

The Role of Nasal Endoscopy in Allergic Rhinitis and House Dust Mite Sublingual Immunotherapy

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Keywords

Allergic rhinitis · Sublingual immunotherapy · House dust mite · Nasal endoscopy · Modified Lund-Kennedy scoring system

Abstract

Introduction: While there exists considerable evidence for efficacy of sublingual immunotherapy (SLIT), its impact on the improvement of nasal signs in allergic rhinitis (AR) patients remains quite unclear. In this study, the endoscopic examination and the modified Lund-Kennedy (MLK) scoring system were performed to describe and evaluate the therapeutic effect of SLIT. **Methods:** A total of 105 patients with AR induced by house dust mites were enrolled and treated with standardized *Dermatophagoides farinae* (*D. farinae*) drops for 1 year. The total nasal symptoms score (TNSS), total medication score (TMS), visual analog scale (VAS), and MLK scores were assessed at baseline and 6 and 12 months. The MLK score was also compared for its correlation with TNSS, TMS, and VAS. **Results:** The TNSS, TMS, and VAS scores statistically decreased after SLIT compared to baseline (all $p < 0.05$). After 12 months of treatment, the rates of well-controlled, partial controlled, and uncontrolled AR patients were 42, 49.5, and 8.5%, respectively. The nasal endoscopy findings showed significant improvement in nasal signs, which mainly included color change of turbinate mucosa,

reduction of nasal secretions, and improvement of nasal edema. A significant decrease was observed in MLK scores, and there was a positive correlation between MLK and VAS scores. **Conclusions:** In addition to commonly utilized subjective assessments (TMS, TNSS, and VAS), our results of endoscopic examination and the MLK scores consistently confirmed that SLIT is an effective therapeutic modality for AR patients. The MLK scores might be considered as an auxiliary tool to evaluate efficacy of SLIT in clinical practice and outcomes research.

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Introduction

In the last 3 decades, sublingual immunotherapy (SLIT) has been widely considered to be a safe and effective therapeutic modality for allergic rhinitis (AR), with the capability to change the natural course of allergic diseases [1–5]. Among numerous measures to evaluate efficacy of SLIT, the subjective assessments such as the total nasal symptoms score (TNSS), total medication score (TMS), and visual analog scale (VAS) are commonly utilized in clinical research [3, 4]. Despite their frequent use, however, these assessments largely depend on patients' perception, with a lack of

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Table 1. Specific daily dosing schedules in AR patients

Time	Up-dosing phase, μL				Maintenance phase, μL
	bottle no. 1, week 1	bottle no. 2, week 2	bottle no. 3, week 3	bottle no. 4, weeks 4 and 5	bottle no. 5, from week 6
Day 1	50	50	50	150 μL daily for 2 weeks	100 μL daily for a dose maintenance
Day 2	100	100	100		
Day 3	150	150	150		
Day 4	200	200	200		
Day 5	300	300	300		
Day 6	400	400	400		
Day 7	500	500	500		
AR, allergic rhinitis.					

auxiliary objective outcome [6]. Given that AR patients are often accompanied by a series of changes in nasal signs, like pale and edematous nasal mucosa, watery nasal discharge, and swollen inferior turbinates, the nasal endoscopy examination appears to be valuable for physicians [4]. Moreover, the modified Lund-Kennedy (MLK) scoring system, proposed by Psaltis and Li et al. [7, 8], was proved to be a more suitable and reliable scoring system in rhinology outcomes research. Therefore, the objectives of this study were to evaluate the improvement of the nasal signs of AR patients with SLIT by performing the endoscopic examination and MLK scoring system and provide a potential auxiliary tool for clinical practice and outcomes research.

Materials and Methods

Study Subjects

In this study, 105 patients aged 14–61 years diagnosed with house dust mite-induced persistent AR were enrolled from December 2017 to May 2018. The inclusion criteria were as follows: diagnosed with moderate to severe AR according to Allergic Rhinitis and Its Impact on Asthma [6]; sensitized to *D. farinae* and/or *D. pteronyssinus* as confirmed by a serum-specific IgE of >0.7 KU/L. The exclusion criteria included the patients allergic to other allergens; with chronic rhinosinusitis with/without nasal polyps; who suffered from other concomitant immune system diseases or severe cardiovascular diseases; being treated with β -blockers or angiotensin-converting enzyme inhibitors; under pregnancy or lactation; and with severe psychological barriers or who are unable to understand the risks and limitations of treatment.

