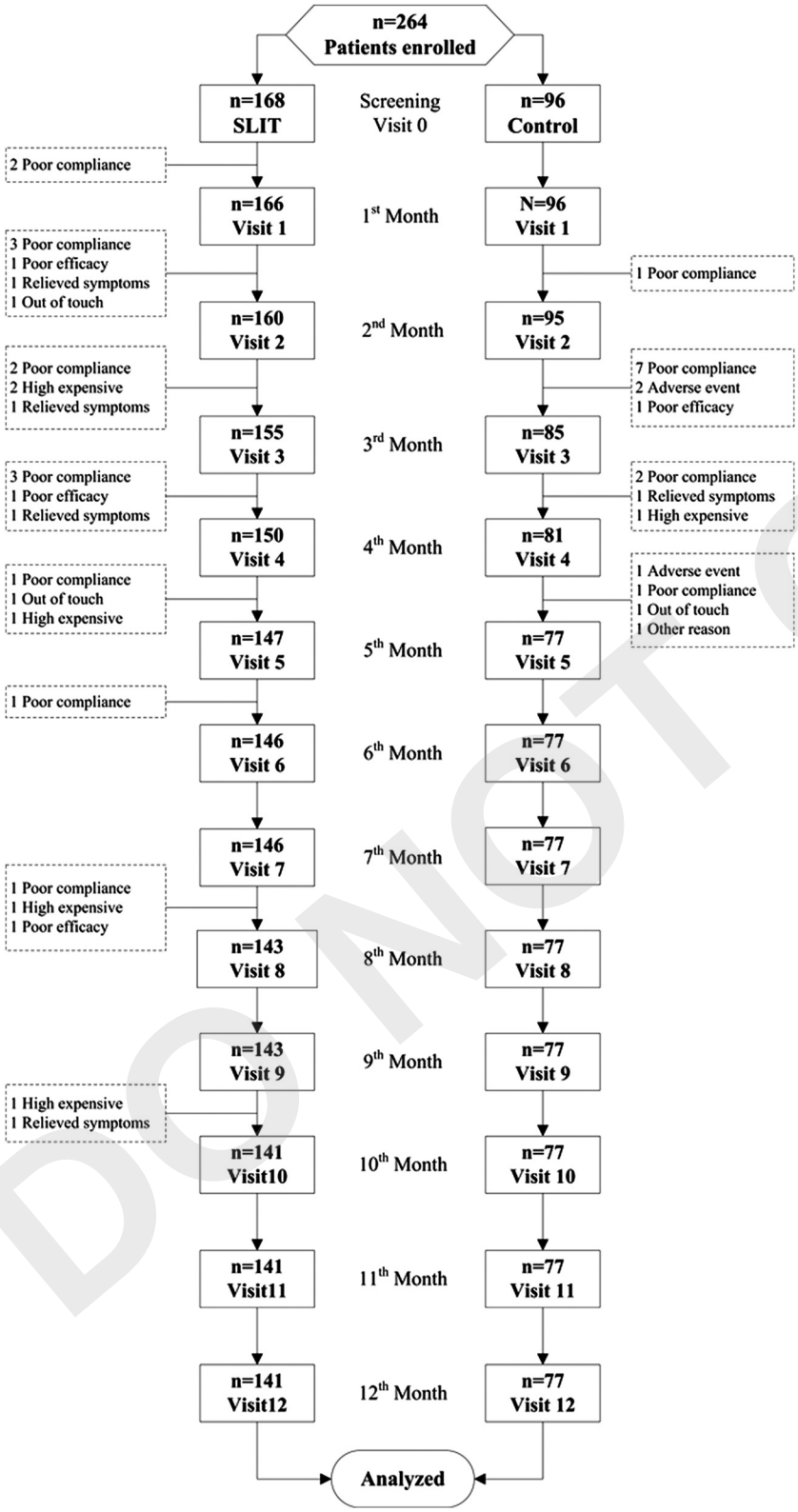

Figure 2. *Flowchart and dropout analysis.*

unchanged ($p > 0.05$, respectively). Notably, more increase of sIgG4 was shown in the SLIT group ($p < 0.01$). The ratio of sIgE and sIgG4 (sIgE/sIgG4) dramatically decreased at the end of study, with much lower expression level in the SLIT group ($p < 0.01$).

