



A Retrospective Cohort Study of Sublingual Immunotherapy with Standardized *Dermatophagoides farinae* Drops for Allergic Rhinitis

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ABSTRACT

Introduction: To evaluate the efficacy and safety of sublingual immunotherapy (SLIT) with standardized *Dermatophagoides farinae* (Df) drops in monosensitized and polysensitized patients with allergic rhinitis (AR) and to analyze the adverse events (AEs).

Methods: A retrospective analysis was performed using data for 68 patients with AR who received SLIT. The patients were divided into a monosensitized group (36 cases) and a polysensitized group (32 cases) based on serum-specific IgE test results. In the two groups of patients, total nasal symptoms score (TNSS), total medication score (TMS), visual analog scale (VAS) score, and AEs before treatment and at 1, 3, 6, and 12 months of treatment were evaluated.

Results: Compared with that before treatment, the TNSS, TMS, and VAS score in the monosensitized and polysensitized groups all decreased significantly at 3, 6, and 12 months of SLIT (all $P < 0.05$). There were no significant differences in treatment efficacy indicators between the two groups at all treatment time points (all $P > 0.05$). In terms of safety, compared with 1 month after initiating SLIT, the incidence of AEs in the monosensitized and polysensitized groups at 6 and 12 months of treatment significantly decreased (all $P < 0.05$). There was a statistically significant decrease in the incidence of AEs in both groups at 6 months compared with 3 months of treatment ($\chi^2 = 1.92$ and 5.85 , respectively, all $P < 0.05$). The difference in incidence of AEs between the monosensitized and polysensitized groups was not statistically significant at any treatment time point (all $P > 0.05$). AEs in all patients were local mild reactions; no serious AEs were found.

Conclusion: SLIT with standardized Df drops has similar efficacy and safety for monosensitized and polysensitized patients with AR. AEs mostly occurred during the first 3 months of SLIT in both the monosensitized and polysensitized groups, and the incidence of AEs gradually decreased as the course of treatment extended.

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Key Summary Points

Why carry out this study?

To evaluate the efficacy and safety of sublingual immunotherapy with standardized *Dermatophagoides farinae* drops in allergic rhinitis (AR) and to analyze the adverse events.

What did the study ask?

There is no longitudinal study on the incidence of AEs treated with sublingual immunotherapy.

What was learned from the study?

Although SLIT with standardized Df drops has similar efficacy and safety for monosensitized and polysensitized patients with AR, AEs mostly occurred during the first 3 months of SLIT in both groups, and the incidence of AEs gradually decreased as the course of treatment extended.

DIGITAL FEATURES

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INTRODUCTION

Allergic rhinitis (AR) is a common chronic inflammatory disease of the upper respiratory tract that not only seriously affects the quality of life of patients but also causes enormous social and economic burdens. As an emerging immunotherapy method, the efficacy and safety of sublingual immunotherapy (SLIT) for AR has been confirmed by a large number of clinical studies and meta-analyses [1–5]. To address the efficacy and safety of single allergens for

polysensitized patients, some studies have shown that SLIT with standardized *Dermatophagoides farinae* (Df) drops is equally effective and safe for monosensitized and polysensitized patients with AR [2, 6–9]. Clinically, SLIT is recommended for AR treatment because of its excellent safety and tolerance. A large number of studies in China have reported that the probability of adverse events (AEs) after patients with AR receive SLIT is 8.4–27.7% and that most AEs are mild local reactions [4, 9–11]; currently, there are no reports of serious AEs in China [12].

Although a number of clinical studies have confirmed the safety of SLIT in patients with AR, no study has reported the changes in the incidence of AEs at each treatment time point. To further guide clinical practice, this study retrospectively analyzed the efficacy of SLIT with standardized Df drops in monosensitized and polysensitized with ARs and focused on comparing changes in the incidence of AEs at different time points of SLIT.

METHODS

Study Participants

This was a retrospective study. A total of 68 patients with AR who were admitted to the Department of Otolaryngology of Zhangjiagang Hospital, China, and received 1-year SLIT with standardized Df drops between December 2018 and April 2019 were included as study participants; the data for these patients were collected and collated. The inclusion criteria were as follows [13]: (1) patients diagnosed with moderate to severe persistent AR according to the Guidelines for the Diagnosis and Treatment of Allergic Rhinitis (Tianjin, 2015); (2) detection results for serum-specific IgE (sIgE) of dust mites and/or house dust mites were positive and were ++ or higher than ++, combined with 1–2 other allergens or no other allergens; and (3) clinical symptoms and medical history of the patients were provided with the detection results. The exclusion criteria were as follows [13]: (1) patients with an active malignant tumor; (2) patients with acquired immunodeficiency

syndrome (AIDS); (3) patients with severe cardiovascular disease; (4) patients who were receiving β -blockers or angiotensin-converting enzyme (ACE) inhibitors; (5) patients who were immunodeficient; and (6) patients who were pregnant (contraindication for SLIT).