Treatment Schedule

All patients were treated with standardized *D. farinae* drops (Chanllergen; Zhejiang Wolwo Biopharmaceutical Co., Ltd.,

Zhejiang, China) for 1 year. The standardized extracts were labeled by the concentration of total protein in $\mu\text{g/mL}$ (bottle No. 1, 1 $\mu\text{g/mL}$; No. 2, 10 $\mu\text{g/mL}$; No. 3, 100 $\mu\text{g/mL}$; No. 4, 333 $\mu\text{g/mL}$; and No. 5, 1,000 $\mu\text{g/mL}$). According to the schedules recommended by the manufacturer, the treatment consisted of an up-dosing phase and a maintenance phase. The specific daily dosing schedule is shown in Table 1. Patients were instructed to self-administer at the same time every day and keep drops under the tongue for 1–3 min before swallowing. Particularly, patients were advised to take the first dose in the physician's office and observed for at least 30 min before being discharged. During the whole study, all patients were treated with appropriate drugs as required, including azelastine nasal spray, levocetirizine tablet, and mometasone furoate nasal spray. The use of any drugs was recorded.

Clinical Assessments

During the treatment, the TNSS, TMS, and VAS scores were assessed at baseline and 6 and 12 months. The efficacy of SLIT was also determined by assessing the patients' condition at 12 months. Moreover, diagnostic nasal endoscopy was performed at 3 time points to determine the endoscopic grading by means of the MLK scoring system.

The TNSS was defined as the sum of the 4 symptom scores, and each of them was assessed on a scale of 0–3: sneezing (number/day, $\leq 2 = 0$, $3-5 = 1$, $6-10 = 2$, $\geq 11 = 3$), rhinorrhea (time/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) [9]. The TMS was assessed according to the daily intake of symptomatic medication: none = 0, oral antihistamines or antileukotrienes = 1, topical glucocorticoid = 2, and oral glucocorticoid = 3 [9]. The VAS was used to evaluate the severity of symptoms through a 10-cm VAS, where 0 indicates “no symptom” and 10 indicates “maximal symptoms” [10].

In this study, the patients' condition at 12 months was defined as follows [11]: well-controlled group: asymptomatic or mild symptoms

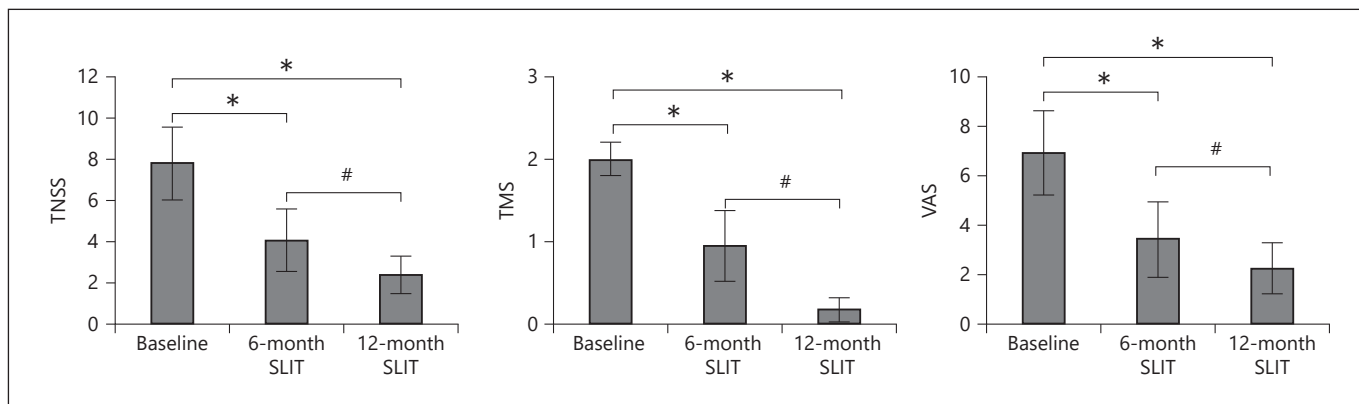


Fig. 1. Changes of TNSS, TMS, and VAS at baseline, 6-, and 12-month treatment. * $p < 0.05$, compared with the baseline; # $p < 0.05$, compared with the 6-month treatment. TNSS, total nasal symptoms score; VAS, visual analog scale; TMS, total medication score.

