

# Fast Onset of Action of Sublingual Immunotherapy in House Dust Mite-Induced Allergic Rhinitis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

De-Hui Wang, MD, PhD; Lei Chen, MD, PhD; Lei Cheng, MD, PhD; Ke-Nan Li, MBBS;  
Hu Yuan, MD; Ji-Hong Lu, RN; Han Li, MD

**Objectives/Hypothesis:** To investigate how quickly an allergic rhinitis (AR) patients' symptoms will improve with sublingual immunotherapy (SLIT).

**Study Design:** Double-blind placebo study.

**Methods:** This is a multicenter, randomized, double-blind, placebo-controlled study of SLIT used to treat house dust mite-induced AR. A total of 120 AR patients, aged 4 to 60 years, were treated for 6 months and randomized into two groups: 1) SLIT with *Dermatophagoides pteronyssinus* (*D.p.*) and *Dermatophagoides farinae* (*D.f.*) extract (n = 60); and 2) matched placebo controls (n = 60). Symptom, medications received, and a visual analog scale score were recorded during the whole study. Serum-specific IgE and IgG4 to *D. p.* and *D. f.* were assessed before and after the treatment.

**Results:** Eighty-five patients (70.8%) completed the study. Twelve patients (20%) chose to withdraw from the SLIT group, but none because of serious adverse effects. The total symptom and visual analog scores VAS in the SLIT group decreased significantly when compared to the placebo controls ( $P < 0.05$ ) after week 14, as well as for the significant ( $P < 0.05$ ) improvement of all individual AR symptoms in the SLIT group (e.g., sneezing, nasal discharge, itching, and nasal obstruction) after week 22. There was a significant ( $P < 0.05$ ) increase of IgG4 to both *D.f.* and *D.p.* in the SLIT, but not in the placebo group after treatment.

**Conclusion:** SLIT with a mixture of *D.f.* and *D.p.* extract is an effective and safe treatment for patients with house dust mite-induced AR. Its onset of action can be observed as early as 14 weeks after treatment.

**Key Words:** Sublingual immunotherapy, house dust mite, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, efficacy, serum sIgG4, serum sIgE.

**Level of Evidence:** 1B.

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## INTRODUCTION

*Dermatophagoides pteronyssinus* (*D.f.*) and *Dermatophagoides farinae* (*D.p.*) are the most common indoor allergens worldwide, causing allergic diseases such as allergic rhinitis (AR) and asthma.<sup>1–3</sup> Although AR is a non-life threatening disease, it will affect a patient's quality of life and may result in social economic problems and the onset of asthma through its natural processes.<sup>4–6</sup> Among available treatments, allergen-specific immunotherapy is known to have long-lasting

clinical efficacy and may prevent the development of new sensitivities.<sup>7</sup> Sublingual immunotherapy (SLIT) has been recommended as a safe and effective therapy by the World Allergy Organization (WAO), based on clinical and research data from many well designed, randomized, double-blind, placebo-controlled trials.<sup>7</sup>

In China, allergen-specific immunotherapy was first used clinically in the early 1950s. The allergen extracts used were prepared by individual hospitals and were not standardized. In 2006, "Chanllergen," a vaccine made with a single extract of *Dermatophagoides farinae* (*D.f.*) (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China), was produced by a Good Manufacturing Practice (GMP) factory. It was introduced for clinical use in China and was approved by the Chinese State Food and Drug Administration (SFDA). Although its efficacy and safety for AR and asthma had been confirmed,<sup>8,9</sup> because a large proportion of AR patients are sensitized to both *D.p.* and *D.f.*, there is need for a mixture of *D.f.* and *D.p.* extracts for SLIT.

This study was carried out in a multicenter, randomized, double-blind, placebo-controlled design investigating the efficacy of AR symptom improvement and changes in serum sIgE and sIgG4, using a mixture of an extract of *D.p.* and *D.f.* for SLIT in patients with

From the Department of Otolaryngology (D-H.W., K-N.L., H.L.), Eye & ENT Hospital, Fudan University, Shanghai; the Department of Otorhinolaryngology (L. CHEN., H.Y.), Chinese PLA General Hospital, Beijing; and the Department of Otorhinolaryngology (L. CHENG., J-H.L.), the First Affiliated Hospital, Nanjing Medical University, Nanjing, People's Republic of China.

