

Enhanced Efficacy of Dust Mite Sublingual Immunotherapy in Low-Response Allergic Rhinitis Patients after Dose Increment at 6 Months: A Prospective Study

Yingqin Gao^a Xia Lin^b Jing Ma^a Xin Wei^b Qiuju Wang^b Meilan Wang^a^aDepartment of Otolaryngology – Head and Neck Surgery, Kunming Children's Hospital, Kunming, China;^bDepartment of Otorhinolaryngology – Head and Neck Surgery, Hainan General Hospital, Haikou, China

Keywords

Allergic rhinitis · Allergen-specific immunotherapy · Sublingual immunotherapy · House dust mite · Dosage

Abstract

Background: Several studies have suggested that sublingual immunotherapy (SLIT) involves a dose-response relationship and inadequate dosage might not achieve a favorable clinical effect. **Objective:** The aim of this prospective study was to investigate the efficacy and safety of increasing SLIT dosage at 6 months in patients with house dust mite-induced allergic rhinitis (AR) who had low response to treatment. **Methods:** A total of 157 AR participants aged 4–60 years were enrolled and received SLIT with *Dermatophagoides farinae* drops. After 6 months of SLIT, patients were interviewed and then classified into a high-response (HR) group and a low-response (LR) group based on the combined symptom and medication score (CSMS) reduction rate. Patients with a CSMS reduction rate over 50% were de-

defined as HR and continued the original dose, while patients with a CSMS reduction rate ranging from 20 to 50% were defined as LR and received an increased dose (percentage of dosage increment, 33.33% for patients aged <14 years and 50% for patients aged ≥14 years). Patients with a CSMS reduction rate below 20% were considered nonresponse (NR) and recommended to withdraw from SLIT. CSMS, visual analog scale (VAS), and adverse events were assessed at 0.5, 1, 2, and 3 years during the 3-year treatment. **Results:** A total of 54 and 56 patients completed the treatment in the HR and LR groups, respectively. The CSMS and VAS of both groups decreased significantly at 6 months ($p < 0.05$). Significant differences between the two groups were found in CSMS and VAS at 6 months and 1 year ($p < 0.05$), but not in later follow-ups ($p > 0.05$). The improvement of adults in the LR group was significantly lower than that of children at 6 months ($p < 0.05$), but there was no difference in later follow-ups ($p > 0.05$). There was no difference in CSMS or VAS in patients with monosensitization and polysensitization in the same treatment group at 1 year and in subsequent visits

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karger@karger.com
www.karger.com/iaaDr. Xia Lin
Department of Otorhinolaryngology – Head and Neck Surgery
Hainan General Hospital, No. 19 Xiuhua Road
Haikou, Hainan 570311 (China)
linxia3073@126.comDr. Jing Ma
Department of Otolaryngology – Head and Neck Surgery
Kunming Children's Hospital, No. 288 Qianxing Road
Kunming, Yunnan 650228 (China)
majing@etyy.cn

($p > 0.05$). Overall, 47 patients withdrew from this study due to NR ($n = 22$) and other reasons ($n = 25$). **Conclusions:** Six months might be a critical time point for efficacy assessment and dosage adjustment for AR patients after SLIT. In patients with low response, dosage enhancement within a certain range may enhance the effectiveness of SLIT.

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Introduction

Sublingual immunotherapy (SLIT), a disease-modifying therapy available for the treatment of allergic diseases, has been recommended as an initial treatment for allergic respiratory diseases, and failure of pharmacological treatment is not an essential prerequisite for its use [1]. Although SLIT has been proven to be effective by a convincing body of evidence [2, 3], it is recognized that SLIT does not work effectively for all patients. It is conjectured that there is probably a relationship between the maintenance dosage of SLIT, the clinical efficacy, and the adherence [4]. Low-dose treatment may not produce clinical benefit to a proportion of patients, whereas increasing the dosage appropriately can achieve a significant improvement in efficacy [5]. The standardized allergen dosage may need to be adjusted individually according to the condition of patients to ensure optimal therapeutic effect. However, there is a lack of basic research about dosage adjustment. In this study, the efficacy and safety of enhancing the maintenance dosage of SLIT were investigated in patients with house dust mite (HDM)-induced allergic rhinitis (AR) who had low response to SLIT.