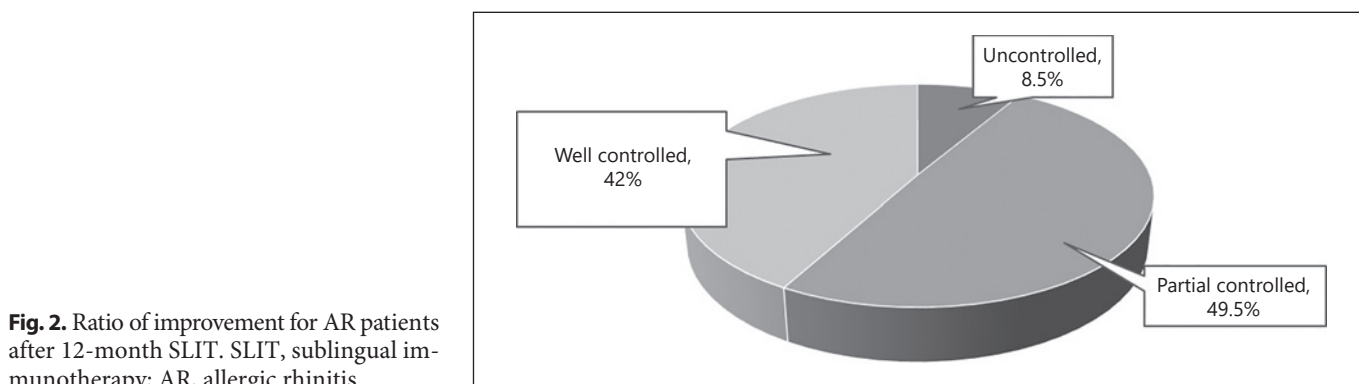


Fig. 2. Ratio of improvement for AR patients after 12-month SLIT. SLIT, sublingual immunotherapy; AR, allergic rhinitis.

that can be completely controlled by mild drugs; partial controlled group: mild or mild to moderate symptoms in the case of moderate medication; uncontrolled group: moderate to severe symptoms occur while taking a large amount of medication. The MLK endoscopy scoring system consisted of 3 terms graded on an ordinal scale from 0 to 2 for each side [8]: nasal polyps (none = 0, confined to middle meatus = 1, beyond middle meatus = 2), discharge (none = 0, clear and thin = 1, thick and purulent = 2), and edema (absent = 0, mild = 1, severe = 2). Each nasal cavity was graded separately and then combined to obtain an overall endoscopy score. Additionally, we randomly selected the results of nasal endoscopy of 2 cases of patients.

Adverse Events

During the whole study, safety was evaluated by the occurrence and severity of adverse events (AEs). All AEs were addressed under the instruction of the physicians.

Statistical Analysis

Statistical analysis was performed with SPSS software 20.0. The intergroup comparisons of clinical characteristics were performed by the Mann-Whitney U test or Wilcoxon signed rank test. The 2-tailed level of statistical significance was set at $p = 0.05$. The Spearman bivariate analysis was performed to determine potential differ-

ences and correlation coefficients between TNSS, TMS, and VAS and the MLK scores. Simple linear regression was then used to assess associations between the 3 subjective parameters and MLK scores.

Results

Effects on TNSS, TMS, and VAS

The changes of TNSS, TMS, and VAS at 3 time points (baseline and 6 and 12 months) were shown in Figure 1. Compared with baseline, the TNSS, TMS, and VAS were statistically decreased after 6 months of treatment (all $p < 0.05$). Similarly, significant reductions of TNSS, TMS, and VAS were also found after 12 months of treatment compared to baseline and 6-month treatment, respectively (all $p < 0.05$). Moreover, after 12 months of SLIT, the rates for well-controlled and partial controlled AR were 42% (39/105) and 49.5% (52/105), respectively, while only 8.5% (9/105) of the patients belonged to the uncontrolled group (Fig. 2).

Effects on MLK Scoring System and Nasal Endoscopy Findings

In this study, the MLK scoring system was used to determine endoscopic grading based on the degree of edema, polyps, and discharge (Fig. 3). Compared to baseline, MLK scores of AR patients significantly decreased after 6 months and subsequently 12 months of SLIT (all $p < 0.05$).