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Send correspondence to De-hui Wang, MD, PhD, Department of Otolaryngology, Eye & ENT Hospital, Fudan University, 83 Fenyang RD, Shanghai, 200031 People's Republic of China.  
E-mail: wd199012@163.com

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| TABLE I.<br>Treatment Protocol and Daily Dose of <i>D.f.</i> and <i>D.p.</i> Extract. |              |             |            |                       |             |
|---------------------------------------------------------------------------------------|--------------|-------------|------------|-----------------------|-------------|
|                                                                                       | Week 1       | Week 2      | Week 3     | Week 4~5 <sup>*</sup> | Week 6+     |
|                                                                                       | (0.75 µg/ml) | (7.5 µg/ml) | (75 µg/ml) | (250 µg/ml)           | (750 µg/ml) |
| Day 1                                                                                 | 0.05 ml      | 0.05 ml     | 0.05 ml    | 0.15 ml/day           | 0.10 ml/day |
| Day 2                                                                                 | 0.10 ml      | 0.10 ml     | 0.10 ml    |                       |             |
| Day 3                                                                                 | 0.15 ml      | 0.15 ml     | 0.15 ml    |                       |             |
| Day 4                                                                                 | 0.20 ml      | 0.20 ml     | 0.20 ml    |                       |             |
| Day 5                                                                                 | 0.30 ml      | 0.30 ml     | 0.30 ml    |                       |             |
| Day 6                                                                                 | 0.40 ml      | 0.40 ml     | 0.40 ml    |                       |             |
| Day 7                                                                                 | 0.50 ml      | 0.50 ml     | 0.50 ml    |                       |             |

<sup>\*</sup>Children younger than 14 years old use 250 µg/ml as maintenance dose; subjects older than 14 years old use 750 µg/ml as maintenance dose after week 5.

house dust mite-induced AR. The use of this extract (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China) was approved by the Chinese State Food and Drug Administration (SFDA).

## MATERIALS AND METHODS

### Study Subjects

A total of 120 patients aged 4 to 60 years with AR were randomly assigned to receive SLIT ( $n = 60$ ) or a placebo ( $n = 60$ ). All of the patients had moderate to severe persistent AR with or without asthma, based on the criteria for diagnosis and the classification of AR from the documents of "Allergic Rhinitis and Its Impact on Asthma."<sup>10</sup> All patients had a positive skin prick test, with a wheal size of  $\geq 3$  mm in diameter for both *D.f.* and *D.p.* using a standardized extract (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China). Also confirmed was the positive serum-specific IgE (ImmunoCAP, Phadia, Uppsala, Sweden),  $\geq 0.7$  kU/L to both *D.f.* and *D.p.* Exclusion criteria included all contraindications for SLIT, participation in other clinical trials within the preceding 3 months, or having received any other vaccinations before this study.

The study was conducted in the Outpatient Clinics of the Departments of Otolaryngology, at the Eye & ENT Hospital, Fudan University; the First Affiliated Hospital, Nanjing Medical University; and Chinese PLA General Hospital (Beijing). This was in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice (2003 revision, China). The study protocol was approved by the Ethics Committees of all three hospitals, and a written informed consent was obtained from each patient (or from their guardians if the subject was less than 18 years old) prior to their participation in the trial.

### Dust Mite Extract

Mixture extracts of *D.f.* and *D.p.* (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China) were used in this study. The extracts included five treatment dosages with different concentrations: 0.75 µg/ml (No. 1 preparation), 7.5 µg/ml (No. 2 preparation), 75 µg/ml (No. 3 preparation), 250 µg/ml (No. 4 preparation), and 750 µg/ml (No. 5 preparation). The solvent used was a physiologic saline solution with 50% glycerol. The step-up dosage protocol was standardized and is shown in Table I. All preparations were taken sublingually, kept under the tongue for 1 to 3 minutes, and then swallowed.

## Study Protocol

This study was carried out from October 2008 to March 2010. Each patient being treated for a 6-month period. A total of 120 patients were randomly allocated into the SLIT group ( $n = 60$ ) and or the placebo group ( $n = 60$ ), following a table of random numbers provided by the Department of Health Statistics of Fudan University, which was not directly involved in the administration of this study. The group allocation number, together with the statistical analysis, was kept unreleased by the administrator until the whole trial was completed.

The SLIT group received an extract mixture of *D.f.* and *D.p.*, while the placebo group received a placebo in the same way. The placebo solutions were the solvent in the extract, which matched the flavor of the actual treatment (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., China).