Materials and Methods

Study Design

In this prospective study, patients were enrolled at the Otolaryngology – Head and Neck Surgery, Kunming Children's Hospital, and the Otorhinolaryngology – Head and Neck Surgery, Hainan General Hospital, from December 2015 to May 2016. Patients were treated using standardized allergen *Dermatophagoides farinae* drops (Chanllergen; Zhejiang Wolvo Bio-Pharmaceutical Co., Ltd., Zhejiang, China) with the drops labeled from 1 to 5 containing proteins of 1, 10, 100, 333, and 1,000 $\mu\text{g/mL}$, respectively. The drug was self-administered at the same time every day, held under the tongue for 1–3 min, and then swallowed. Information regarding normal drug dosage is shown in Table 1. After 6 months of treatment, patients were interviewed and then classified based on the combined symptom and medication score (CSMS) reduction rate. Patients with a CSMS reduction rate over 50% were defined as high-response (HR) patients and continued

Table 1. SLIT normal dosage regimen for the HR group

Week	Drug No.	Dose, mL						
		1 d	2 d	3 d	4 d	5 d	6 d	7 d
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
4–5	4	0.15						
≥6	4	0.15 for age <14 years						
	5	0.10 for age ≥14 years						

HR, high-response; d, day.

Table 2. SLIT adjusted dosage regimen for the LR group

Week	Drug No.	Dose, mL						
		1 d	2 d	3 d	4 d	5 d	6 d	7 d
<24		Same as normal dosage						
≥24	4	0.20 for age <14						
	5	0.15 for age ≥14						

LR, low-response; d, day.

the original dose, while patients with a CSMS reduction rate ranging from 20 to 50% were defined as low-response (LR) patients and received a higher dose. Moreover, patients whose CSMS reduction rate was below 20% were considered nonresponse (NR) patients and therefore recommended to withdraw from SLIT. In the LR group, 0.20 mL of drops No. 4/day was used for patients aged <14 years, whereas patients aged ≥14 years were treated with 0.15 mL of No. 5/day (Table 2). Patients returned to hospital for scheduled follow-up at 0.5, 1, 2, and 3 years and their symptoms and medication use were recorded. All patients were informed of the relevant information prior to their participation in the study. This study was approved by the Ethics Committee and was in compliance with the Ethical Guidelines for Clinical Studies and Good Clinical Practice.

Subjects

Subjects, aged 4–60 years, with HDM-induced intermittent or persistent AR but without other allergic diseases were included in the study. The inclusion criteria were: (1) diagnosed with moderate-to-severe AR according to Allergic Rhinitis and Its Impact on Asthma [6]; and (2) sensitization to *D. farinae* and/or *D. pteronyssinus* as confirmed by a serum-specific IgE of >0.7 KU/L. Patients were excluded from the study if they had one of the following conditions: (1) severe systemic diseases such as poorly controlled cardiovascular diseases, immune diseases, or malignant tumors; (2) receiving β -blockers or angiotensin-converting enzyme inhibitors; (3) serious psychological barriers or failed to understand the risks and limitations of treatment; and (4) in pregnancy or lactation, or planning pregnancy within 1 year. Patients only sensitized to *D. farinae* and/or *D. pteronyssinus* were allocated to the monosensi-