The nasal endoscopic examinations were performed at 3 time points (baseline and 6 and 12 months), and the representative endoscopy findings of 2 cases of AR patients were shown in Figure 4. For both patients A and B, the nasal signs were improved significantly after SLIT compared with the baseline level, and the improvements included color change of the turbinate mucosa (from pale to light red), reduction of nasal secretion, and disappearance of nasal mucosal edema. Besides, adenoid growth was also observed in the nasopharynx of patient A at baseline, while by 12 months of treatment, this phenomenon was no longer observed.

Correlation Analysis

In this study, the correlations of TNSS, TMS, and VAS with MLK scores were compared at all 3 time points. As shown in Figure 5, the MLK endoscopy scores showed no correlation with TNSS ($r = 0.132$, 95% CI: -0.070 to 0.307) and TMS ($r = 0.042$, 95% CI: -0.150 to 0.232). A positive correlation of MLK score was observed with the VAS ($r = 0.282$, 95% CI: 0.067 to 0.442 , $p < 0.05$).

Adverse Events

No severe systemic AEs, anaphylaxis, or use of adrenaline were reported during the whole treatment. Overall, 26 AEs occurred in 12 patients (involving 12 for oral pruritus or numbness, 7 for mouth edema, 4 for throat irritation, and 3 for local rash). All AEs in this study were mild and relieved within a week with or without medication.

Discussion

With application for >30 years, SLIT is widely regarded as the treatment with disease-modifying properties for AR patients due to its clinical efficacy and safety [12–16]. In recently published guidelines and consensus positions, subjective assessments, such as TMS, TNSS, and VAS, were recommended for the measures of efficacy of SLIT [3, 4]. In a randomized, controlled, open-label study on children with house dust mite-induced AR who underwent SLIT for 1 year, Shao et al. [17] recorded the TMS, TNSS, and VAS scores at monthly visits and found significant improvement in clinical scores compared to the

control group. Our results, consistently, demonstrated significant reductions in TNSS, TMS, and VAS after 1 year of SLIT. Additionally, referring to the arbitrary classification system established by Lin et al. [11], the ratio of improvement for all patients after SLIT was also evaluated. In this study, the overall controlled rate (including the well- and partially controlled group) reached 91.5%, which was higher than that in the previous report by Lin et al. [11]. We postulated possible reasons to be complications and the course of treatment. Overall, the subjective outcomes in the present study confirmed SLIT is an effective treatment for AR patients by reducing respiratory symptoms and medical usage.

To date, subjective assessments remain the primary and most frequently utilized method in outcomes research of allergen immunotherapy; however, given that AR patients are often accompanied by a series of nasal signs and it is difficult to quantify the subjective symptoms due to the fact that they depend largely on patients' perception, a nasal examination appears to be necessary and valuable [4, 6]. The availability of nasal endoscopy enables physicians to visualize the nasal cavity of AR patients. In China, the majority of hospitals have been equipped with endoscopic ex-