The screening period lasted for 8 weeks, and was followed by a 2-week washout period prior to starting the treatment (week 0) (Fig. 1). Ten visits were arranged for the first day of weeks 1, 2, 3, 4, 6, 10, 14, 18, and 22, as well as the last day of week 25 during the treatment period. In both the screening period and visit 10, 3 ml of peripheral blood was taken from the study patients for the measurement of serum sIgE and sIgG4 against *D.p.* and *D.f.*, plus clinical chemistry parameters for safety evaluations together with a routine urine test. Meanwhile, the demographic information, skin prick test (to a common panel of inhalant allergens including *D.p.* and *D.f.*), and vital signs were recorded at visit 1 for a baseline assessment. A visual analogue scale,<sup>11</sup> symptom, and medicine score were recorded at all study visits.

### Symptom and Medication Scoring

During the treatment, patients (or their parents for the children) were required to fill out a symptom and medicine score on a diary card that was evaluated by the investigators at every visit. Each nasal symptom was scored (Table II) from 0 to 3, including sneezing (number/day, 0 = none, 1 = 3–5, 2 = 6–10, and 3 =  $\geq 11$ ), nasal discharge (times/day, 0 = none, 1 =  $\leq 5$ , 2 = 5–9, and 3 =  $\geq 10$ ), itching (0 = none, 1 = intermittent itching, 2 = tolerable itching, and 3 = intolerable itching), and nasal obstruction (0 = none; 1 = congestion, but no mouth breathing; 2 = severe congestion, with occasional mouth breathing; 3 = severe congestion, with mouth breathing during the whole day). The total symptom score was the sum of the four individual symptom scores.

Patients were allowed to use only loratadine for controlling rhinitis' symptoms. Medication scores were recorded following the formula 1 point = 20 mg loratadine. Other medicines for AR (only if needed) were calculated as 1 additional point. Subjects who used systemic glucocorticoid steroids were excluded from the trial.

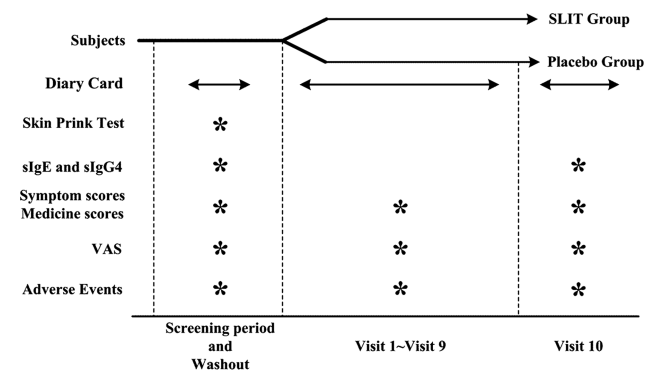


Fig. 1. Treatment phase.

TABLE II.  
Grading Criteria for the Severity of Nasal Symptom Score.

| Score                       | Severity |                                         |                                                         |                                                  |
|-----------------------------|----------|-----------------------------------------|---------------------------------------------------------|--------------------------------------------------|
|                             | 0        | 1                                       | 2                                                       | 3                                                |
| Sneezing (numbers/time)     | 0        | 3–5                                     | 6–10                                                    | ≥11                                              |
| Nasal discharge (times/day) | 0        | ≤5                                      | 5–9                                                     | ≥10                                              |
| Nasal itching               | None     | Intermittent itching                    | Itching, but tolerable                                  | Severe itching, intolerable                      |
| Nasal obstruction           | None     | No oral breathing, but nasal congestion | Severe nasal congestion, with occasional oral breathing | Complete congestion, with oral breathing all day |

Adapted from the Practical Guideline for the Diagnosis and Treatment of Allergic Rhinitis in Lanzhou, China, 2004.

### Visual Analogue Scale<sup>11</sup>

A 10-point scoring system based on neuro-biophysics and physiology was used to assess the patients' subjective symptoms. This system links the patient's feelings to an objective representation. Patients were asked to subjectively assess the severity of their symptoms on a 100-mm visual analogue score (VAS)<sup>11</sup>; the 0-point mark represented no symptoms, while the 10-point mark indicated symptoms that were extremely severe. At each visit, study patients were asked to mark a line on the VAS. The investigator would then read the actual point on the back side of the VAS, which was then recorded.

### Serum-Specific Antibody Assays

Serum-specific IgE levels to *D.p.* and *D.f.* were determined using the Pharmacia UniCAP System (ImmunoCAP, Phadia, Uppsala, Sweden). IgG4 levels were tested using commercial kits purchased from the Dr. Focke Laboratorien GmbH (Neuss, Germany) through the Standard Operating Procedures (SOP). IgE values were expressed as kU/L, and IgG4 were expressed in µg/ml.