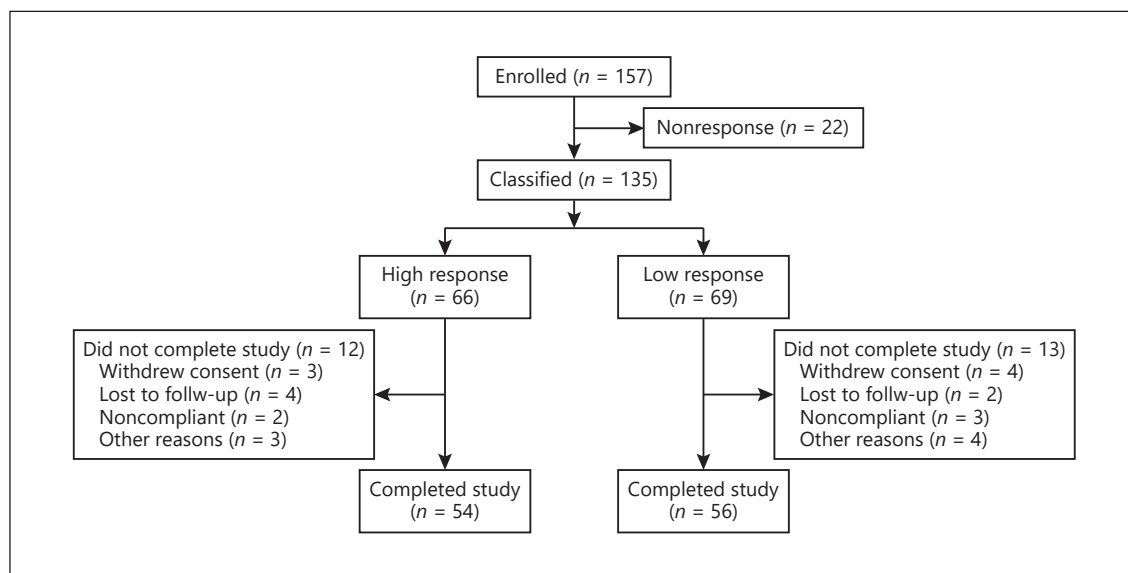


Fig. 1. Flow chart of the number of study subjects.

tized group, while patients who were sensitive to *D. farinae* and/or *D. pteronyssinus* and other coexisting inhaled allergens (no more than 3 species of allergen) were allocated to the polysensitized group.

Clinical Assessments

During the treatment, patients (or their guardians) were required to keep a diary recording of symptom and medication use. The investigators calculated the weekly average scores at every visit. Four nasal symptoms were assessed and scored from 0 to 3 [7], including sneezing (number/day, $\leq 2 = 0$, $3-5 = 1$, $6-10 = 2$, $\geq 11 = 3$), rhinorrhea (times/day, none = 0, $1-4 = 1$, $5-9 = 2$, $\geq 10 = 3$), nasal itching (no symptom = 0, intermittent itching = 1, tolerable itching = 2, intolerable itching = 3), and nasal obstruction (no symptom = 0, congestion without mouth breathing = 1, severe congestion with occasional mouth breathing = 2, severe congestion with mouth breathing almost all day = 3). The total nasal symptoms score (TNSS) was the sum of the four symptom scores. Patients were prescribed pharmacologic therapy for controlling AR symptoms, including oral antihistamines, oral antileukotrienes, and nasal glucocorticoid. Medication scores were assessed according to the daily dosage recommended by the drug instructions [8, 9] (None = 0, oral antihistamines or antileukotrienes = 1, topical glucocorticoid = 2, oral glucocorticoid = 3). The total medication score (TMS) was the sum of the medication scores. CSMS was calculated ultimately with the following formula [7]:

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

A 10-cm visual analog scale (VAS) was used for evaluation [10]. Patients were asked to subjectively assess the severity of their symptoms at every visit and score their disease severity where 0 indicated “no symptom” and 10 indicated “maximal symptoms.” Investigators recorded the actual point on the back side of the scale.

Adverse Events

The occurrence rate, duration, and severity were recorded to assess adverse events (AEs). All AEs were addressed under the instruction of the physicians.

Patient Management

Initial clinical education and follow-up education were carried out for all the patients. The patient files were established to record symptoms, medication use, and AEs of patients at the beginning of the treatment. Telephone follow-ups were provided to patients to solve problems that occurred in the treatment process and to arrange the next follow-up visit.

Statistical Analysis

Statistical analysis was performed in demographic analysis and efficacy assessment with IBM SPSS Statistics 21.0. The differences between the HR and LR groups in baseline demographic characteristics were analyzed by χ^2 test. The intragroup comparisons of clinical characteristics were performed by the Friedman M test and the intergroup comparisons of clinical characteristics were performed by the Mann-Whitney U test. The 2-tailed level of statistical significance was set at $p = 0.05$.

Results

Study Participants

Initially, 157 patients were enrolled in the study and received SLIT. A total of 135 patients were subsequently selected based on CSMS reduction rate after 6 months of treatment and divided into two groups (Fig. 1); 54 patients in the HR group and 56 patients in the LR group completed the 3-year treatment. Study compli-