The patients were divided into a monosensitized group (36 cases) and a polysensitized group (34 cases) based on the sIgE detection results. Among them, the monosensitized group was positive only for dust mites and/or house dust mites; the polysensitized group also had 1–2 other types of allergens in addition to being positive for dust mites and/or house dust mites.

The study was performed in accordance with relevant guidelines and regulations, following the approval of the licensing committee of Zhangjiagang Hospital of Soochow University, Suzhou, China, and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Treatment Regimen

In this study, all patients were treated with standardized Df drops (Changdi, Zhejiang Wolwo Bio-pharmaceutical Co., Ltd., China), and standardized SLIT was performed according to the manufacturer's instructions. The treatment included a dose escalation phase and a dose maintenance phase. The specific administration regimen was as follows: for patients over 14 years of age, Df drop No. 1 (1 μ g/ml), No. 2 (10 μ g/ml), and No. 3 (100 μ g/ml) were administered at week 1, week 2, and week 3, respectively. Df drops were administered in the order of 1, 2, 3, 4, 6, 8, and 10 drops from day 1 to day 7. Df drop No. 4 (333 μ g/ml) was administered during weeks 4–5, with three drops each; from the 6th week, Df drop No. 5 (1000 μ g/ml) was administered as two drops each time, until the end of the entire treatment course. For children younger than 14 years of age, usage methods and dosage in the first 3 weeks were the same as those for patients older than 14 years. From the 4th week, Df drop No. 4 (333 μ g/ml) was administered as three drops each time, until the end of the treatment course. Except for the initial administration of

the drugs at the hospital, the remainder of the treatments were self-administered by the patients at home once a day. Each Df drop was placed under the tongue and swallowed after 1–3 min. Daily dosing at a fixed time was recommended.

All patients received initial education and follow-up education. Detailed patient records were established to record each patient's basic information, symptoms and signs, medical history, allergen test results, and medication usage. Regular follow-up visits were scheduled. During treatment, if a patient had systemic or local AEs, under the guidance of the clinician, symptomatic medication was combined with the drops in a timely manner or the dosage was adjusted appropriately to alleviate the adverse symptoms.

Efficacy Evaluation

This study assessed and analyzed the total nasal symptoms score (TNSS), total medication score (TMS), and visual analog scale (VAS) scores before treatment (baseline) and at 1, 3, 6, and 12 months during treatment. This information was collected during patient visits and from records of follow-up visits.

TNSS

A 4-point rating scale [14] (0 = asymptomatic, 3 = most severe) was used to evaluate four nasal symptoms (nasal obstruction, sneezing, nasal itching, and rhinorrhea). The scores for each symptom ranged from 0 to 3 points. The sum of the four items was the TNSS, ranging from 0 to 12.

VAS Score

Improvements in nasal symptoms in patients with AR were assessed using a 0–10.0 point scale, with 0 representing no symptoms and 10.0 representing the most severe symptoms.

Drug Evaluation

Medications were scored on the basis of the World Allergy Organization (WAO) guidelines [14]: one point for nasal, ophthalmic, or oral administration of antihistamines; two points

for inhaled or nasal glucocorticoids; and three points for oral glucocorticoids. The total score for all drugs was the TMS.

Statistical Analysis

Measurement data that conformed to a normal distribution are described as the mean $\pm$ standard deviation ($\bar{x} \pm s$). The χ^2 test was used for comparisons between groups of count data. The nonparametric Friedman's test for multiple correlated samples was used for intragroup comparisons, and the q test was used for pair-wise comparisons within groups. Intergroup comparisons of two independent samples were performed using the Wilcoxon rank sum test or the Mann–Whitney U test. A t test was used for comparison of mean age in Table 1. $P < 0.05$ was considered statistically significant. SPSS 20.0 statistical software was used for data processing.

RESULTS

Baseline Characteristics of the Patients

A total of 68 patients with AR (38 male, 30 female) with a mean age of 19.0 ± 12.8 years (range 4–52 years old) were included in this study. As shown in Table 1, before treatment (baseline), there was no significant difference in age or in the sex ratio between the monosensitized and polysensitized groups (all $P > 0.05$).

