ORIGINAL ARTICLE

Eur Ann Allergy Clin Immunol Vol 57, N.2, 68-76, 2025

Jing Pei, Zhaoran Ding, Ling Cai, Huifen Yang, Yuejin Tao*, Caiqin Huang*

Clinical efficacy and safety evaluation of *Dermatophagoides farinae* drops in the treatment of allergic rhinitis with epistaxis

Department of Otolaryngology, The Affiliated Jiang Ning Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
*The authors contributed equally to this work

Key words

Allergic rhinitis; epistaxis; house dust mite; sublingual immunotherapy; efficacy.

Corresponding author
Caiqin Huang
Department of Otolaryngology
The Affiliated Jiang Ning Hospital of Nanjing Medical University
Hu Shan Road 169
Jiang Ning, Nan Jing
Jiang Su 211100, China
ORCID: 0009-0008-1965-6014
E-mail: jnyyhcq@163.com

Doi
10.23822/EurAnnACI.1764-1489.342

Impact statement

The symptoms of rhinitis and epistaxis were both improved after SLIT treatment, indicating the remarkable efficacy and safety for AR patients with epistaxis.

Summary

Background*. Epistaxis is frequently observed in allergic rhinitis (AR) patients. However, few studies focus on the outcome of epistaxis with treatment of AR patients. This study aimed to retrospectively analyze the efficacy and safety of AR patients with epistaxis treated with sublingual immunotherapy (SLIT).* ***Methods****. A total of 74 patients aged 4-60 years with house dust mite (HDM)-induced AR accompanied by epistaxis and who completed 1 year of SLIT treatment with standard Dermatophagoides farinae (D. farinae) drops were enrolled in this study. The symptom scores, total medication scores (TMS), combined symptom and medication score (CSMS), visual analog scales (VAS), and bleeding score (BS) were assessed, as well as the nasal endoscopic examinations were performed to observe nasal signs.* ***Results.*** *The levels of symptom scores, TMS, CSMS, VAS, and BS at 0.5 year and 1 year of SLIT treatment were significantly lower than those at the baseline (all $p < 0.01$). Also, statistical differences were seen in CSMS ($p < 0.05$) and VAS ($p < 0.01$) between 0.5 year and 1 year. As expected, BS was positively correlated with CSMS ($r = 0.617$, 95%CI 0.517-0.699) and VAS ($r = 0.777$, 95%CI 0.719-0.822) at all three time points.* ***Conclusions****. SLIT with D. farinae drops was effective and safe for AR patients with epistaxis, resulting in improving the symptoms of rhinitis while relieveing the symptoms of epistaxis.*

Introduction

Allergic rhinitis (AR) has evolved as the most common allergic disease during the past few decades, which carries a significant disease burden both at individual and societal levels (1-3). In China, a huge economic burden of 51.28 billion EUR per year was constituted by ARs (4). Not only that, the life quality of AR patients was also seriously affected. In outpatient practice, epistaxis is a common concomitant symptom and frequently observed in AR patients (5-9). Potentially, the pathological changes including edema of the nasal mucosa, nasal vasodilatation, angiogenesis, and increased vascular permeability associated with AR lead to increased fragility of the nasal mucosa, which is prone to blood vessel damage and epistaxis (5). At the same time, repeated picking/rubbing and nose blowing behavior related to itching/rhinorrhea caused by AR could also damage the nasal mucosa and

frequently lead to epistaxis (8, 9). In general, epistaxis makes AR patients bear greater psychological and physiological burden. Until now, few studies have focused on epistaxis and AR (7-9). A preceding study reported on the outcome of epistaxis with treatment of underlying AR. The result had shown that there was a clinically significant improvement in the frequency and severity of epistaxis after symptomatic drug treatment of AR, indicating that the valid treatment of AR could be beneficial to the prevention and treatment of epistaxis (9). Compared with drug therapy, AIT was regarded as an etiotropic therapy with remarkable clinical efficacy and safety, especially the emerging immunotherapy method of sublingual immunotherapy (SLIT) (10-13). In clinical practice, SLIT could improve the nasal signs including nasal mucosa edema and telangiectasia, the nasal symptoms, and the use of anti-allergic drugs in AR patients (14-16). These improvements could further lead to a healthier nasal mucosa, reduced picking/rubbing and nose blowing behavior, and less risk of epistaxis for higher doses of intranasal corticosteroids used to treat AR (17). As far as we know, only a few studies were reported on the outcome of SLIT for the treatment of AR with epistaxis (18). Therefore, this retrospective study aimed to further investigate the clinical efficacy and safety of SLIT treatment with *D. farinae* drops in AR patients accompany with epistaxis.

Materials and methods

Ethical approval and consent to participate

This study protocol was approved by the Medical Ethics Committee of the Affiliated Jiang Ning Hospital of Nanjing Medical University (No.2023-03-055-K01) and the patients (or their guardians) signed informed consent forms.

