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ORIGINAL ARTICLE

# Clinical evaluation for sublingual immunotherapy with *Dermatophagoides farinae* drops in adult patients with allergic asthma

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**Abstract**
*Purpose* The efficacy and safety of sublingual immunotherapy (SLIT) in house dust mite-induced allergic asthma (AA) have yet to be firmly established, especially in adult patients. Our objective is to evaluate the efficacy of SLIT with *Dermatophagoides farinae* drops in adult patients with AA.
*Methods* One hundred and thirty-four adult patient data with house dust mite (HDM)-induced AA who had been treated for 2 years were collected. These patient data that we collected were divided into the SLIT group ($n = 85$) and control group ($n = 49$). All patients were treated with low to moderate dose of inhaled glucocorticoid and long-acting β2 agonists. Patients in the SLIT group were further treated with *D. farinae* drops. Clinical scores including the total asthma symptom score (TASS), total asthma medicine score (TAMS), asthma control test (ACT), and peak flow percentage (PEF%) were assessed before treatment and at yearly visits. The presence of adverse events (AEs) were recorded once a month.
*Results* Before treatment, the PEF% in the SLIT group was significantly lower than that in the control group ($p < 0.05$). After 2 years, both treatments were effective in the clinical scores when compared with baseline values (all $p < 0.001$). Meanwhile, the SLIT group showed significantly lower TASS and TAMS (all $p < 0.001$) and higher ACT ($p < 0.001$) and PEF% ($p < 0.05$) when compared with the control group. No severe systemic AEs were reported.
*Conclusions* SLIT with *D. farinae* drops plus pharmacotherapy is more effective than routine drug treatment in adult patients with AA.

**Keywords** Adult patient · Allergic asthma · Sublingual immunotherapy

## Introduction

Allergic asthma (AA) is characterized by chronic inflammation which results in recurrent attacks of cough, wheezing, sometimes chest tightness, and variable airflow obstruction [1]. It is a major public health problem affecting over 300 million people worldwide. It is estimated that by 2025, an additional 100 million people may develop AA [2]. The prevalence of asthma is 1 to 18% [3], with two thirds of all asthma estimated to be of an allergic etiology [4].

In patients with allergic rhinitis and/or asthma tested for allergic causality, a prevalence of house dust mite (HDM) sensitization around 48% has been reported [5]. In China, asthma affects 20 million people (prevalence 2.1%) [6]. HDM is the most prevalent allergen in this context [7]. The causal role of HDM in allergic asthma is well-established [8]. In China, the overall prevalence of positive skin prick responses was 59.0% for *Dermatophagoides farina* (DF), 57.6% for *Dermatophagoides pteronyssinus* (DP), 40.7% for *Blomia tropicalis*, 16.1% for American cockroach, 14.0% for dog, 11.5% for *Blatella germanica*, 11.3% for *Artemisia vulgaris*, 10.3% for cat, 6.5% for *Ambrosia artemisifolia*, 6.3% for mixed mold I, 4.4% for mixed mold IV, 3.5% for mixed grass pollen, and 2.2% for mixed tree pollen [9]. The allergen protein homology between DF and DP is as high as 80%. Therefore, there is high cross-reaction between the two allergens [10–12].

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According to the World Health Organization, the only currently available causal treatment for respiratory allergic disease is allergy immunotherapy (AIT). The use of AIT in allergic respiratory disease has long been acknowledged [13]. This unique therapy is the only effective disease-modifying treatment method for respiratory allergy, which may change the natural evolution of allergic diseases [14]. Its immunological mechanisms of action have been demonstrated as induction of allergen-specific immune tolerance by giving allergens to patients in repeated and increasing doses [15].

Recent meta-analyses and systematic reviews showed that sublingual immunotherapy (SLIT) may be beneficial to AA, while the effect size was small and highly variable [16–19]. Most studies were performed in children rather than adults. As *Dermatophagoides farinae* drops are the only standardized SLIT product in China, this retrospective study was aimed at evaluating the efficacy of SLIT with *D. farinae* drops in adult patients with AA.