### Assessment of Potential Side-Effects

Clinical chemistry parameters were measured at the screening visit and visit 10 to assess for potential adverse events. In addition, all potential adverse events (AE)<sup>12</sup> were recorded, and the cause of AEs was assessed by the investigator. AEs were divided into five levels, as recommended by the European Academy of Allergy and Clinical Immunology (EAACI).<sup>13</sup> The duration, treatment, and final consequence of each AE were also recorded.

### Statistical Analysis

Statistical analysis was carried out using SAS9.2. All tests were two-tailed, and the level of significance was set at 0.05. ANOVA or chi-square test was used for a baseline assessment, as well as for testing the values within the group (baseline vs. each study visit). Both the *t* test and the Wilcoxon test were used to determine the difference between SLIT and placebo groups. For unordered categorical variables, a Fisher test was used, but a CMH chi-square test was used for ordinal categorical variables. All data are shown as mean ± SD.

## RESULTS

### Patients

A total of 143 patients were screened; 120 patients were recruited and randomized into the SLIT and placebo groups. Twenty percent of the subjects dropped out

from the SLIT group (12 out of 60), while 38% in the placebo group (23 out of 60) dropped out. One subject in the placebo group did not follow the protocol and was excluded right before the treatment. The main reason for dropout in both study groups was the patients' personal wish to end the study. There were no known health-related issues (Fig. 2). All study subjects showed a normal result in clinical chemistry parameters of the blood and routine urine test before and after the study. Demographic and baseline measurements data are summarized in Table III. There were no significant differences between the SLIT and placebo groups.

### Improvement of AR Symptoms

The total and mean symptom scores of sneezing, nasal discharge, itching, and nasal obstruction at each visit are shown in Figure 3. A significant decrease in the total symptom scores (Fig. 3, A) between the SLIT and placebo groups ( $P < 0.05$ ) started at week 14. In the SLIT group (Fig. 3, A), all four individual symptoms had steadily decreasing scores, while there was no change in the placebo group throughout the study. In the SLIT group, the nasal itching score was significantly lower than the placebo group after week 14 ( $P < 0.05$ ), while nasal obstruction and sneezing scores showed a significant difference after week 22 ( $P < 0.05$ ).

### Medication Score

In general, there was no significant difference between the SLIT and placebo groups in the daily medication score at each visit. In the SLIT group, daily medications at visits 7, 9, and 10 were significantly lower than the baseline scores ( $P < 0.05$ ), but no significant change was found in the placebo group compared to its baseline.

### Visual Analogue Scale

A significant decrease ( $P < 0.05$ ) in the VAS scores was found starting from week 2 in the SLIT group, but also in the placebo group from week 3. For comparison between the groups, a statistically significant difference with a lower VAS is found in the SLIT group starting at week 14 (Fig. 3, B). This difference becomes more pronounced until the end of treatment.