Study subjects

This was a retrospective study conducted in the Affiliated Jiangning Hospital of Nanjing Medical University from April 2020 to May 2022. The complete data of 74 patients aged 4-60 years with house dust mite (HDM)-induced intermittent or persistent AR with epistaxis were included in the study. All patients met the treatment criteria of SLIT and had received one whole year treatment with standard *Dermatophagoides farinae* (*D. farinae*) drops. The treatment criteria of SLIT included: 1) patients have been diagnosed with moderate-to-severe AR according to Allergic Rhinitis and Its Impact on Asthma and combined with epistaxis; 2) patients have a clinical history of mite allergy and sensitization to *D. farinae* with/without *Dermatophagoides pteronyssinus* (*D. pteronyssinus*) as assessed by a positive skin prick test (SPT) with grade ≥ 2 (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., Zhejiang, China); 3) patients without immunodeficiency, non-stable or severe systemic diseases such as poorly controlled cardiovascular diseases, immune diseases, or malignant tumors, receiving β-blockers or angiotensin-converting enzyme inhibitors, serious psychological barriers or failed to understand the risks and limitations of treatment; pregnancy or lactation, or planning pregnancy within 1 year.

Sublingual immunotherapy

Patients were treated with standardized *D. farinae* drops (Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., Zhejiang, China) labeled from No. 1 to No. 5. The total protein concentration of No. 1-5 was 1, 10, 100, 333, and 1,000 μg/mL, respectively. In the up-dosing phase of SLIT, patients were administrated with increasing doses starting from No. 1 to No. 3 during the first 3 weeks and 50, 100, 150, 200, 300, 400, and 500 μL were given day after day in a week, respectively. Then, the patients aged < 14 years were instructed to have 150 μL of No. 4 per day from the fourth week to the end of the treatment. While patients aged ≥ 14 years were instructed to have 150 μL of No. 4 per day during the fourth and fifth weeks, and then take 100 μL of No. 5 per day from the sixth week until the end of the treatment. Drops were instructed to be kept under the tongue for 1-3 minutes before being swallowed. The first SLIT administration was given in doctors' office and the patient should be observed for at least 30 minutes.

Clinical assessments

During the treatment, patients (or their guardians) were required to record symptoms and medicine use through the electronic diary. The symptom scores, total medication scores (TMS), combined symptom and medication score (CSMS), visual analog scales (VAS), and bleeding score (BS) were assessed at baseline, 0.5 year, and 1 year after SLIT. The total nasal symptom score (TNSS) was defined as the sum of 4 nasal symptom scores, including sneezing (number/day, ≤ 2 = 0, 3 to 5 = 1, 6 to 10 = 2, ≥ 11 = 3), rhinorrhea (times/day, none = 0, 1 to 4 = 1, 5 to 9 = 2, ≥ 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). TMS were assessed according to the daily dosage recommended by the drug instructions for controlling AR symptoms (none = 0, oral antihistamines or anti leukotrienes = 1, topical glucocorticoid = 2, oral glucocorticoid = 3). Then, CSMS was calculated ultimately according to the formula: CSMS = TNSS/4 + TMS, which is used to reflect the severity of symptoms and medication intake simultaneously (15, 16, 19-22). VAS ranges from 0 to 10 and assesses the severity of patients' symptoms by themselves. 0 expressed "no symptoms" and 10 indicated "maximum symptoms". BS were scored from 0 to 4 (none or bleeding less than 5 times/year = 0; mild, bleeding more than 5 times/year or each bleeding time less than 10 minutes = 1; moderate, bleeding more than 10-20 times/year, and each bleeding time more than 20 minutes = 2; relatively

severe, require bandage, cauterize, or administer antifibrinolytic drugs = 3; severe, require blood transfusion, decompression, or emergency hospitalization = 4) (23). The score in baseline is the average situation of the previous week reviewed by the patient. The scores at 0.5 year and 1 year were the average daily scores of 1 week before and 1 week after each follow-up time point.

Considering that AR patients were often accompanied by a series of changes in nasal signs, such as pale edema of the nasal mucosa, runny nose, swelling of the inferior turbinate, *etc.*, the nasal signs of patients at 3 time points were also collected through nasal endoscopy in this study.

Adverse events

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

Patient management

Initial clinical education and follow-up education were carried out for all patients. The patient education includes: 1) the nature causes and hazards of AR with epistaxis; 2) the characteristics of SLIT and its relationship with anti-allergic drugs; 3) the methods, courses of treatment, costs, efficacy, and safety of SLIT; and 4) advices on how to avoid allergen and deal with AEs. The patient files were established to record the symptoms, medication use, and AEs during the whole treatment. Telephone follow-ups were provided to solve problems during the treatment process.

