

Long-Term Efficacy of Sublingual Mite Immunotherapy in Monosensitized and Polysensitized Children with Allergic Rhinitis: A 7-Year Prospective Study

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Keywords

Long-term efficacy · Sublingual immunotherapy · Monosensitization · Polysensitization · Allergic rhinitis

Abstract

Background: Several foreign studies have shown long-term efficacy of sublingual immunotherapy (SLIT), but data on the long-term efficacy of SLIT in China are still lacking. **Objective:** We aimed to prospectively evaluate the long-term efficacy of a 2-year SLIT with *Dermatophagoides farinae* (*D. farinae*) drops in mono- and polysensitized children with allergic rhinitis (AR). **Methods:** Eighty house dust mite (HDM)-sensitized children (aged 4–11 years) with AR were enrolled in this prospective study. There were 40 children in both the mono-sensitized (to HDM only) and polysensitized groups. Both groups were treated with standardized SLIT (*D. farinae* drops) for 2 years, combined with pharmacotherapy according to their individual requirements, and were followed up for 7 years. A combined symptom and medication score (CSMS) was assessed and compared between the 2 groups during

and after SLIT. Safety was evaluated based on adverse events (AEs). **Results:** There were 31 (77.5%) monosensitized and 29 (72.5%) polysensitized children who completed the study. After 2-year SLIT, the CSMS of 2 groups significantly decreased compared to baseline. The improvement persisted during the first 5 years at each visit, with a significant difference (all $p < 0.01$). In the monosensitized group, the CSMS significantly increased during the 6th and the 7th year compared to year 2 (both $p < 0.05$). Meanwhile, the polysensitized group showed a significant worsening of CSMS from the 5th to the 7th year (all $p < 0.05$). Furthermore, there was a statistical difference between the 2 groups in the 5th year of the study ($p < 0.05$). No severe AEs were reported. **Conclusions:** The study confirmed the long-term effects which lasted for 7 years after 2-year SLIT in mono- and polysensitized children. Compared with the polysensitized children, the monosensitized children noted a more sustained benefit.

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Introduction

Allergic rhinitis (AR) is a common respiratory allergic disease which is characterized with immunoglobulin E (IgE)-mediated inflammatory reactions and possesses the potential to gradually deteriorate into allergic asthma (AS) [1]. It is reported that the standardized prevalence of self-reported adult AR in the 18 cities of China was 17.6% in 2011 and still shows a trend of increasing year by year [2]. The house dust mite (HDM) has been confirmed to be the most common allergen in allergic disease in China [3]. At present, the treatment of allergic diseases is based on allergen-specific immunotherapy (ASIT) and pharmacotherapy [4]. Besides pharmacotherapy, ASIT is considered to be the only treatment that may modify the nature course of allergic diseases [5].

Currently, ASIT has been promoted as the first-line treatment for AR, widely used for the treatment of respiratory allergic diseases including AR [6]. As a new ASIT approach, sublingual immunotherapy (SLIT) is considered to be the safest route of administration and has been recommended for the treatment of AR and AS in recent years [7]. Indeed, the efficacy of SLIT has been confirmed by clinical research studies and systematic reviews worldwide [8, 9]. At the same time, research has also been performed to prove the long-term efficacy of SLIT, but the available data on this in China is still sparse [10, 11]. In this study, we evaluated the long-term efficacy of 2-year SLIT in mono- and polysensitized children with AR.

Materials and Methods

Study Design

This prospective study was performed in the Children's Hospital of Wuhan City, China. Data about the study design appears in Figure 1. A total of 80 children aged 4–11 years with HDM-sensitized AR in the period from May 2010 to December 2010 were enrolled in the study. They were divided into a monosensitized group and a polysensitized group according to the results of testing for serum IgE (sIgE). They were then treated with a standardized SLIT for 2 years. After therapy completion, there was a yearly follow-up visit for 7 years (2011–2018). All patients were evaluated for the long-term efficacy of SLIT and this was compared in mono- and polysensitized children.

Patients and Diagnosis

All patients suffering with AR were diagnosed according to the ARIA (Allergic Rhinitis and Its Impact on Asthma) guidelines [1]. The inclusion criteria were: (1) a clinical history of allergy and/or clinical criteria including typical symptoms of rhinitis (nasal itch-

ing, sneezing, rhinorrhea, and nasal congestion); (2) sensitization to *D. farinae* and/or *D. pteronyssinus* as assessed according to sIgE detection (>0.7 KU/L); (3) a forced expiratory volume in 1 s (FEV₁) within the normal limit ($>70\%$ of predicted volume). Exclusion criteria included: (1) suffering from uncontrolled asthma; (2) suffering from other systemic immunological disorders; (3) on β -blockers during the previous 6 months.