Comparison of Intragroup and Intergroup Efficacy Between the Monosensitized and Polysensitized Groups

The results of the comparison of clinical efficacy before and after treatment in the monosensitized and polysensitized groups are provided in Table 2. There was no significant difference in the TNSS, TMS, or VAS score between the two groups at baseline (all $P > 0.05$). Compared with that before treatment, the TNSS, TMS, and VAS score in the monosensitized and polysensitized groups all significantly decreased at 3, 6, and 12 months of treatment (all $P < 0.05$). There was no significant difference in the TNSS, TMS, and VAS score between the two groups at each treatment time point ($P > 0.05$).

Safety Assessment

The results of the comparison of the incidence of AEs at each treatment time point in the monosensitized and polysensitized groups are provided in Table 3. Compared with that after receiving 1 month of SLIT, the incidence of AEs was significantly decreased in the monosensitized and polysensitized groups at 6 and 12 months of treatment (all $P < 0.05$). The incidence of AEs at 6 months of treatment in patients in both groups significantly decreased compared to that at 3 months ($\chi^2 = 1.92$ and 5.85 , respectively, all $P < 0.05$). In addition, the difference in incidence of AEs between the monosensitized group and the polysensitized group was not statistically significant at each treatment time point (all $P > 0.05$).

Table 1 Baseline characteristics of patients

Group	Case number	Age	Sex	
			Male (<i>n</i>)	Female (<i>n</i>)
Monosensitized	36	21.7 ± 15.1	19	17
Polysensitized	32	16.5 ± 9.9	19	13
$\chi^2/t/z$		$t = -1.732$	$\chi^2 = 0.431$	
<i>P</i> value		0.09	0.51	

Note: t test was used for comparison of mean age

Table 2 Comparison of clinical efficacy scores before and during SLIT for patients with AR in the monosensitized and polysensitized groups

	Baseline	1 month	3 months	6 months	12 months
Monosensitized group					
TNSS	6.70 ± 2.44	6.57 ± 2.73	4.46 ± 2.38 ^a	2.73 ± 1.54 ^a	2.63 ± 2.22 ^a
TMS	2.32 ± 1.07	2.41 ± 1.32	1.27 ± 1.37 ^a	0.27 ± 0.64 ^a	0.51 ± 0.95 ^a
VAS	7.6 ± 1.4	7.5 ± 2.1	5.4 ± 2.2 ^a	3.1 ± 1.9 ^a	2.5 ± 2.2 ^a
Polysensitized group					
TNSS	6.94 ± 2.22	6.74 ± 3.20	4.74 ± 2.67 ^a	2.74 ± 1.61 ^a	2.28 ± 2.41 ^a
TMS	2.44 ± 1.14	2.26 ± 1.40	1.03 ± 1.29 ^a	0.26 ± 0.66 ^a	0.21 ± 0.58 ^a
VAS	7.38 ± 1.55	6.88 ± 2.67	5.21 ± 2.59 ^a	3.12 ± 1.78 ^a	2.18 ± 2.26 ^a

TNSS total nasal symptoms score, TMS total medication score, VAS visual analog scale

^a Compared to baseline, $P < 0.05$

Table 3 Comparison of the incidence of AEs in the monosensitized and polysensitized groups (n, %)

Group	1 month	3 months	6 months	12 months
Monosensitized	16 (44.4%)	11 (30.5%)	3 (8.3%) ^{ab}	6 (16.7%) ^a
Polysensitized	16 (50.0%)	11 (34.4%)	3 (9.4%) ^{ab}	4 (12.5%) ^a

^a Compared with 1 month of treatment, $P < 0.05$

^b Compared with 3 months of treatment, $P < 0.05$

The AEs that occurred were local mild reactions, including itchy throat, vomiting, urticaria, fatigue, itchy eyes, and mild cough. Among them, fatigue, itchy throat, and vomiting were all left untreated and resolved on their own, while other AEs resolved after the oral administration of antihistamines.