## Materials and methods

### Study subjects

One hundred thirty-four adult patient data with HDM-induced mild to moderate AA (83 females, aged 20–68 years), who had been treated for 2 years, were collected from June 2011 to June 2013. Mandatory inclusion criteria were as follows: (1) All patients have non-acute exacerbation of mild to moderate asthma according to the Global Initiative for Asthma [20]. (2) Patients have a clinical history of mite allergy and sensitization to *D. farina* with/without *D. pteronyssinus* as assessed by a positive skin prick test (SPT) with a wheal size of ≥ 3 mm in diameter and grade ≥ 2 in area. (3) Before treatment, all vital signs of the patients, including body temperature, respiration, heart rate, and blood pressure, were normal, excluding gastrointestinal tract, liver, kidney, lung, and cardiovascular diseases. The exclusion criteria included the following: (1) patients with immunodeficiency; (2) patients with non-stable diseases or other concomitant system diseases; (3) patients with severe asthma or nasal polyposis, the peak expiratory flow being ≤ 70% of the predicted volume; and (4) patients with AR, AD, allergic conjunctivitis, or other allergic disease. The allergen skin prick kits were provided by Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd. SPT was performed according to standard protocol before treatment, using histamine (positive control) and normal saline (negative control) for comparison. A wheal size ≥ 3 mm was deemed as positive. The patients in the SLIT group and control group had no statistical differences in age, sex, vital signs, and patient's condition before therapy. This study was approved by the local ethical committee and was conducted in accordance with the ethical standards established in the declaration of Helsinki of 1946, and the patients provided informed consent.

### SLIT with HDM extract

All patients were treated with low to moderate dose of inhaled glucocorticoid and long-acting β2 agonists. Patients in the SLIT group were further treated with *D. farinae* drops. The standardized HDM allergen extract (CHANLLERGEN, *D. farinae* drops) used for SLIT was domestically manufactured by Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd. The biologically standardized extracts approved by the China Food and Drug Administration were labeled in concentration of total protein and used in the form of drops (No. 1, 1 μg/mL; No. 2, 10 μg/mL; No. 3, 100 μg/mL; No. 4, 333 μg/mL; and No.5, 1000 μg/mL). In the up-dosing phase of SLIT, patients were administrated with increasing dose starting from No. 1 to No. 3 during the first 3 weeks and one, two, three, four, six, eight, and ten drops were given day after day in a week, respectively. Then, the patients were instructed to have three drops of No.4 solution once daily during the fourth and fifth weeks. Maintenance therapy has two drops of No.5 per day from the sixth week to the end of the treatment. Drops were instructed to be kept under the tongue for 1–3 min before being swallowed.

### Clinical evaluation

During the whole course of the treatment, patients were instructed to keep a diary card and record all symptoms, medicine consumption, and side effects; meanwhile, all the patients were asked to accept follow-up visit at three time points, half a year, 1 year, and 2 years, with total asthma symptom score (TASS), total asthma medicine score (TAMS), asthma control test (ACT), and peak expiratory flow rate (PEF%) recorded. Outcome measures were as follows: (1) TASS was the sum of daytime asthma symptoms scores and nocturnal asthma symptoms scores. 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 [21]; (2) TAMS was calculated as follows (per day): 1 point for long-acting β2 agonists and 2 points for inhaled glucocorticoids. TAMS is the sum of all the recorded medicine scores [22]; (3) Asthma control test is an effective tool to assess the degree of asthma control. Twenty-five points mean well-controlled, 20–24 points mean partially controlled, and it is uncontrolled when the points are below 20 [23]; (4) Peak expiratory flow rate was calculated as a percentage of predicted normal value (PEF%).

**Table 1** The demographic and clinical characteristics before treatment in the SLIT group and control group

| Character | SLIT group | Control group | *p* value |
|---|---|---|---|
| Case no. | 85 | 49 | > 0.05 |
| Male | 32 | 19 | > 0.05 |
| Female | 53 | 30 | > 0.05 |
| Age (years) | 36 ± 12 | 40.1 ± 10.7 | > 0.05 |
| TASS | 5.38 ± 1.24 | 5.37 ± 1.20 | > 0.05 |
| TAMS | 7.73 ± 1.53 | 7.63 ± 0.97 | > 0.05 |
| ACT | 14.84 ± 2.46 | 14.70 ± 2.28 | > 0.05 |
| PEF% | 0.73 ± 0.11 | 0.79 ± 0.14 | < 0.05 |
| Monosensitization to DF (%) | 24% | 22% | > 0.05 |
| Sensitization to DF with DP (%) | 76% | 78% | > 0.05 |

*ACT* asthma control test, *TASS* total asthma symptom score, *TAMS* total asthma medicine score, *PEF%* peak expiratory flow rate, *SLIT* sublingual immunotherapy

### Statistical analysis

All data are expressed as mean ± standard deviation (SD). These data were analyzed using SPSS 20.0. The level of significance was set at 0.05. Baseline assessment was tested by the analysis of variance (ANOVA) or chi-squared test. The statistical significance of the difference between baseline and treatment values was determined using the Student *t* test, the non-parametric Mann-Whitney *U* test, or the Wilcoxon signed rank test. The Friedman test and *q* test were used for intergroup comparison for the data not conforming to normal distribution law or homogeneity of variance.