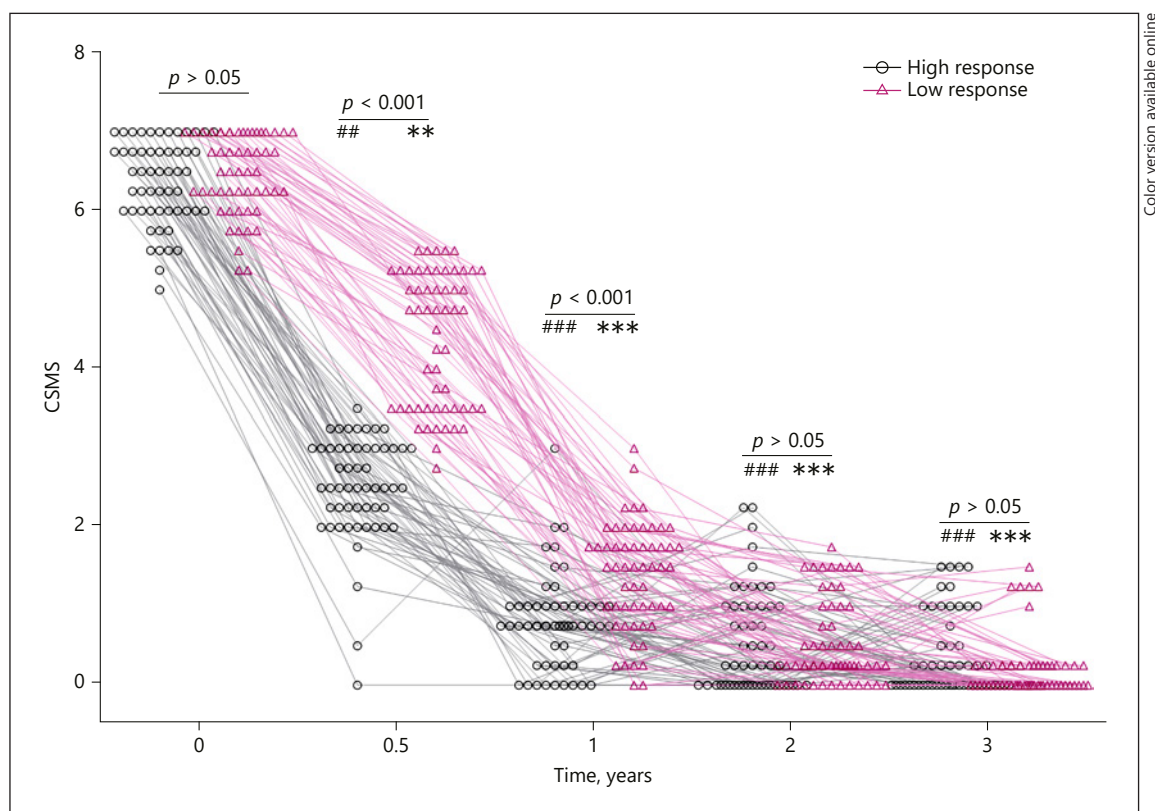


Fig. 2. Change of CSMS during 3-year SLIT. ## $p < 0.01$, ### $p < 0.001$, significant difference in the HR group compared to baseline; * $p < 0.01$, *** $p < 0.001$, significant difference in the LR group compared to baseline.

Table 3. Characteristics of the study subjects

Characteristics	HR group (n = 66)	LR group (n = 69)	Total (n = 135)	p value
Age				
Mean, years	18.39±15.27	15.45±11.09	16.89±13.33	>0.05
4–13 years	43 (65.15)	42 (60.87)	85 (62.96)	>0.05
14–60 years	23 (34.85)	27 (39.13)	50 (37.04)	>0.05
Gender				
Male	39 (59.09)	49 (71.01)	88 (65.19)	>0.05
Female	27 (40.91)	20 (28.99)	47 (34.81)	>0.05
Sensitization status				
Monosensitized	46 (69.70)	45 (65.22)	91 (67.41)	>0.05
Polysensitized	20 (30.30)	24 (34.78)	44 (32.59)	>0.05
Clinical data scores				
Baseline CSMS	5.95±1.16	6.21±0.98	6.08±1.08	>0.05
Baseline VAS	6.83±1.09	6.97±0.98	6.90±1.04	>0.05

Data are presented as n (%) or mean ± SD as appropriate. p values designate significant difference between the HR group and the LR group.