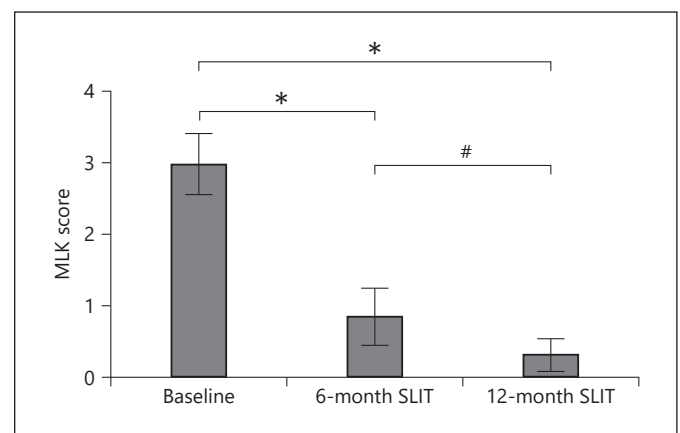
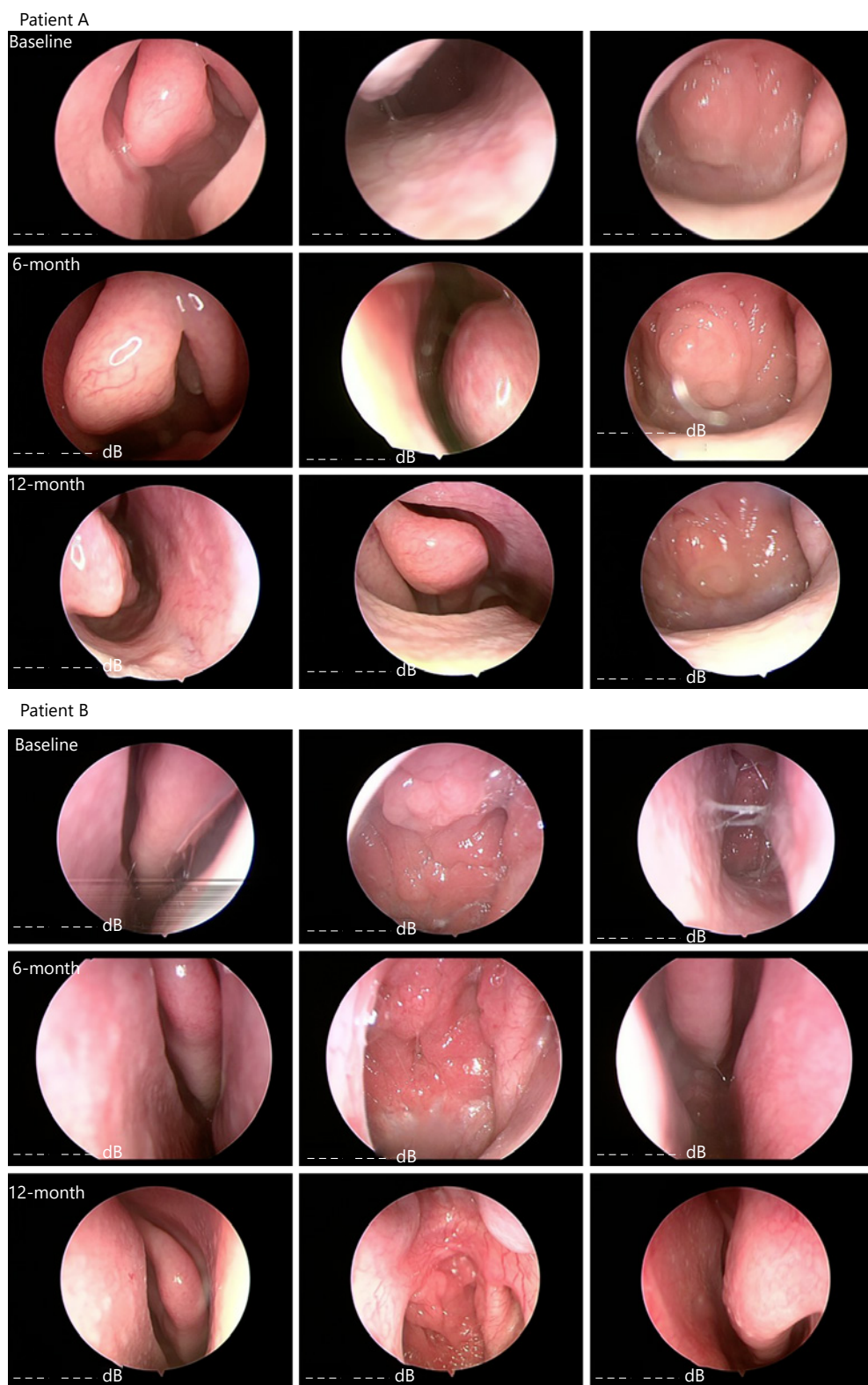


Fig. 3. MLK scores at baseline, 6-, and 12-month treatment. * $p < 0.05$, compared with the baseline; # $p < 0.05$, compared with the 6-month treatment). MLK, modified Lund-Kennedy.

Fig. 4. Representative endoscopy findings in 2 cases of AR patients at baseline, 6-, and 12-month treatment. For patient A, it could be observed that after SLIT treatment, the color of turbinate mucosa changed from pale to light red, nasal secretions decreased, and nasal mucosa edema disappeared significantly. The similar improvements of nasal signs were also founded in patient B. SLIT, sublingual immunotherapy; AR, allergic rhinitis.

(For figure see next page.)