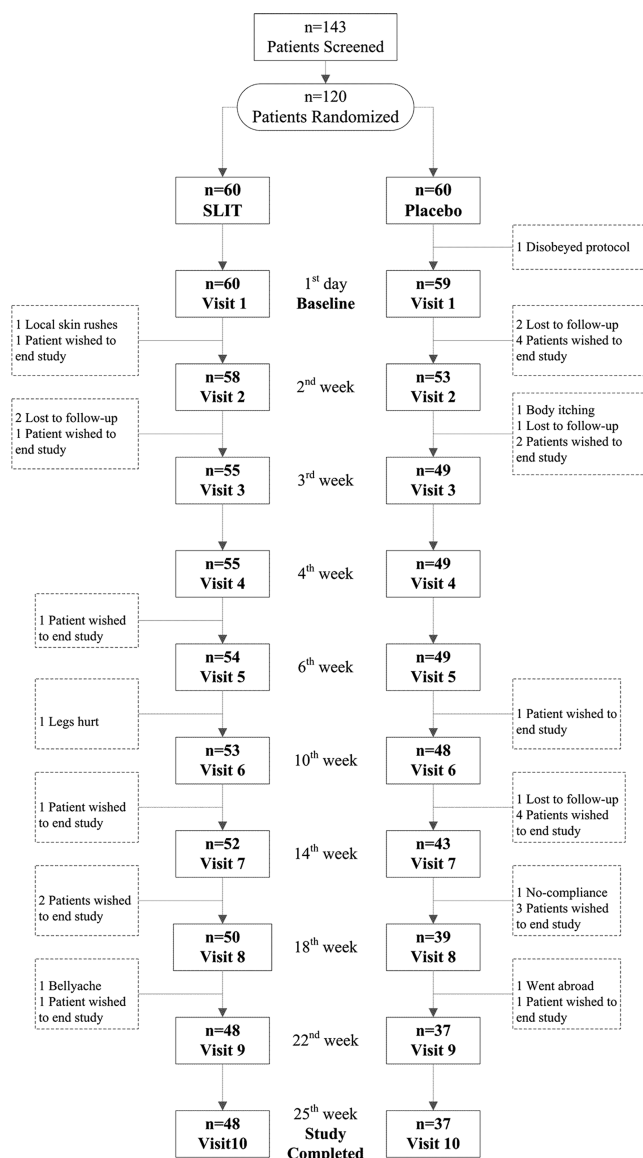


Fig. 2. Flow charter of study design, randomization and follow-up of study patients.

### Serum-Specific IgE and IgG4 Antibodies

There was no statistical difference in the concentrations of serum-specific IgE antibodies between the SLIT and placebo groups before and after treatment.

There is a significant increase in the concentration ( $\mu\text{g/ml}$ ) of serum-specific IgG4 to both *D.f.* and *D.p.* in the SLIT group, but not in the placebo group. The changes of IgG4 to *D.f.* and *D.p.* were significantly higher in the SLIT group when compared to the placebo groups ( $P < 0.05$ ) (Table IV).

### Assessment of the Potential Side-Effects

There were no serious adverse events reported throughout the study. Adverse events reported were only mild to moderate (Table V).<sup>12</sup> There were no significant differences between the two study groups in the number

and severity of AEs or the number of patients who developed AEs.

## DISCUSSION

This multicenter, randomized, double-blind, placebo-controlled trial investigated the efficacy and the safety of SLIT with *D.f.* and *D.p.* mixture extracts in the treatment of house dust mite-induced AR. This study focused on answering some common and important clinical questions in SLIT practice, such as the onset of AR/asthma symptom improvement, potential side-effects, common reasons for dropout, and changes of biomarkers (e.g., serum-specific IgE/G4 to house dust mite allergens)

TABLE III.  
Demographic and Clinical Characteristics of the Study Patients at the Baseline.

| Characteristics                                 | SLIT<br>(n = 60) | Placebo<br>(n = 60) |
|-------------------------------------------------|------------------|---------------------|
| Gender (male/female)                            | 35/25            | 31/29               |
| Age (years)                                     | 22.7 $\pm$ 10.9  | 26.8 $\pm$ 13.2     |
| Height (cm)                                     | 1.6 $\pm$ 0.2    | 1.6 $\pm$ 0.1       |
| Weight (Kg)                                     | 54.9 $\pm$ 17.3  | 57.1 $\pm$ 11.8     |
| Body temperature ( $^{\circ}\text{C}$ )         | 36.6 $\pm$ 0.3   | 36.6 $\pm$ 0.3      |
| Breath (/min)                                   | 19 $\pm$ 2       | 19 $\pm$ 2          |
| Heart Rate (/min)                               | 76 $\pm$ 10      | 75 $\pm$ 9          |
| SeSBP (mmHg)                                    | 107 $\pm$ 12     | 111 $\pm$ 15        |
| SeDBP (mmHg)                                    | 68 $\pm$ 11      | 71 $\pm$ 10         |
| Physical examination<br>(normal/abnormal)       | 6/54             | 6/53                |
| ECG (% normal)                                  | 80               | 75                  |
| Specific IgE <i>D.f.</i> (KUA/L)                | 50.9 $\pm$ 37.5  | 44.1 $\pm$ 36.7     |
| Class of specific IgE <i>D.f.</i>               | 4.3 $\pm$ 1.3    | 4.1 $\pm$ 1.3       |
| Specific IgE <i>D.p.</i> (KUA/L)                | 50.9 $\pm$ 38.5  | 43.0 $\pm$ 38.2     |
| Class of specific IgE <i>D.p.</i>               | 4.3 $\pm$ 1.3    | 4.1 $\pm$ 1.3       |
| Level of skin prick test <sup>*</sup>           |                  |                     |
| <i>D.f.</i> (%)                                 |                  |                     |
| +                                               | 0.0              | 0.0                 |
| ++                                              | 15.0             | 18.3                |
| +++                                             | 26.7             | 31.7                |
| ++++                                            | 58.3             | 50.0                |
| <i>D.p.</i> (%)                                 |                  |                     |
| +                                               | 0.0              | 0.0                 |
| ++                                              | 15.0             | 16.7                |
| +++                                             | 28.3             | 33.3                |
| ++++                                            | 56.7             | 50.0                |
| Allergic rhinitis coexisting<br>asthma (yes/no) | 3/56             | 2/58                |
| Symptom score <sup>†</sup>                      | 6.7 $\pm$ 1.8    | 6.8 $\pm$ 1.8       |
| Medicine score <sup>‡</sup>                     | 0.4 $\pm$ 1.1    | 0.3 $\pm$ 0.7       |
| Visual Analogue Scale score                     | 6.8 $\pm$ 1.7    | 6.2 $\pm$ 1.7       |