## Results

### All patients

In this study, 134 records of adult patients with mild to moderate AS who had been treated for 2 years were collected from June 2011 to June 2013 in the Wuzhou Red Cross Hospital and were divided into two groups. In the SLIT group, 20 (24%) patients were sensitized to DF and 65 (76%) patients were sensitized to DF with DP. In the control group, 11 (22%) patients were sensitized to DF and 38 (78%) patients were sensitized to DF with DP. The initial overall demographic and clinical characteristics in both groups are presented in Table 1. There were no statistical differences in age, sex, and patient's condition between the two groups before therapy.

### Change of symptom score

As shown in Fig. 1, after 1- and 2-year treatments, the TASS in both groups significantly decreased compared with the baseline value (all $p < 0.001$). However, there were no significant differences between the 1-year treatment and the 2-year treatment in both groups (Fig. 1a). After the 1-year treatment and 2-year treatment, TASS values in the SLIT group were both significantly lower than the control group ($p < 0.01$) (Fig. 1b).

### Total asthma medicine score

As shown in Fig. 2, after 1- and 2-year treatments, the TAMS in both groups significantly decreased compared with the baseline value (all $p < 0.001$). There were also significant differences between the 1-year treatment and the 2-year treatment in both groups (Fig. 2a). After the 1-year treatment and 2-year treatment, TAMS values in the SLIT group were both significantly lower than those in the control group ($p < 0.01$) (Fig. 2b).

### Asthma control test

As shown in Fig. 3, after 1 year, the ACT in both groups significantly improved compared with the baseline value (all $p < 0.001$). There was also significant difference between the 1-year treatment and the 2-year treatment in the SLIT group,

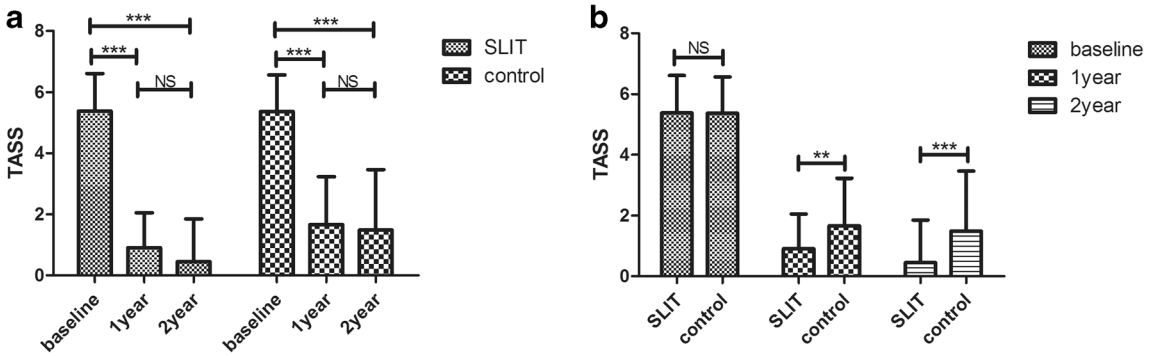


**Fig. 1** TASS in the SLIT group and control group at different time points (mean ± SD). **a** Comparison of scores at different time points within group. **b** Comparison of scores at different time points between groups (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). TASS, total asthma symptom score; SLIT, sublingual immunotherapy