Effect on New Sensitization

The number of positive allergens in children ($n = 218$) who had completed the SPT before and after treatment were compared. The

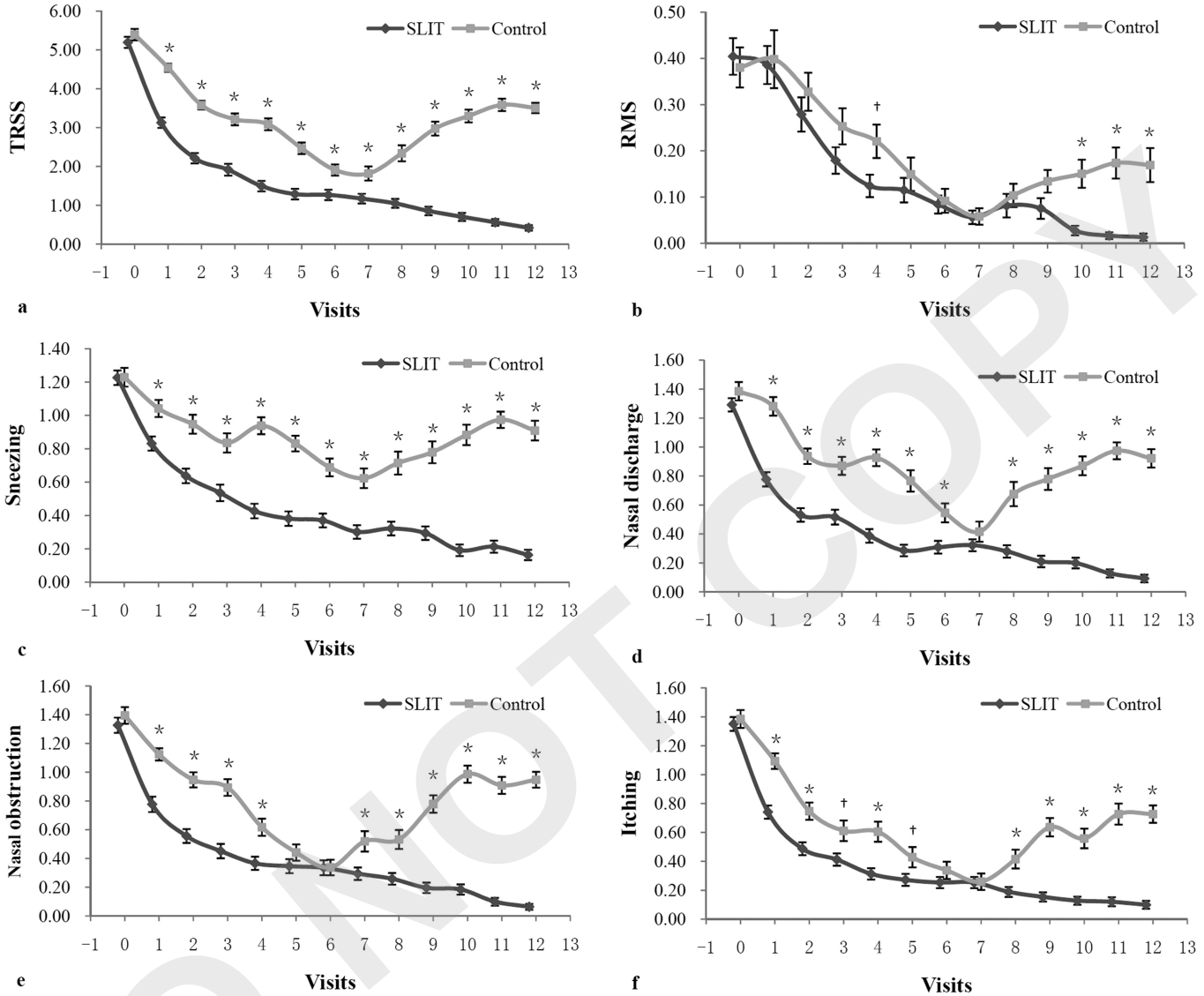

Figure 3. *TRSS, RMS, and four individual rhinitis symptom scores in the SLIT and control group (mean ± SE). (a) TRSS; (b) RMS; (c–f) the scores of (c) sneezing, (d) nasal discharge, (e) nasal obstruction, and (f) itching (†$p < .05$; *$p < 0.01$ compared between groups). TRSS, total rhinitis symptoms score; RMS, rhinitis medications score; SLIT, sublingual immunotherapy.*

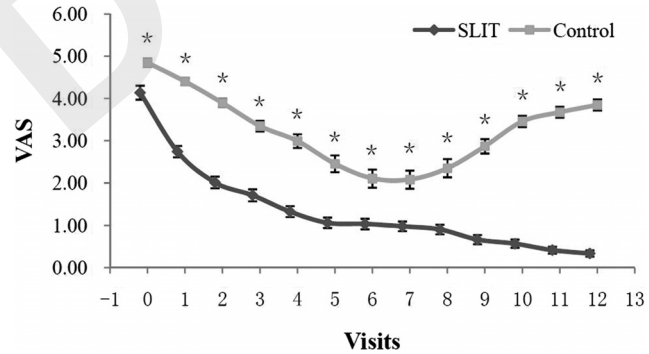

Figure 4. *VAS score in the SLIT and control group (mean ± SE; *$p < 0.01$ compared between groups). VAS, visual analog scale; SLIT, sublingual immunotherapy.*

onset of new sensitizations was observed in 3.55% of children in the SLIT group and 27.27% of children in the control group, with a significant difference between groups ($\chi^2 = 15.0686$; $p < 0.01$). The number of positive allergens had decreased in 11.35% of children in the SLIT group only ($\chi^2 = 7.8349$; $p < 0.01$).

Safety