Data present in this table are mean  $\pm$  standard deviation.

<sup>\*</sup>The diameter of tested wheel divided by the diameter of standard positive control solution; + = 25~50%, ++ = 51~100%, +++ = 101~200%, ++++ = >200%.

<sup>†</sup>The sum of 4 symptoms' score (sneezing, nasal discharge, itching and nasal obstruction).

<sup>‡</sup>Daily medication score in the baseline.

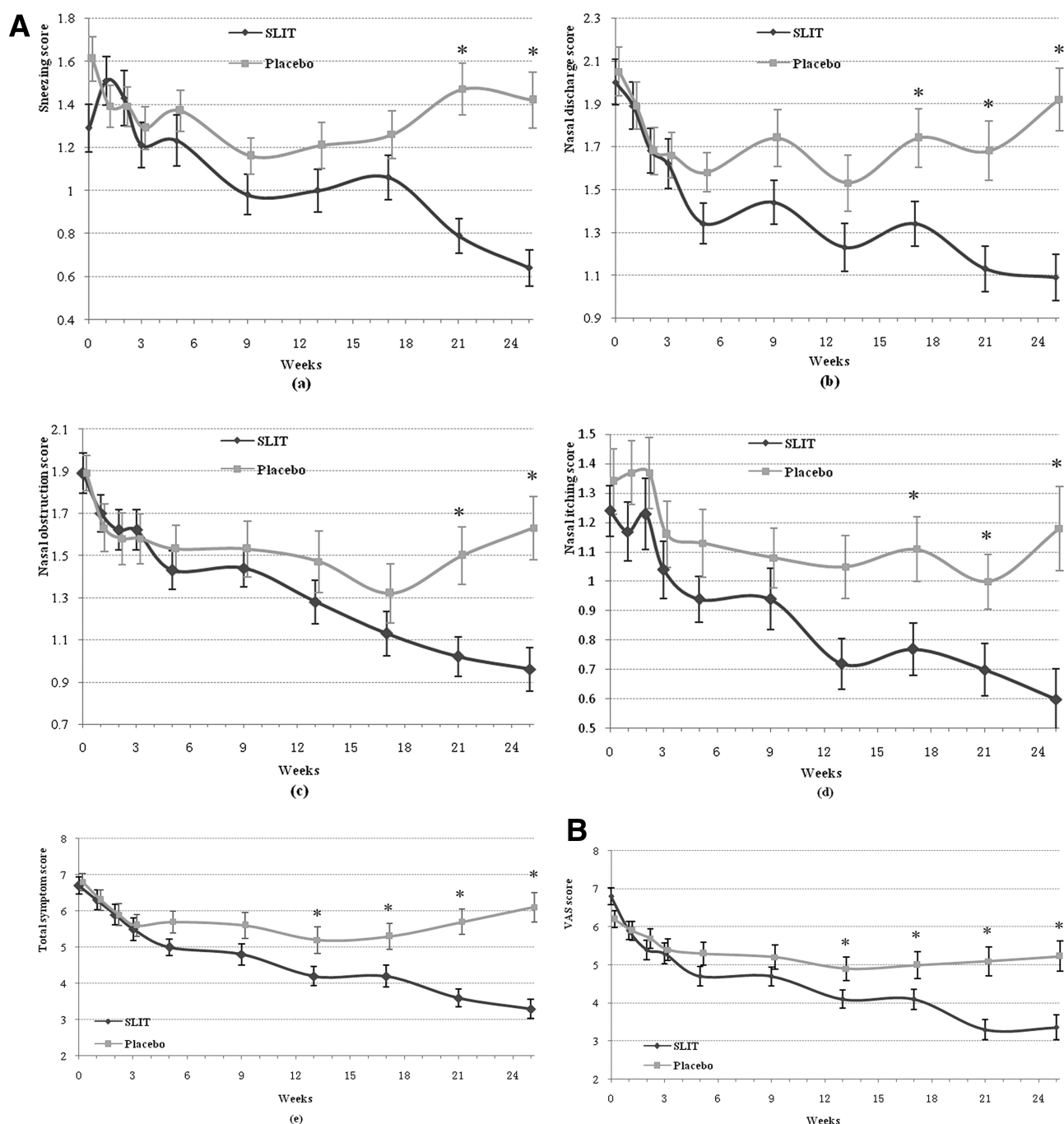


Fig. 3. The mean individual and total symptom scores (A) and VAS scores (B) in the SLIT and placebo groups. \* $P < 0.05$  (between group, ANOVA test; Bars are standard errors). A = Symptom scores B = VAS score.

during the initial 6 months of SLIT. The majority of dropouts were commonly found during this initial 6-month period in other clinical studies.<sup>14,15</sup> Our results show that after a 6-month treatment, patients in the SLIT group have shown a significant improvement in AR symptom. This is consistent with two review articles where SLIT therapy for 6 months or less could significantly improve AR symptoms.<sup>16,17</sup> Furthermore, our data shows that the onset of clinical efficacy can be found as early as 14 weeks after starting treatment.

This finding is also supported by the improvement in VAS after 14 weeks of treatment.

In the literature, it is reported for SLIT that a different cumulative dose might generate a different clinical efficacy,<sup>18–20</sup> a daily lower-dose regimen might be more effective in reducing the medicine score,<sup>21</sup> and the choice of maintenance dose and duration could also affect the outcomes of SLIT.<sup>14</sup> Lombardi et al. reviewed 41 studies, which found that the up-dosing phase was unnecessary and once-a-day administration had the

TABLE IV.  
Comparison Between Serum sIgG4 to *D.f.* and *D.p.* Between the SLIT and Placebo Groups.

|                                                    | SLIT          |               |               | Placebo       |               |               | Group Difference |