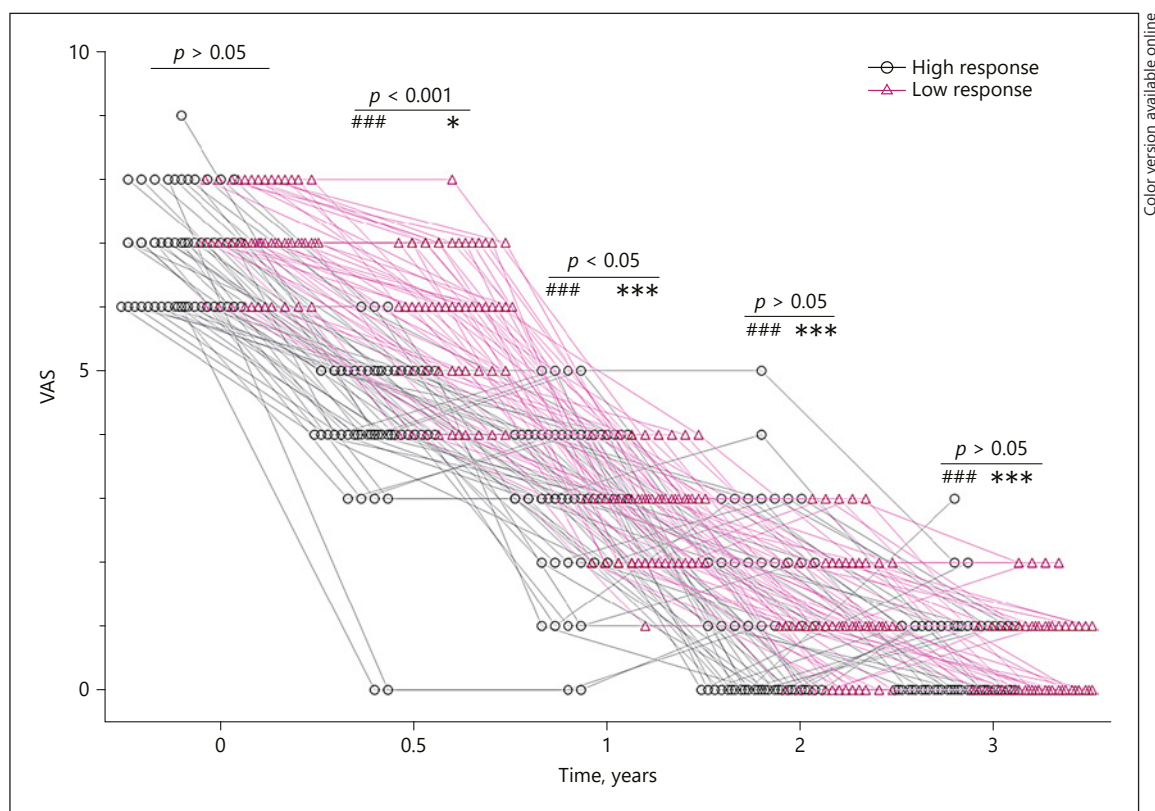


Fig. 3. Change of VAS during 3-year SLIT. ### $p < 0.001$, significant difference in the HR group compared to baseline; * $p < 0.05$, *** $p < 0.001$, significant difference in the LR group compared to baseline.

ance was 81.82 and 81.16%, respectively. Among patients with response to SLIT, 25 patients (18.52%) failed to complete the entire treatment, whereas no subjects withdrew because of AEs. No significant difference was discovered between the two groups regarding patient demographics or the clinical scores before SLIT (Table 3; all $p > 0.05$).

CSMS Evaluation

A highly significant reduction of CSMS was found during the entire treatment of each dosage group compared to baseline (Fig. 2; $p < 0.01$). No statistically significant difference was shown between the two different dosage groups at baseline ($p > 0.05$). Highly statistically significant differences were detected at 6 months and 1 year ($p < 0.001$) but not in later follow-ups ($p > 0.05$).

VAS Evaluation

The VAS of patients in both groups decreased significantly during the treatment compared to baseline (Fig. 3; $p < 0.05$). Significant differences between two groups oc-

curred at 6 months and 1 years ($p < 0.05$) and disappeared after 2 years of SLIT ($p > 0.05$).

Children versus Adults in the LR Group

The differences in SLIT efficacy between children (aged < 14 years) and adults (aged ≥ 14 years) in the LR group are shown in Figure 4. No significant difference was found in CSMS or VAS at baseline ($p > 0.05$). However, CSMS and VAS of adults were significantly higher than those of children at 6 months ($p < 0.05$). After dosage enhancement, this significant difference disappeared in CSMS at 1 year and in subsequent follow-ups ($p > 0.05$). The VAS of adults showed significant decrement compared with that of children at 1 year ($p < 0.05$) but not in later visits ($p > 0.05$).