No children required hospitalization or withdrew from the study because of AEs. No severe systemic AEs, anaphylaxis, acute attack of asthma, or use of adrenaline were reported. Thirty-nine patients in the SLIT group and nine patients in the control group reported 54 AEs and 11 AEs, respectively ($\chi^2 = 10.7174$; $p < 0.01$). The AEs are listed in Table 4 and analyzed (Table 5). To summarize, most of the AEs were grade 1, occurred during the first three visits (50%), and were relieved within a week with or without medication. Furthermore, 11 AEs reported in the SLIT group were related/maybe related to treatment, of which 10 were grade 1; 7 AEs were relieved without any treatment and nine were relieved within a week. In the SLIT group, the incidence of AEs (6/19) in children with other history of allergy

Table 3 **Comparison of immunologic parameters between SLIT and the control group at visits 0 and 12 (mean ± SE)**

	SLIT Group		Control Group	
	Visit 0	Visit 12	Visit 0	Visit 12
sIgE (kU/L)	67.16 ± 2.41§	64.74 ± 2.66§	81.74 ± 2.22	82.63 ± 2.51
sIgG4 (mg/L)	640.38 ± 16.59§	1165.11 ± 32.86#§	718.62 ± 24.43	890.52 ± 29.27#
sIgE/sIgG4	0.11 ± 0.00	0.06 ± 0.00#§	0.12 ± 0.01	0.10 ± 0.01*

*$p < 0.05$; #$p < 0.01$ compared with visit 0; §$p < 0.01$ compared with the control group.
sIgE = Dermatophagoides farinae–*specific IgE; sIgG4* = Dermatophagoides farinae–*specific iIgG4; SLIT = sublingual immunotherapy.*