|----------------------------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|------------------|
|                                                    | Day 1         | Week 25       | Change        | Day 1         | Week 25       | Change        | Change           |
| Specific sIgG4 to <i>D.f.</i> ( $\mu\text{g/ml}$ ) |               |               |               |               |               |               |                  |
| Mean $\pm$ SD                                      | 2.3 $\pm$ 1.9 | 4.3 $\pm$ 3.8 | 2.2 $\pm$ 3.7 | 2.6 $\pm$ 2.1 | 4.6 $\pm$ 9.7 | 1.8 $\pm$ 8.5 |                  |
| <i>P</i> value                                     |               |               | $p < 0.05$    |               |               | $p > 0.05$    | 0.0295           |
| Specific sIgG4 to <i>D.p.</i> ( $\mu\text{g/ml}$ ) |               |               |               |               |               |               |                  |
| Mean $\pm$ SD                                      | 2.1 $\pm$ 1.7 | 3.8 $\pm$ 3.2 | 1.8 $\pm$ 3.1 | 2.4 $\pm$ 2.0 | 2.6 $\pm$ 2.4 | 0.1 $\pm$ 1.5 |                  |
| <i>P</i> value                                     |               |               | $p < 0.05$    |               |               | $p > 0.05$    | 0.0303           |

advantage of convenience and compliance in SLIT for pollen allergens.<sup>14</sup> In this study we have chosen a once-a-day regimen that has been proven to be effective and has good patient compliance. A worldwide SLIT optimal maintenance dose for dust mite-induced AR has not been established. Even though each extract's unit has been translated into micrograms for the major allergens, it is still not possible to show the potency of the allergens.<sup>22</sup> Thus, it will be important in future studies to investigate the specific dose schedule of SLIT using *D.p.* and *D.f.* extracts in the treatment of AR.