According to the results of sIgE detection, the children were divided into a monosensitized ($n = 40$) and a polysensitized group ($n = 40$). Patients who were only sensitive to *D. farinae* and/or *D. pteronyssinus* were enrolled in the monosensitized group, and patients sensitive to *D. farinae* and/or *D. pteronyssinus* and other combined inhaled allergens were entered into the polysensitized group (with ≤ 3 species of allergen).

SLIT Combined Symptomatic Medication

Both groups received SLIT with biologically standardized *D. farinae* extract (Chanllergen, Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd.), which were labeled with increasing concentrations of total protein (No. 1, 1 μ g/mL; No. 2, 10 μ g/mL; No. 3, 100 μ g/mL; No. 4, 333 μ g/mL). *D. farinae* drops were administered under the tongue for 1–3 min before swallowing, and the treatment was performed according to the manufacturer's instructions. All patients were administered Nos. 1–3 for the first 1–3 weeks, defined as the initiation therapy; 1, 2, 3, 4, 6, 8, and 10 drops were given each day of the week, respectively. Children younger than 14 years were instructed to start taking 3 drops of No. 4 once daily after week 4, entering a maintenance therapy. All patients were treated with appropriate symptomatic drugs as required by the ARIA guidelines during and after SLIT.

Combined Symptom and Medication Score

All patients were required to keep a diary recording symptoms and medication intake every year from December to January. This specific period was chosen because a minimum exposure to pollen was expected at this time of year, i.e., polysensitized patients would be affected less than at other times [12]. The total nasal symptom score (TNSS) was defined as the sum of 4 nasal symptom scores including nasal discharge, nasal obstruction, itching, and sneezing. Each nasal symptom was assessed on a scale of 1–3: 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. All patients were prescribed pharmacotherapy to be taken on demand including an oral antihistamine, an oral or topical corticosteroid, and antileukotrienes. The total medication score (TMS) was assessed according to the daily intake of symptomatic medication: 0 = none; 1 = antihistamine or antileukotrienes; 2 = topical corticosteroid; 3 = oral corticosteroid. Finally, the combined symptom and medication score (CSMS) was calculated with the following formula [13]:

$$\text{CSMS} = \text{TNSS}/4 + \text{TMS}$$

Adverse Events

All patients were instructed to keep a record of adverse events (AEs) in detail throughout the treatment and these were promptly addressed under the instruction of the physician. AEs of SLIT were determined according to the World Allergy Organization (WAO) Immunotherapy Committee [14].

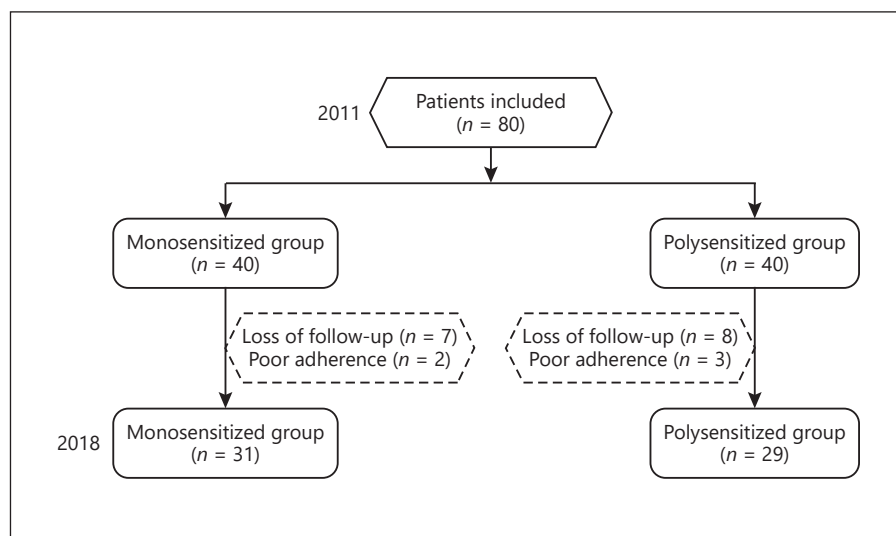


Fig. 1. Flow chart of study subject numbers.