Table 4 **Reported AEs during the study period**

	SLIT Group	Control Group
Total no. of AEs	54	11
Aggravating rhinitis	13 (24.07%)	0 (0%)
Aggravating asthma	8 (14.82%)	0 (0%)
Upper respiratory tract infection	23 (42.59%)	7 (63.64%)
Nosebleed	1 (1.85%)	1 (9.09%)
Headache	0 (0%)	1 (9.09%)
Local rashes	5 (9.26%)	0 (0%)
Gastrointestinal intolerance	2 (3.70%)	2 (18.18%)
Oral intolerance	1 (1.85%)	0 (0%)
Eye itching	1 (1.85%)	0 (0%)

AEs = adverse events; SLIT = sublingual immunotherapy.

was higher than that (33/149) in the others, but there was no significant difference ($\chi^2 = 0.3950$; $p > 0.05$). Moreover, none of children with atopic dermatitis reported skin reaction and only two children with moderate asthma in the control group reported two AEs (not related to the treatment).

Effect on Allergic Asthma

Over 80% of children also suffered from concomitant asthma in this study. The change in trends of TASS (Fig. 5 *a*) and AMS (Fig. 5 *b*) in these children were consistent with the trends shown by clinical scores of AR. At the end of the study, the SLIT had achieved more reduction of TASS and AMS; meanwhile, a significant decrease of AMS was observed in the SLIT group only ($p < 0.01$). The significant reduction of TASS in the SLIT group was found after visit 1, which is 1 month earlier than that in the control group ($p < 0.01$ respectively), and no significant decline of AMS could be found until visit 3 in the SLIT group ($p < 0.01$) and visit 5 in the control group ($p < 0.05$). The pulmonary function of children in both groups had dramatically improved at visit 7 (Fig. 5 *c*; $p < 0.01$, respectively). The continuous improvement of PEF (percent predicted) was shown in the SLIT group (all. $p < 0.01$) but not in control group (visit 7 versus visit 12, $p > 0.05$).

Comparison of Efficacy and Safety between Children 3–5 Years Old and Children 6–13 Years Old

To compare the efficacy and safety of SLIT in children younger or older than 5 years of age, the SLIT group was divided into two subgroups. There was no significant difference between children in the two subgroups in terms of sex ratio, diseases distribution, TRSS, RMS, TASS, AMS, and concentration of sIgE and sIgG4 at baseline (visit 0; all, $p > 0.05$). As shown in Fig. 6 *a*, the TRSS and RMS in both subgroups significantly decreased at visit 1 ($p < 0.01$) and visit 3 ($p < 0.01$). There was no significant difference in TRSS and RMS between subgroups after visits 2 and 1. As shown in Table 6, a significant increase of sIgG4 and decrease of sIgE were observed in both subgroups after treatment, but there was no significant difference between the subgroups. There was no significant difference in incidence of AEs between the two subgroups ($\chi^2 = 0.0223$; $p > 0.05$), as well as remission time ($\chi^2 = 0.9270$; $p > 0.05$), treatment ($\chi^2 = 1.3224$; $p > 0.05$), occurrence time ($\chi^2 = 6.826$; $p > 0.05$), and incidence of AEs related/maybe related to SLIT ($\chi^2 = 0.3781$; $p > 0.05$; Table 5). Meanwhile, the incidence of grade 2 AEs in children 3–5 years old was higher ($t = 2.635$; $p < 0.05$), but most of them were not related or maybe not related to SLIT and all of them improved within 1 week.

DISCUSSION

This study has documented the efficacy and safety of SLIT in children and, particularly, provided more detailed information a group of young children. Our results indicate that both SLIT and pharmacotherapy are effective, with more improvements in the SLIT group. Consistent with results reported by Ferres *et al.*,[24] the uppermost reductions of the global clinical scores in both groups were achieved during the first 7 months, and the reductions in the SLIT group continued and were maintained during the following months. It is interesting to note this divergence of clinical scores between groups after the 7th month in this study. There are few studies focused on this aspect that reported similar results in the literature. Costa *et al.*,[25] found that immunotherapy shows faster and more striking improvements during the 1st months and a lower rate of relapse after disruption of drug therapy when compared with drugs alone. Similar results were also reported by Shaikh.[26] These results indicate that immunotherapy can provide long-term and continuous benefits after disruption or reduction of drug therapy. Otherwise, the divergence may provide evidence for the appropriate time point to appreciate the efficacy of SLIT. Furthermore, this study shows that there is no significant difference in efficacy and onset time of SLIT between children 3–5 years old and children 6–13 years old. This study indicates that SLIT with *D. farinae* extracts is effective in subjective and objective symptom improvements in children aged 3–5 years.