It is recommended in the WAO position article (2009) that serum-specific IgG4, but not IgG1, IgG2, and IgG3, is the most important immune globulin in circulating IgG and could be biologically (or clinically) relevant in functional assays for immunotherapy.<sup>7</sup> In one study, the change in serum-specific IgG4 was found associated with a decrease in AR symptoms.<sup>23</sup> Furthermore, it was reported that higher maintenance doses could generate higher specific serum IgG4 levels, and in general they reached a plateau (2–30 folds) after 12 months of immunotherapy.<sup>22</sup> In this study, we have only measured serum-specific IgG4 to house dust mite allergens (*D.f.* and *D.p.*) in order to monitor the systemic immune response after SLIT. In the literature, however, other biomarkers have been reported in association with SLIT, such as: 1) specific antibodies (IgE, CD23, IgA, IgG4, and IgG); 2) effector cells (eosinophils, neutrophils, mast cells, and basophils); 3) T cells and cytokines (Th1, Th2, and regulatory T cells, e.g., CD4+, CD8+, CD25+, and Foxp3+/CD127lo cells), and their related cytokines (e.g., IL3, IL4, IL5, IL9, IL10, IL13, IL17, IL18, IFN- $\gamma$ ), and the signaling lymphocytic activation molecule (SLAM).<sup>7,22,24</sup>

In our study, we did not see a significant change in serum sIgE antibody to *D.f.* and *D.p.* in either the SLIT or control groups. In contrast to other studies, Guez et al. found that after 12 and 24 months of SLIT treatment, sIgE did not change significantly in either the active or placebo group.<sup>25</sup> Tonnel et al. found a significant decline in sIgE after 12-month treatment with SLIT.<sup>26</sup> A 3-year SLIT trial in children mono-sensitized to house dust mites suggested that serum sIgE could increase spontaneously with the onset of allergic disease.<sup>27</sup> A meta-analysis showed that a total of 1,334 patients who were allergic to house dust mites and pollen and then treated with SLIT for 6 to 12 months

did not show a significant change in sIgE.<sup>16</sup> In a meta-analysis report (Willson et al. 2005), six SIT studies showed no significant relation between allergen-specific IgE and the change of clinical symptoms. In another eight studies, there was no significant differences between the treatment and placebo groups in serum sIgE.<sup>17</sup>

From our study, serum sIgG4 to *D.f.* and *D.p.* increased significantly after SLIT, but not with placebos. sIgG4 may engage the low-affinity Fc receptors and act as blocking antibodies,<sup>28</sup> while it might also inhibit the release of histamine and systemic increases of the IgE response.<sup>29,30</sup> However, the clinical significance of measuring serum sIgG4 remains unclear as some studies did not find any relevance between serum sIgG4 levels and the AR symptom scores.<sup>25,31,32</sup> Bush and colleagues found that with improving AR symptoms, serum sIgG4 increased,<sup>18</sup> which probably means SLIT had an effect on the subjects' immune system.

It is reported in two recent review articles that SLIT had an average adherence rate of 75% to 90%.<sup>14,33</sup> The initial period of SLIT is crucial for compliance as the majority of dropouts occurred during this period.<sup>19,20</sup> In our study, the overall compliance rate was 70%, which is similar to other reports in the literature. As SLIT is still new in China, data from this study will be useful in gaining clinical information about SLIT. The dropout rate was higher in the placebo group (38%) than in the SLIT group (16%). It appears that there were no known health-related issues (Table V), and the main

TABLE V.  
Drug-Related AEs in the Study.

|                                   | Study Group   |                 |
|-----------------------------------|---------------|-----------------|
|                                   | SLIT (n = 15) | Placebo (n = 7) |
| Aggravating rhinitis              | 5             | 5               |
| Local rashes                      | 3             | 1               |
| Bellyache                         | 3             | 0               |
| Upper respiratory tract infection | 0             | 1               |
| Diarrhea                          | 1             | 0               |
| Thirst                            | 1             | 0               |
| Oral itch                         | 1             | 0               |
| Local swell                       | 1             | 0               |

reason for dropout in both study groups was the patients' personal wish to end the study.

All the adverse events reported in our study were also commonly reported in other SLIT studies.<sup>34–37</sup> These included oral itching, local rashes, and aggravation of the patient's rhinitis. In compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice (in China), the study subjects were allowed to withdraw from the study without giving any explanation. SLIT is still considered a new therapy for AR in China. In order to improve the patients' compliance in both clinical treatment and trials, as well as to achieve good clinical results and their participation in future SLIT trials, it is important to introduce a comprehensive program that increases knowledge.

## CONCLUSION

SLIT with a mixture of *Dermatophagoides farinae* (*D.f.*) and *Dermatophagoides pteronyssinus* (*D.p.*) extracts have shown a significant improvement in allergic rhinitis symptoms, with an onset of action by 14 weeks and acceptable safety profiles.

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