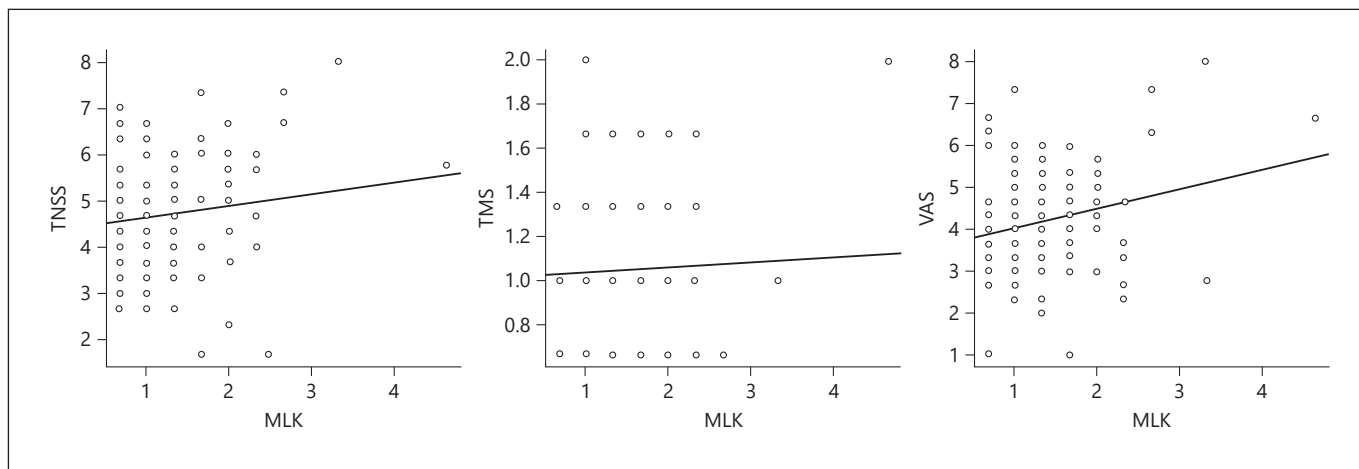


Fig. 5. Correlation between MLK scores and TNSS, TMS, and VAS (95% confidence interval). MLK, modified Lund-Kennedy; TNSS, total nasal symptoms score; VAS, visual analog scale; TMS, total medication score.

amination equipment [4]. Among the existing common endoscopic scoring systems, the MLK scoring system based on the degree of edema, polyps, and discharge was proven to have improved reliability and clinical correlation [7, 8]. In this study, the results of endoscopic examination demonstrated that SLIT was able to improve the nasal signs of AR patients, and the improvements mainly included changes in the color of the turbinate mucosa, reduction of nasal secretions, and improvement of nasal edema. Furthermore, we also observed a significant decrease in MLK scores and a positive correlation between the MLK and VAS scores. Above all, our results suggested that the endoscopic scoring system might be a reasonable and auxiliary tool to evaluate the clinical efficacy of SLIT.

The safety and tolerability of SLIT have been well documented and led to its widespread use in clinical application [2–5]. The most commonly encountered AEs were mild and involved local allergic reactions, which tended to recover without treatment in most cases [18–21]. So far, no severe systemic AEs were reported in published research or trials [2, 4]. Consistent with the previous reports, there were no serious AEs in all patients throughout the study, confirming that SLIT therapy has a good safety profile for AR patients.

The main limitation in this study is the absence of a pharmacotherapy control group. More clinical data and additional studies evaluating the utility of the MLK system in outcomes research of SLIT treatment will be our primary foci in the future.

In conclusion, besides the commonly utilized subjective assessments (TMS, TNSS, and VAS), our results of endo-

scopic examination and the MLK scores consistently confirmed that SLIT was efficacious in improving nasal signs of AR patients. The MLK endoscopic scoring system might be considered as an auxiliary tool to evaluate the clinical efficacy of SLIT in clinical practice and outcomes research.

Acknowledgement

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Statement of Ethics

The research protocol for this clinical study was approved by the Ethics Committee of Sir Run Run Shaw Hospital, Medical College of Zhejiang University (20210421-34). Subjects (or their guardians) provided written consent to participate in the study.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Author Contributions

S.H.: wrote the manuscript and critically reviewed the manuscript. S.H. and B.L.: examined patients and analyzed data. J.F.: collected the data and did statistical analysis.

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