Clinically, only a small proportion of allergic patients are monosensitized; therefore, the efficacy of a single allergen vaccine in polysensitized patients has created wide concerns. A double-blind, placebo-controlled study[27] with *Phleum pratense* tablet found significant reduction of symptom and medication scores in both monosensitized patients and polysensitized patients. In this study, >90% of children were sensitized to *D. farinae* and *D. pteronyssinus*. The results may also imply that this single allergen vaccine is also effective in children sensitized to HDMs with or without other aeroallergens. Although more data from a well-designed, strict enrolled study are needed, our results may inspire additional research.

SLIT was well tolerated in this study. Most of the AEs are reported during the induction phase, which is consistent with other studies,[28,29] and incidence of AEs gradually decline as SLIT progressed during the following visits. It may suggest a progressive tolerance in children during immunotherapy. Although differences in moderate asthma and history of other allergic diseases are shown during initial randomization (Table 2), they appear to have limited effects on AEs.

Table 5 **Analysis of AEs in subgroups**

Group	Age (yr)	Total	Grade	No.	Occurrence Time				Relationship with Treatment				Treatment			Remission Time	
					Visits 0–1	Visits 1–3	Visits 4–6	Visits 7–9	Visits 10–12	Not Related	Maybe Not Related	Maybe Related	Related	None	Pharmacotherapy	Others	0–7 Days	8–14 Days
SLIT	3–5	29	Grade 1	20	4	4	6	2	1	9	7	4	0	11	9	0	16	4
			Grade 2	9	0	2	4	5	1	5	3	1	0	2	7	0	9	0
	6–13	25	Grade 1	23	7	9	5	2	0	6	11	5	1	12	10	1	17	6
			Grade 2	2	0	1	0	1	0	1	1	0	0	0	2	0	2	0
Control	3–13	11	Grade 1	10	1	9	1	0	0	6	1	4	0	8	3	0	11	0
			Grade 2	1														

AEs = adverse events; SLIT = sublingual immunotherapy.

Figure 5. *The TASS, AMS, and PEF (percent predicted) in the SLIT and control group during the study (mean ± SE). (a) TASS; (b) AMS; (c) The PEF (percent predicted; †$p < 0.05$ and *$p < 0.01$ compared between groups). TASS, total asthma symptoms score; AMS, asthma medications score; PEF, peak expiratory flow; SLIT, sublingual immunotherapy.*

Therefore, whether asthma severity or history of other allergic diseases puts children at a higher risk of AEs may need more investigation. The AEs in this study mainly occurred in the respiratory tract, whereas few of them were related to treatment. This study further confirmed the safety of SLIT in very young children and provided more information in details, which is consistent with other postmarketing studies.[17,18]

The main limitation of this study is the absence of a placebo-controlled group. However, the reductions of clinical scores in this study were above the possible placebo effect, which may account for up to 30%[30] and the scope of SLIT effect (10–45%), which is summarized from previous studies.[22,31] Therefore, the improvements in clinical scores in this study may not be simply attributed to a psychological effect. On the other hand, it is difficult to determine the accurate onset time of SLIT efficacy in open studies as a result of possible placebo effects. The placebo-controlled studies[32–34] have indicated that the onset time of SLIT efficacy ranges from 14 to 24 weeks and also suggests that SLIT is usually effective within 2–4 months.[16]