Monosensitized versus Polysensitized Patients

A total of 68 monosensitized patients ($n = 34$ in each group) and 42 polysensitized patients ($n = 20$ in the HR group and $n = 22$ in LR group) completed the treatment. The therapeutic effects in monosensitized and polysensi-

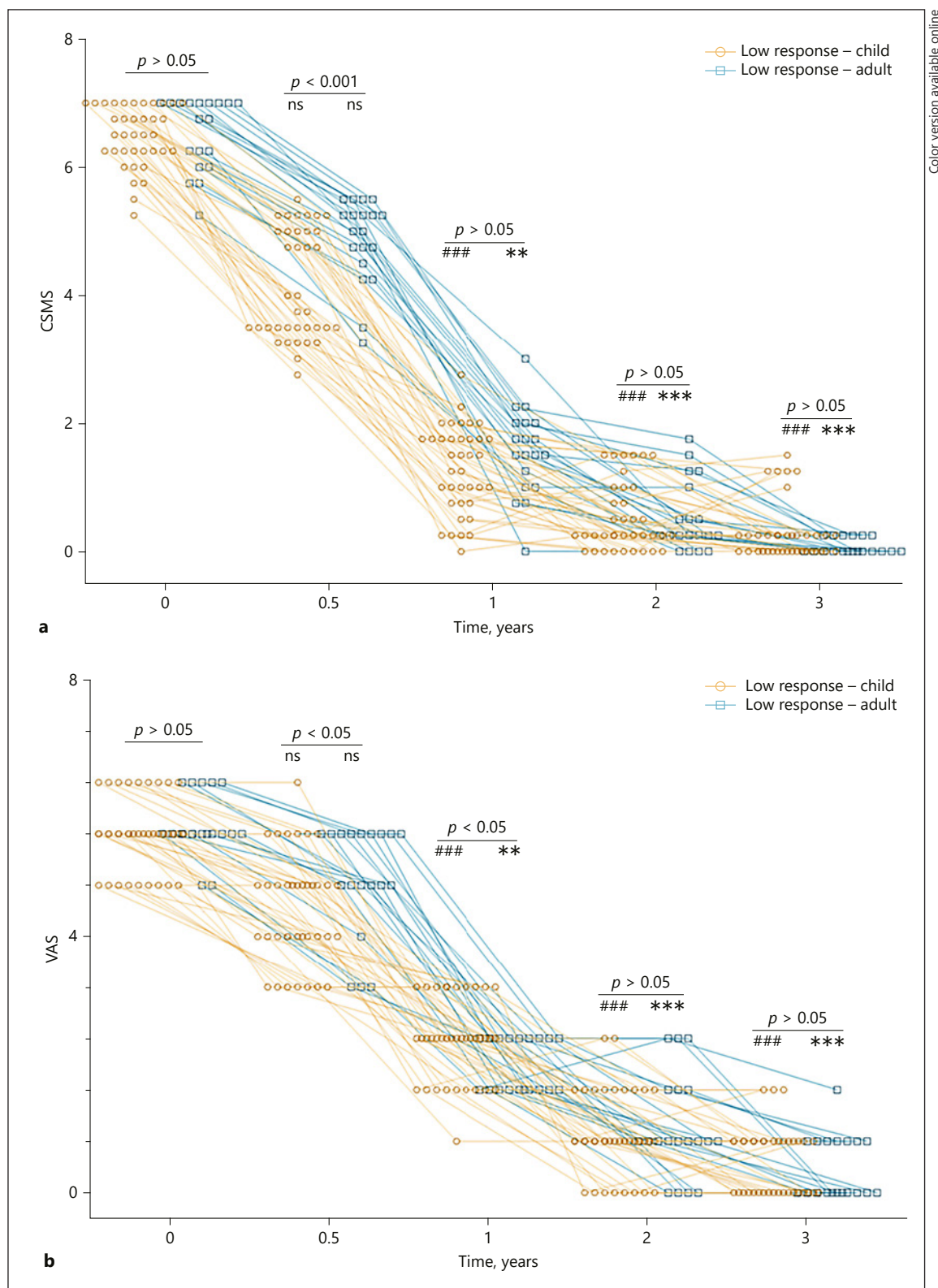
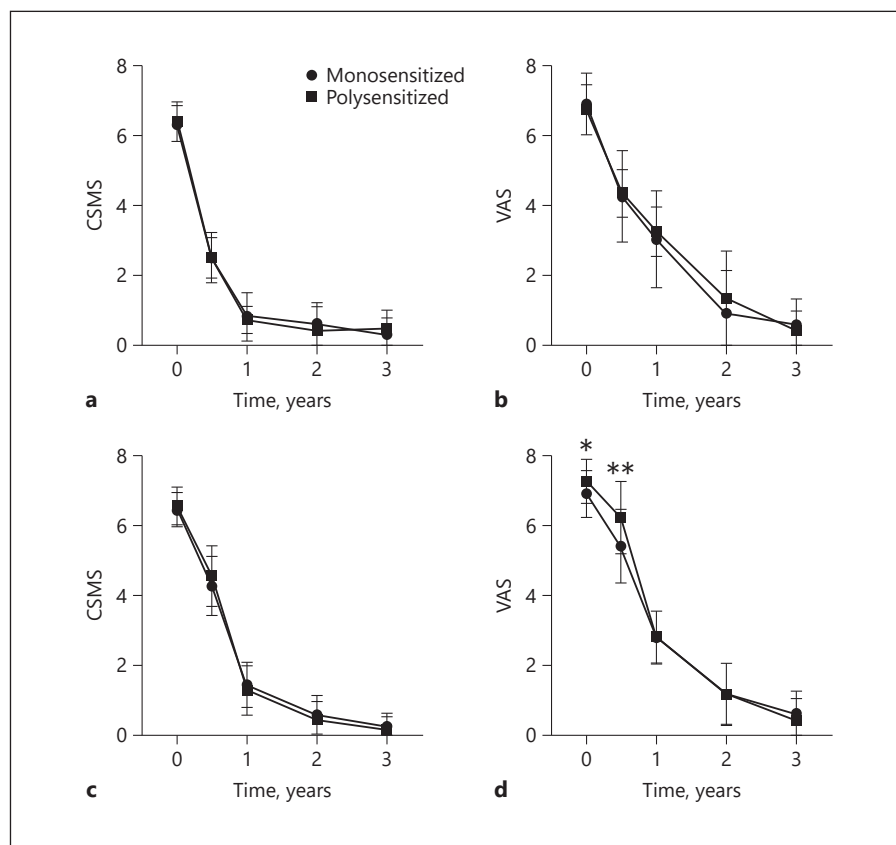