DISCUSSION

A large number of clinical studies and meta-analyses have shown that SLIT can effectively improve the nasal symptoms of patients with AR, reduce the use of symptomatic drugs, and improve the quality of life of patients. Therefore, SLIT is recommended as the first-line therapy for the treatment of AR [1–5, 15]. Liu

et al. [16] reported that in 573 patients with AR who received 1 year of SLIT, there were significant improvements in the TNSS, TMS, and VAS score compared with baseline, indicating significant efficacy of SLIT for the treatment of dust mite-induced AR in both children and adults. In this study, the intragroup comparison of patients in the monosensitized and polysensitized groups revealed that all clinical indicators improved significantly in both groups after SLIT, further confirming the efficacy of SLIT in patients with AR. A multicenter, randomized, double-blind, placebo-controlled study [17] showed that the onset of action for SLIT in the treatment of patients with AR was 14 weeks and that efficacy continued in the subsequent treatment process. In this study, the TNSS, TMS, and VAS score significantly improved in

patients in both groups at 3 months of SLIT, consistent with results from previous reports [17, 18], suggesting that rhinitis symptoms in and medication use by patients with AR significantly improved at 3 months of treatment.

Clinical observations have shown that the proportion of polysensitized patients is much higher than that of monosensitized patients [16]. A cross-sectional study conducted in China showed that more than 90% of the participants were allergic to two or more types of allergens [19]. The efficacy of SLIT with a single Df preparation in polysensitized patients has been confirmed in some clinical trials. Huang et al. [7] reported that after SLIT with a Df preparation for 2 years, the nasal symptoms and symptomatic drug use in monosensitized and polysensitized children markedly improved and that the differences between these groups were not statistically significant. Chen et al. [6] compared the efficacy scores for 69 patients with AR before and after treatment; the results indicated that SLIT is effective for both monosensitized and polysensitized patients. The results of this study showed that the differences in the TNSS, TMS, and VAS score between these two groups were not statistically significant, further confirming that SLIT with standardized Df drops has similar efficacy for monosensitized and polysensitized patients with AR.

SLIT is a safe alternative to traditional subcutaneous immunotherapy injections. It has excellent safety and tolerance for both monosensitized and polysensitized patients. Cui et al. [2] found that only 11 of 162 pediatric patients who received SLIT had mild or moderate AEs and that the difference in incidence of AEs between monosensitized and polysensitized patients was not statistically significant. Consistent with previous reports, in this study, AEs in all patients were local and mild, mainly manifesting as itchy throat, vomiting, urticaria, fatigue, itchy eyes, and mild cough. By comparing the incidence of AEs between monosensitized and polysensitized patients with AR, this study confirmed that the safety profile for SLIT was not significantly different between these two patient groups.

Notably, although a large number of clinical studies have confirmed the safety of SLIT in

patients with AR, no study has reported changes in the incidence of AEs at different time points of treatment. In this study, we compared the incidence of AEs at different treatment time points and found that AEs mostly occurred during the first 3 months of SLIT in both monosensitized and polysensitized patients and that the incidence of AEs gradually decreased with the extension of the treatment course. Considering that SLIT is mostly self-administered by patients at their homes and is not directly monitored by medical staff, the results of this study suggest that patients should be closely monitored for AEs during the first 3 months of SLIT so as to respond to patients' problems in a timely manner. Importantly, AEs are one of the most important factors affecting patient compliance [20]. Therefore, it is essential to educate patients in advance (especially to inform them about identifying and dealing with AEs) and during follow-up and to communicate with them regularly, so as to enhance their treatment compliance and confidence. One may raise the question whether type II error may be at play as a result of the size of clinically important differences or given point estimates and confidence intervals for between-group differences. Notably, the sample size of patients enrolled in this retrospective study was relatively small, and the types of different local AEs were not well documented for shorter intervals (e.g., weekly) during the first 3 months of SLIT. We will carry out more in-depth follow-up and observations on these issues in future studies.

CONCLUSION

This study further confirmed the efficacy and safety of SLIT with standardized Df drops in monosensitized and polysensitized patients with AR. By comparing the incidence of AEs at different treatment time points, this study showed that AEs mostly occurred during the first 3 months of SLIT in both monosensitized and polysensitized patients and that the incidence of AEs gradually decreased during the course of treatment.

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Disclosures. Xingkai Ma, Yu Zhang, Xiaodan Gu, Geping Wu, Jianyong Liu, Jianbin Lu, and Huijun Yang have nothing to disclose.

Compliance with Ethics Guidelines. The study was performed in accordance with relevant guidelines and regulations, following the approval of the licensing committee of Zhangjiagang Hospital of Soochow University, Suzhou, China, and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. We thank the participants of the study.