Table 1. Clinical characteristics

	Monosensitized group (n = 31)	Polysensitized group (n = 29)	p value
Age range, years	4–11	4–11	
Age, years	7.10±2.09	6.62±1.63	0.36
Male/female, n	14/17	11/18	0.57
sIgE, KU/L	56.75±2.86	53.34±2.02	0.60
CSMS	4.31±0.51	4.30±0.51	0.84

Values are expressed as means ± SD, unless otherwise indicated. sIgE, serum immunoglobulin E; CSMS, combined symptom and medication score.

Patients' Management

All patients received initial clinical education and follow-up education. Meanwhile, detailed patient files consisting of essential and contact information were established and used to record symptoms and medication of patients in a timely manner. Regular telephone follow-up was performed, to discuss problems concerning taking medicine during SLIT and remind patients about their next consultation (to ensure the compliance).

Statistical Analysis

Statistical analysis was performed with SPSS v22.0 software. The analysis of sex ratio and the presence/absence of AEs in the treatment groups was performed with the χ^2 test. The data was analyzed by means of the nonparametric Mann-Whitney U test for intergroup comparisons, and Friedman's two-way analysis of variance (ANOVA) test for intragroup comparisons. Values were shown as mean ± standard deviation (SD) and the 2-tailed level of significance was set at $p = 0.05$.

Results

Population Characteristics

Sixty patients (25 males and 35 females) aged 4–11 years (mean 6.87 ± 1.88 years) completed the study. During the 7 years, 9 and 11 patients, respectively, withdrew from the study due to loss of follow-up or poor adherence in the mono- and polysensitized groups. There were no significant differences in age, sex ratio, the level of sIgE, and CSMS between the 2 groups (Table 1).

Clinical Evaluation

In the monosensitized group, the CSMS of patients after SLIT decreased significantly throughout the study compared with baseline ($p < 0.01$, Fig. 2a). Compared with the 2nd year, no significant difference in CSMS was seen in the 3rd, 4th, or 5th years ($p > 0.05$), but a significant increase was seen in the 6th year ($p < 0.05$).

In the polysensitized group, there was a significant decrease of CSMS starting from the 1st year of SLIT when comparing baseline and the end of the study ($p < 0.01$, Fig. 2b). Meanwhile, the CSMS was significant increased from the 5th year compared with in the 2nd year ($p < 0.05$).

Finally, we compared the CSMS each year throughout the study between the 2 groups. Interestingly, there was no significant difference in CSMS in any year except for the 5th year. In the 5th year, i.e., 3 years after SLIT was discontinued, the CSMS of the polysensitized children was significantly higher than that of monosensitized children ($p < 0.05$, Fig. 2).