Fig. 4. Analysis of clinical evaluation between children and adults in the LR group. **a** CSMS. **b** VAS. ns, not significant. ### $p < 0.001$, significant difference in children compared to baseline; ** $p < 0.01$, *** $p < 0.001$, significant difference in adults compared to baseline.

Fig. 5. Analysis of clinical evaluation between monosensitized and polysensitized patients. **a** CSMS in the HR group. **b** VAS in the HR group. **c** CSMS in the LR group. **d** VAS in the LR group. * $p < 0.05$, ** $p < 0.01$, significant difference between the two subgroups.



tized patients in the same dosage group were compared. Patients had similar improvement in the HR group (Fig. 5; $p > 0.05$). CSMS was consistent in monosensitized and polysensitized patients of the LR group at baseline and during the entire treatment ($p > 0.05$), whereas significant differences occurred in VAS at baseline and the 6-month follow-up ($p < 0.05$).

Adverse Events

No severe systemic AEs were reported during the entire study. Overall, 15 AEs occurred in the HR group (involving 8 for oral numbness or pruritus, 3 for mild gastrointestinal reaction, 1 for local rash, and 3 for aggravation of allergic symptoms). There were 18 AEs reported in the LR group (involving 10 for oral numbness or pruritus, 4 for mild gastrointestinal reaction, 2 for local rash, and 2 for aggravation of allergic symptoms). The most common AEs in both groups were oral numbness or pruritus. The AE rate was 22.73% in the HR group and 26.09% in the LR group, with no significant difference between the two groups ($p > 0.05$). All AEs were relieved without any treatment within a week.

Discussion

SLIT has been used worldwide for more than 30 years. Its efficacy and safety for AR have been confirmed from an abundance of published data [2, 3]. Studies revealed that a significant improvement in rhinitis symptoms and medication use of AR patients occurred after 8–14 weeks of treatment and sustained throughout the therapy [11, 12]. In a randomized double-blind single-site trial, significant reductions in symptom scores of subjects with AR were observed at 8 and 16 weeks and peaked at 24 weeks [13]. These data supported that 6-month therapy was optimal for the onset of clinical efficacy. In this study, most patients (135/157, 85.99%) obtained significant efficacy improvement at 6 months compared to baseline. Considering the specific conditions in clinical practice in China, dosage adjustment within 6 months could enable LR patients to obtain clinical benefits quickly and continue the treatment.