Data Availability. The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Cheng L, Zhou WC. Sublingual immunotherapy of house dust mite respiratory allergy in China. *Allergol Immunopathol.* 2019;47:85–9.
2. Cui L, Li J, Li Y, Xia Z. Long-term efficacy of sublingual mite immunotherapy in monosensitized and polysensitized children with allergic rhinitis: a 7-year prospective study. *Int Arch Allergy Immunol.* 2019;180:144–9.
3. Lin Z, Liu Q, Li T, Chen D, Chen D, Xu R. The effects of house dust mite sublingual immunotherapy in patients with allergic rhinitis according to duration. *Int Forum Allergy Rhinol.* 2016;6:82–7.
4. Wang C, Wang K, Liu S, Qin X, Chen K, Zhang T. Decreased level of osteopontin in children with allergic rhinitis during sublingual immunotherapy. *Int J Pediatr Otorhinolaryngol.* 2016;81:15–20.
5. Zhang Y, Zhang L. Increasing prevalence of allergic rhinitis in China. *Allergy Asthma Immunol Res.* 2019;11:156–69.
6. Chen BY, Long ZM, Huang YJ, Zeng JM. Efficacy of sublingual immunotherapy with *Dermatophagoides farinae* drops in monosensitized and polysensitized patients with allergic rhinitis. *Chin J Otorhinolaryngol Head Neck Surg.* 2013;48:549–54.
7. Huang S, Xie X, Chen Y, et al. Study on the efficacy and safety of sublingual immunotherapy with standardized *Dermatophagoides farinae* drops for allergic rhinitis. *J Clin Otorhinolaryngol Head Neck Surg.* 2015;29:618–21.
8. Liu J, Hu X, Fu S, Wu C, Chen H, Zhang M. Efficacy of individualized sublingual immunotherapy with *Dermatophagoides farinae* drops on patients with allergic rhinitis of different age groups. *J Clin Otorhinolaryngol Head Neck Surg.* 2014;28:289–92.
9. Shao J, Cui YX, Zheng YF, et al. Efficacy and safety of sublingual immunotherapy in children aged 3–13 years with allergic rhinitis. *Am J Rhinol Allergy.* 2014;28:131–9.
10. Lin X, Lin H, Wei X, Huang Q. The efficacy and safety of sublingual immunotherapy in children and adult patients with allergic rhinitis. *Allergol Immunopathol.* 2017;45:457–62.
11. Lin Z, Zhou L, Luo X, et al. Suppression of TIM-1 predicates clinical efficacy of sublingual immunotherapy for allergic rhinitis in children. *Int J Pediatr Otorhinolaryngol.* 2013;77:1345–9.

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12. Li H, Chen S, Cheng L, et al. Chinese guideline on sublingual immunotherapy for allergic rhinitis and asthma. *J Thorac Dis.* 2019;11:4936–50.
 13. Cheng L, Chen J, Fu Q, et al. Chinese society of allergy guidelines for diagnosis and treatment of allergic rhinitis. *Allergy Asthma Immunol Res.* 2018;10:300–53.
 14. Canonica GW, Baena-Cagnani CE, Bousquet J, et al. Recommendations for standardization of clinical trials with Allergen Specific Immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) taskforce. *Allergy.* 2007;62:317–24.
 15. Subspecialty Group of Rhinology, E.B.o.C.J.o.O.H., Neck, S., Subspecialty Group of Rhinology, S.o.O.H., Neck Surgery, C.M.A. Chinese guidelines for diagnosis and treatment of allergic rhinitis. *Chin J Otorhinolaryngol Head Neck Surg.* 2016;51:6–24.
 16. Liu X, Ng CL, Wang Y. The efficacy of sublingual immunotherapy for allergic diseases in Asia. *Allergol Int.* 2018;67:309–19.
 17. Wang DH, Chen L, Cheng L, et al. Fast onset of action of sublingual immunotherapy in house dust mite-induced allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial. *Laryngoscope.* 2013;123:1334–40.
 18. Okamoto Y, Fujieda S, Okano M, Yoshida Y, Kakudo S, Masuyama K. House dust mite sublingual tablet is effective and safe in patients with allergic rhinitis. *Allergy.* 2017;72:435–43.
 19. Li J, Sun B, Huang Y, Lin X, et al. A multicentre study assessing the prevalence of sensitizations in patients with asthma and/or rhinitis in China. *Allergy.* 2009;64:1083–92.
 20. Senna G, Ridolo E, Calderon M, Lombardi C, Canonica GW, Passalacqua G. Evidence of adherence to allergen-specific immunotherapy. *Curr Opin Allergy Clin Immunol.* 2009;9:544–8.