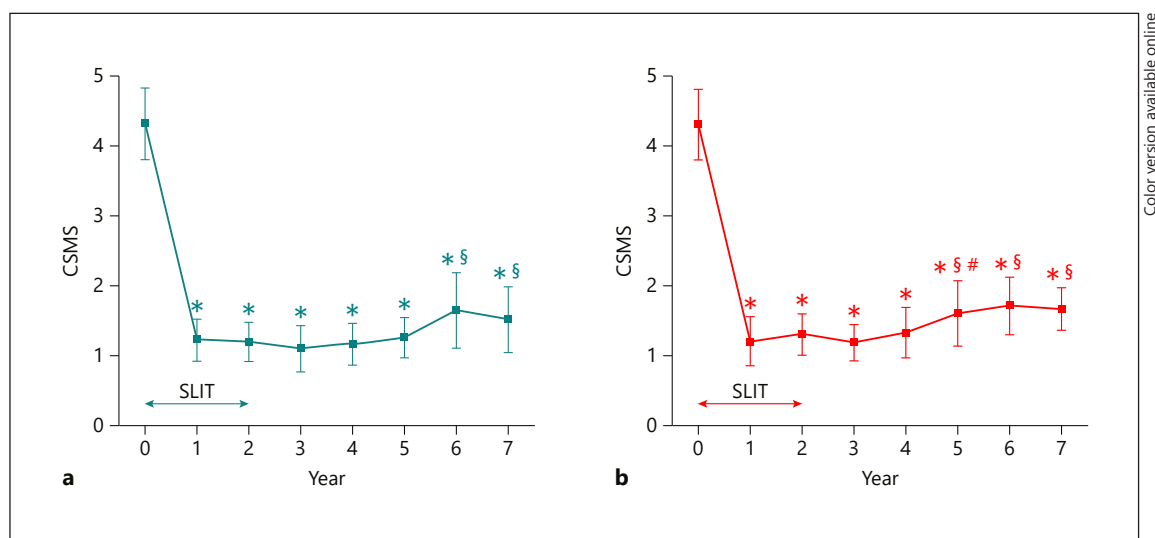


Fig. 2. CSMS of patients in the monosensitized (a) and polysensitized (b) groups throughout the 7 years of the study. The duration of SLIT is indicated by the arrow at the bottom. * significant difference compared to baseline; § significant difference compared to the 2nd year of SLIT; # significant difference between the 2 groups.

Table 2. Analysis of adverse events during the study

Adverse event	Monosensitized group, n	Polysensitized group, n
Total	6	5
Oral intolerance	2	2
Gastrointestinal intolerance	1	1
Local rashes	1	1
Aggravating symptoms	2	1

Safety

No severe systemic AEs were reported during the whole study in either group. 31 children in the monosensitized group and 29 in the polysensitized group reported 6 and 5 AEs, respectively. The AEs recorded in the study are listed in Table 2. There was no difference in the total number of AEs between the 2 groups ($\chi^2 = 0.0447$; $p > 0.05$). The most common AEs were oral intolerance, gastrointestinal intolerance, and local rashes, which were common and mild, and could be relieved without any treatment within a week. Several AEs such as aggravating symptoms were relieved with appropriately symptomatic medication or by reducing the dose of *D. farinae* drops.

Discussion

As a disease-modifying treatment, SLIT has become the main method of desensitization, and it has been strongly recommended for the treatment of AR and AS during its application over >10 years in China. Meanwhile, a lot of clinical studies and reviews show that SLIT is effective for the treatment of AR. This is evaluated by the observation of reduced respiratory symptoms, decreased use of medication, and improved quality of life [15, 16]. In this prospective study, the CSMS of both mono- and polysensitized children with AR was significantly decreased after SLIT compared with baseline, thereby verifying that SLIT is effective.

SLIT has been used internationally for >30 years. However, studies on the long-term efficacy of allergic diseases including AR are still scarce. A randomized study conducted by Lin et al. [17] proved that patients with AR achieved 1-year long-term clinical benefit after 3-year SLIT. Ours is the first 7-year prospective study on the long-term effects of SLIT in China, and it provides powerful evidence of and support for the further application of SLIT. In this study, in children receiving 2-year SLIT, the clinical benefit persisted for 7 years, both in the mono- and polysensitized groups. The increased CSMS in both groups of children indicated some recurrence of symptoms, but the CSMS was still significantly lower than at baseline. If the long-term efficacy of SLIT is not sustained,

a secondary desensitization called a “booster year of allergen immunotherapy” will achieve a quick clinical effect, as reported abroad [18].

The clinical effect of HDM SLIT in polysensitized patients is under continuing debate; a multicenter study revealed that in China >90% of individuals are sensitized to ≥ 2 allergens [3]. Li et al. [19] investigated the efficacy of HDM SLIT in mono- and polysensitized children with respiratory allergic diseases. The results indicated that there was no significant difference in the clinical effects of SLIT between these 2 groups; many other studies have reported that the effects of SLIT in mono- and polysensitized patients are indeed similar [20]. In our study, the clinical efficacy, as assessed by the CSMS of patients, showed no difference during the treatment between the 2 groups, similar to the results of the abovementioned studies. We confirmed the differences in the long term after SLIT. Our results revealed that in the 5th year of the study, i.e., 3 years after SLIT discontinuation, the CSMS of polysensitized children was significantly higher than that of the monosensitized children. It is possible that the long-lasting effect of HDM SLIT is better in monosensitized children; more research is needed in the future.

This was a 7-year prospective study on the long-term efficacy of 2-year SLIT in mono- and polysensitized children with AR. In both these groups, the clinical benefits of the therapy persisted for 7 years. Compared with

the polysensitized children, the long-term effect for the children in the monosensitized group seemed to be better.

Statement of Ethics

Subjects (or their parents or guardians) gave their written informed consent and the study protocol was approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y.L. and Z.X. designed the study. L.C. wrote the article. All authors contributed to the analysis, interpretation, revision, and final preparation of the manuscript.

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