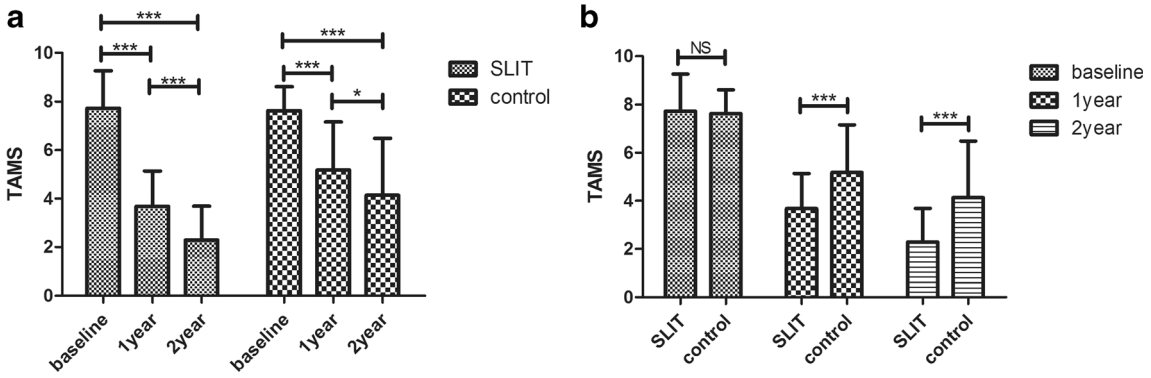


**Fig. 2** TAMS in the SLIT group and control group at different time points (mean ± SD). **a** Comparison of scores at different time points within group. **b** Comparison of scores at different time points between groups (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). TAMS, total asthma medicine score; SLIT, sublingual immunotherapy

while there was no significant difference in the control group (Fig. 3a). After the 1-year treatment and 2-year treatment, ACTs in the SLIT group were both significantly higher than those the control group ($p < 0.001$) (Fig. 3b).

### Peak flow percentage

As shown in Fig. 4, after 1 year, the PEF% in both groups significantly improved compared with the baseline value (all $p < 0.001$). There was also significant difference between the 1-year treatment and the 2-year treatment in the SLIT group, while there was no significant difference in the control group (Fig. 4a). Before the treatment, only the PEF% in the SLIT group was significantly lower than that in control group ($p < 0.05$). After the 1-year treatment, there was no significant difference between the SLIT and control groups. After the 2-year treatment, ACT in the SLIT group was significantly higher than that in the control group ($p < 0.05$) (Fig. 4b).

### Safety

No severe systemic adverse effects (AEs), anaphylaxis, asthma acute attack, or use of adrenaline was reported during the entire treatment period. Twelve patients in the SLIT group and three patients in the control group reported AEs. All local AEs that the patients suffered during SLIT were mainly oral or sublingual itching, swelling, and diarrhea. All the local AEs spontaneously disappeared within a week, with or without medicine. Two patients in the SLIT group experienced a mild asthma attack during the maintenance period and were relieved through adjusting the dose of *D. farinae* drops and/or using inhaled glucocorticoids or long-acting β2 agonists.

## Discussion

The first study which evaluated the efficacy of AIT in asthmatic patients was published by Abramson in 1995 [24]. From then on, lots of investigations focusing on the effectiveness and safety of AIT in asthmatic patients had been reported [25–28]. However, most of these studies were conducted just for subcutaneous immunotherapy (SCIT). Thus, clinical study about SLIT in the HDM-sensitized AA patients was rarely reported [29–31], especially in adult patients.

This study was designed to confirm the efficacy and safety of SLIT in adult patients with HDM-induced AA. TASS and TAMS are the primary outcomes of this study. There are lots of studies using TASS and TAMS to analyze the efficacy of

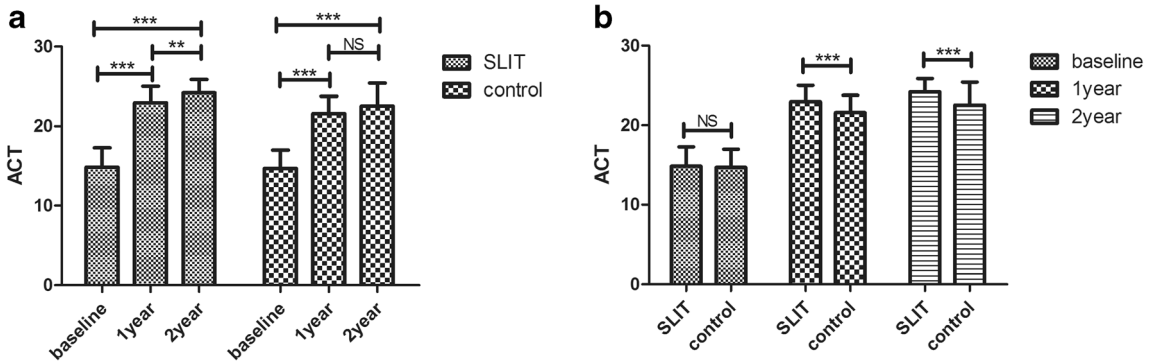


**Fig. 3** ACT in the SLIT group and control group at different time points (mean ± SD). **a** Comparison of scores at different time points within group. **b** Comparison of scores at different time points between groups (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). ACT, asthma control test; SLIT, sublingual immunotherapy