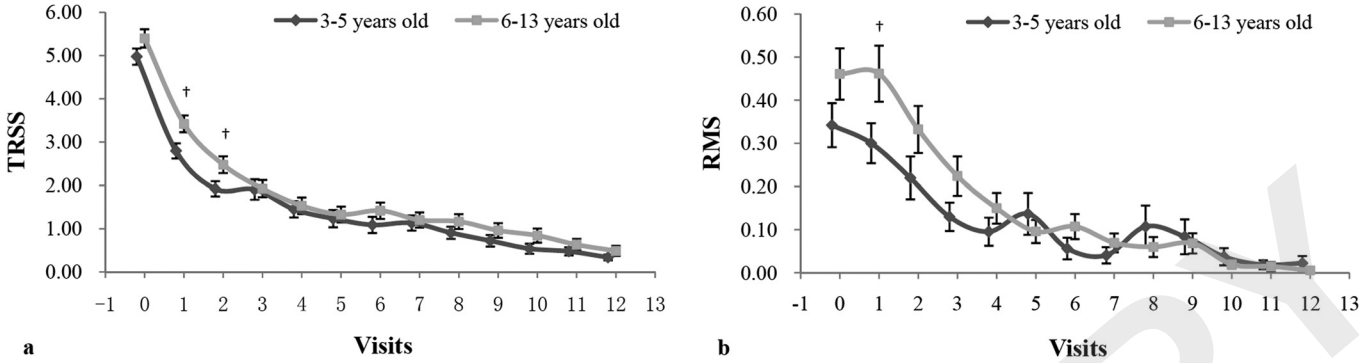

Figure 6. The TRSS and RMS in children 3–5 years old and 6–13 years old during the SLIT procedure (mean ± SE). (a) TRSS; (b) RMS (†$p < 0.05$ compared between groups). TRSS, total rhinitis symptoms score; RMS, rhinitis medications score; SLIT, sublingual immunotherapy.

Table 6 **Comparison of sIgE, sIgG4, and sIgE/sIgG4 between children 3–5 yr old and 6–13 yr old at visits 0 and 12 (mean ± SE)**

	3–5 yr Old		6–13 yr Old	
	Visit 0	**Visit 12**	**Visit 0**	**Visit 12**
sIgE (kU/L)	68.38 ± 3.64	65.82 ± 3.68*	65.82 ± 4.01	62.96 ± 3.89*
sIgG4 (mg/L)	626.62 ± 28.21	1142.62 ± 48.27*	645.13 ± 24.69	1186.18 ± 44.42*
sIgE/sIgG4	0.12 ± 0.01	0.06 ± 0.00*	0.11 ± 0.01	0.05 ± 0.00*

$p < 0.01$ compared with visit 0.
sIgE = Dermatophagoides farinae–*specific IgE; sIgG4* = Dermatophagoides farinae–*specific IgG4.*

Therefore, the fast significant improvement in the first few months in this study may be derived from multiple and synergism effects and the heterogeneity of onset time among studies may be owing to the differences in the dose, administration intervals, composition and activities of vaccines, patients and disease severity, *etc*. Furthermore, studies[32,34,35] of immunotherapy have also indicated that the placebo effect may decrease or stagnate over time, and the review article[31] also suggests that the effects of immunotherapy in the open-label clinical trials could be appreciated after several months. The subsequent improvements in this study, especially those after the 7th month, may also not be simply attributed to psychological effects, because they are only continued and maintained in the SLIT group as reported by other studies.[25,26] In other words, these results may also imply that the benefits from SLIT treatment may become increasingly apparent as the treatment is performed. The other limitation is the short time of study. Despite that, a significant divergence of clinical scores between groups has arisen and was maintained during the last few months. The long-term observation of efficacy and safety of SLIT is under way.

In conclusion, this study indicates that adding SLIT to pharmacotherapy is effective and safe for children aged 3–13 years with HDM-induced AR with or without asthma. For physicians, adjustment of medication and evaluation of efficacy of SLIT can be reliable and should be taken into consideration after ~7 months of SLIT. This study addressed SLIT in children <5 years old, which is rarely reported in the literature.

ACKNOWLEDGMENTS

The authors thank De-Yun Wang (Singapore) for kindly reviewing this article.

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