Regardless of its efficacy, SLIT does not improve disease status in a proportion of patients. Studies have suggested that there is likely a relationship between the SLIT dosage

of allergen and clinical efficacy. Low-dose SLIT is generally ineffective [14] and it is important to deliver an adequate dosage. A study by Durham et al. [15] reported a significant improvement in symptom and medication use in patients treated with high dosage, whereas there was no improvement in patients with low dosage. There is a SLIT allergen-specific dosing range that could be effective in treatment. For patients who have achieved the desired level of improvement with the current SLIT dosage, it is reasonable to continue that dosage. If patients have not obtained sufficient success, the current dosage might be below the effective dose and doctors have the option to increase the dosage to assess whether better clinical improvement can be achieved. Thus, we maintained the dosage of patients in the HR group and increased the dosage of patients in the LR group at 6 months. A significant improvement was observed in CSMS of LR patients compared to that at 6 months, and no difference was shown between the HR and LR groups after 2 years of treatment. We considered that the dosage adjustment strategy in our study was effective for LR patients to improve the therapeutic effect and receive maximum benefit. Furthermore, this study found that children in the LR group showed significantly better efficacy than adults before the dosage increment at 6 months, while adults had significantly greater response than children after the dosage increment. There was no significant difference between the two subgroups in therapeutic effects after 2 years of treatment.

Patient compliance is crucial in the clinical management of SLIT. Existing studies have suggested that one of the most common reasons for early termination in SLIT was failure to obtain a satisfactory clinical response. Wang et al. [16] found that 54% of AR patients terminated SLIT in the first year of treatment with ineffectiveness being the second primary cause. Due to the high drop-out rate, LR patients might have no willingness to continue the treatment without timely clinical intervention (such as dosage increment). In our study, dosage adjustment of LR patients was provided at 6 months, and only 18.84% of those patients discontinued treatment in 3 years. A retrospective analysis revealed that only 7% of SLIT users completed the 3-year treatment [17]; a large pharmacy database reported that 84–87% of SLIT patients discontinued after the 3-year treatment [18]. The dropout rate in our study was lower than those in the published data and no significant difference was shown between the HR and LR groups (18.18 and 18.84%, respectively). That might be because a significant improvement was achieved in LR patients after dosage enhancement. It has been suggested that increasing the dosage of patients who did not receive favorable efficacy in 6

months might provide early intervention and reduce the rate of discontinuation in SLIT.

The majority of AR patients who need to be treated are polysensitized. Published data in the US and Europe demonstrated that polysensitization was more prevalent than monosensitization in the general population [19], while Li et al. [20] reported a multiple sensitization (sensitized to two or more allergens) rate beyond 90% in atopic patients in a large cross-sectional study. The efficacy of HDM SLIT in polysensitized AR patients has been well documented in numerous trials. Li et al. [21] found no significant difference between the monosensitized and polysensitized groups in efficacy enhancement throughout the SLIT in children with allergic diseases. Another study indicated that SLIT produced improvements in polysensitized AR patients comparable to monosensitized patients [22]. HDM-sensitized patients in our study received efficacy regardless of other positive allergens and it was speculated that SLIT provided similar efficacy improvement in both monosensitized and polysensitized patients.

Safety is of utmost concern in immunotherapy. The safety of SLIT has been demonstrated in multiple reviews of a large number of clinical trials [23]. No severe systemic AEs were reported in published randomized controlled trials [24]. However, a higher dosage than the necessary amount of antigen may lead to additional risk of immunotherapy [25]. In this study, no serious AEs were reported in all patients, and there was no significant difference in the number or severity of AEs between the HR and LR groups, between children and adults, between monosensitized and polysensitized patients, and in LR patients before and after dose adjustments. These results were consistent with the previous reports [26, 27]. Therefore, we confirmed that in AR patients with low response to SLIT, dosage enhancement (33.33% for patients aged <14 years and 50% for patients aged ≥14 years) at 6 months might enhance the effectiveness with good tolerance and safety.

The main limitation in this study is the open design and there is absence of a control group with no dose adjustment in LR patients. We are preparing a prospective study that investigates whether an increase in SLIT dose at 6 months after treatment for LR patients is the most appropriate time point and the optimal dose of increment, in order to enhance the efficacy of SLIT in both children and adults.

In conclusion, 6 months is considered to be an important time point for efficacy evaluation for AR patients undergoing SLIT. For patients without a favorable clinical effect, it is possible to improve the efficacy by enhancing the SLIT dose within an optimal range, which may also improve the compliance of the patients.

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Statement of Ethics

Subjects (or their guardians) provided written consent to participate in the study. The study protocol was approved by the research institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Author Contributions

Y.G. and X.L.: designed the study and wrote the manuscript. J.M.: examined patients and critically reviewed the manuscript. X.W.: examined patients and analyzed data. Q.W. and M.W.: collected the data and performed statistical analysis. Y.G. and X.L. contributed equally to this work.

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