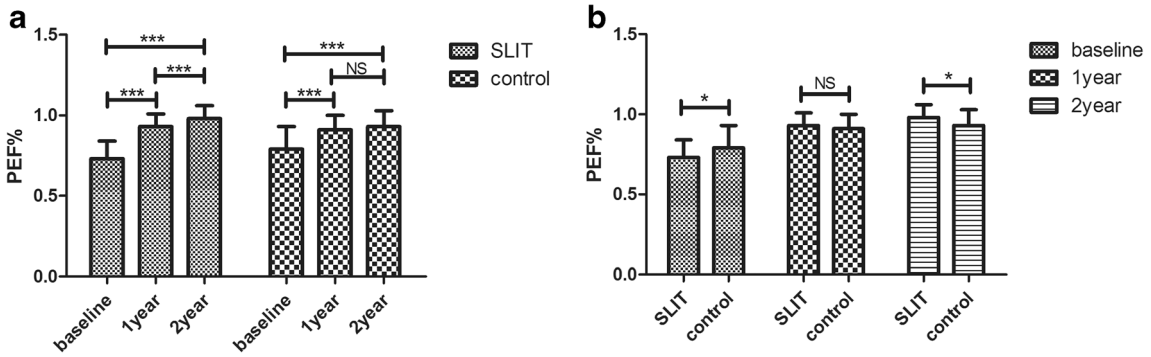


**Fig. 4** PEF% in the SLIT group and control group at different time points (mean ± SD). **a** Comparison of scores at different time points within group. **b** Comparison of scores at different time points between groups (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). PEF%, peak expiratory flow rate; SLIT, sublingual immunotherapy

SLIT [32, 33]. After 1- and 2-year treatments, we found significant reductions in TASS and TAMS for AA patients who received therapy of SLIT and pharmacotherapy, which was consistent with the few previous studies [34]. Meanwhile, the ACT score and PEF% were significantly improved as well. Furthermore, after the 1-year treatment and 2-year treatment, the TASS and TAMS in the SLIT group were both significantly lower than those in the control group. Our results indicated that both SLIT and pharmacotherapy were effective in adult patients with HDM-induced AA, but the SLIT group showed better efficacy.

In the present study, we particularly compared the efficacy of the SLIT group and control group. An interesting and important observation was found: The baseline PEF% in the SLIT group is significantly lower than that in the control group. However, after 2-year treatment, it became significantly higher than that in the control group. Thus, we provided more evidence that SLIT was more efficacious for HDM-induced AA adults than the single pharmacotherapy.

Local side effects (oral itching or mild swelling) may be encountered in three fourths of patients especially in the early phase of SLIT. In the study of Dahl et al. [35], the safety of SLIT was investigated specifically in grass pollen-allergic patients with asthma. They evaluated the side effects which may be related with treatment, e.g., cough and wheezing, and no significant difference in the number of such effects was found between active and placebo groups. In our study, the incidence of AEs in the SLIT group is higher than that in the control group. This result is consistent with the previous study [36]. All the AEs were mainly local AEs such as transient oral itching and swelling. All the AEs were relieved within a week, with or without therapy.

In conclusion, pharmacotherapy in the control group also showed improvement in all clinical scores because of a better compliance, better control of treatment, or better follow-up. However, our investigation demonstrated that SLIT with *D. farinae* drops combined with regular anti-allergic drug is much more effective, safe, and convenient for HDM-induced adult AA patients. Meanwhile, the SLIT group showed much more better improvement than the control group in all the clinical parameters. On the other hand, several limitations of this study, such as the non-double blind and no placebo arm, should be taken into account for the result analysis. In the future, we will further focus on evaluating the retained effect of SLIT in post-treatment years.

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**Compliance with ethical standards** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

**Conflict of interest** The authors declare that they have no conflict of interest.

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