Statistical analysis

Statistical analysis was performed with SPSS software 21.0. 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 $p = 0.05$ and the effect size was calculated using Cliff's Delta. The Spearman bivariate analysis was performed to determine potential differences and correlation coefficients between CSMS, VAS, and BS. The 95% confidence interval of the correlation coefficient was estimated by the bootstrap method.

Results

The evaluation of four nasal symptoms

The four typical symptom scores of AR were drawn in **figure 1**. Compared with the baseline (sneezing: $\bar{x}$ = 1.46, 95%CI 1.27-1.64; rhinorrhea: $\bar{x}$ = 1.42, 95%CI 1.23-1.61; nasal obstruction: $\bar{x}$ = 1.59, 95%CI 1.39-1.80; nasal itching: $\bar{x}$ =1.58, 95%CI 1.36-1.80), the individual nasal symptom score of 0.5 year (sneezing: = 0.82, 95%CI 0.68-0.97, effect size = 0.42; rhinorrhea: $\bar{x}$ =0.77, 95%CI 0.61-0.93, effect size = 0.42; nasal obstruction:$\bar{x}$ = 0.74, 95%CI 0.57-0.92, effect size = 0.51; nasal itching: $\bar{x}$ = 0.73, 95%CI 0.54-0.92, effect size = 0.49; all $p < 0.01$) and 1 year (sneezing: $\bar{x}$ = 0.46, 95%CI 0.32-0.60, effect size = 0.65; rhinorrhea: $\bar{x}$ = 0.42, 95%CI 0.27-0.57, effect size = 0.63 ; nasal obstruction: $\bar{x}$ = 0.41, 95%CI 0.26-0.55, effect size = 0.69; nasal itching: $\bar{x}$ = 0.42, 95%CI 0.27-0.57, effect size = 0.66; all $p < 0.01$) after SLIT treatment both significantly declined. Meanwhile, the score of sneezing (effect size = 0.31, $p < 0.01$), rhinorrhea (effect size = 0.30, $p < 0.01$), and nasal obstruction (effect size = 0.26, $p < 0.05$) exhibited significant differences between 0.5 and 1 year. As for nasal itching, the score at 1 year showed a lower level compared with 0.5 year, but there was no significant difference ($p > 0.05$).

The evaluation of TMS, CSMS, VAS, and BS

Except for the improvement of symptoms, the levels of TMS, CSMS, VAS, and BS were also evaluated in detail. Compared with the baseline (TMS: $\bar{x}$ = 1.84, 95%CI 1.75-1.92; CSMS: $\bar{x}$ = 3.35, 95%CI 3.16-3.54; VAS: $\bar{x}$ = 7.49, 95%CI 7.14-7.83; BS: $\bar{x}$ =1.81, 95%CI 1.63-1.99), the level of these outcomes at 0.5 year (TMS: $\bar{x}$ = 0.01, 95%CI -0.01-0.04, effect size = 1.00; CSMS: $\bar{x}$ = 0.78, 95%CI 0.66-0.90, effect size = 0.98; VAS: $\bar{x}$ = 3.04, 95%CI 2.58-3.50, effect size = 0.92; BS: $\bar{x}$ =0.42, 95%CI 0.27-0.57, effect size = 0.80; all $p < 0.01$) and 1 year (TMS: $\bar{x}$ = 0.08, 95%CI 0.02-0.14, effect size = 0.99; CSMS: $\bar{x}$ = 0.51, 95%CI 0.35-0.66, effect size = 0.98; VAS: $\bar{x}$ = 1.86, 95%CI 1.43-2.30, effect size = 0.96; BS: $\bar{x}$ =0.19, 95%CI 0.10-0.28, effect size = 0.92; all $p < 0.01$) after SLIT treatment were significantly declined (**figure 2**). Not only that, but there were also statistical differences in CSMS (effect size = 0.37, $p < 0.05$) and VAS (effect size = 0.36, $p < 0.01$) between 0.5 year and 1 year. However, no statistical difference was seen in TMS and BS scores between the two time points ($p > 0.05$).

Nasal endoscopy finding

The nasal endoscopic examinations were performed at baseline, 0.5 year, and 1 year. And the representative endoscopy findings of 2 cases of AR patients were shown in **figure 3**. For both patients, A and B, the nasal signs were significantly improved after SLIT treatment compared with the baseline, with the improvements including color change of the turbinate mucosa (from pale to light red), reduction of nasal secretion and blood, and disappearance of nasal mucosal edema.

Correlation analysis

In this study, the correlation of BS with CSMS and VAS was calculated and analyzed. A positive correlation of BS was observed with CSMS (r = 0.617, 95%CI 0.517-0.699, **figure 4A**) as well as VAS (r = 0.777, 95%CI 0.719-0.822, **figure 4B**).

Adverse events

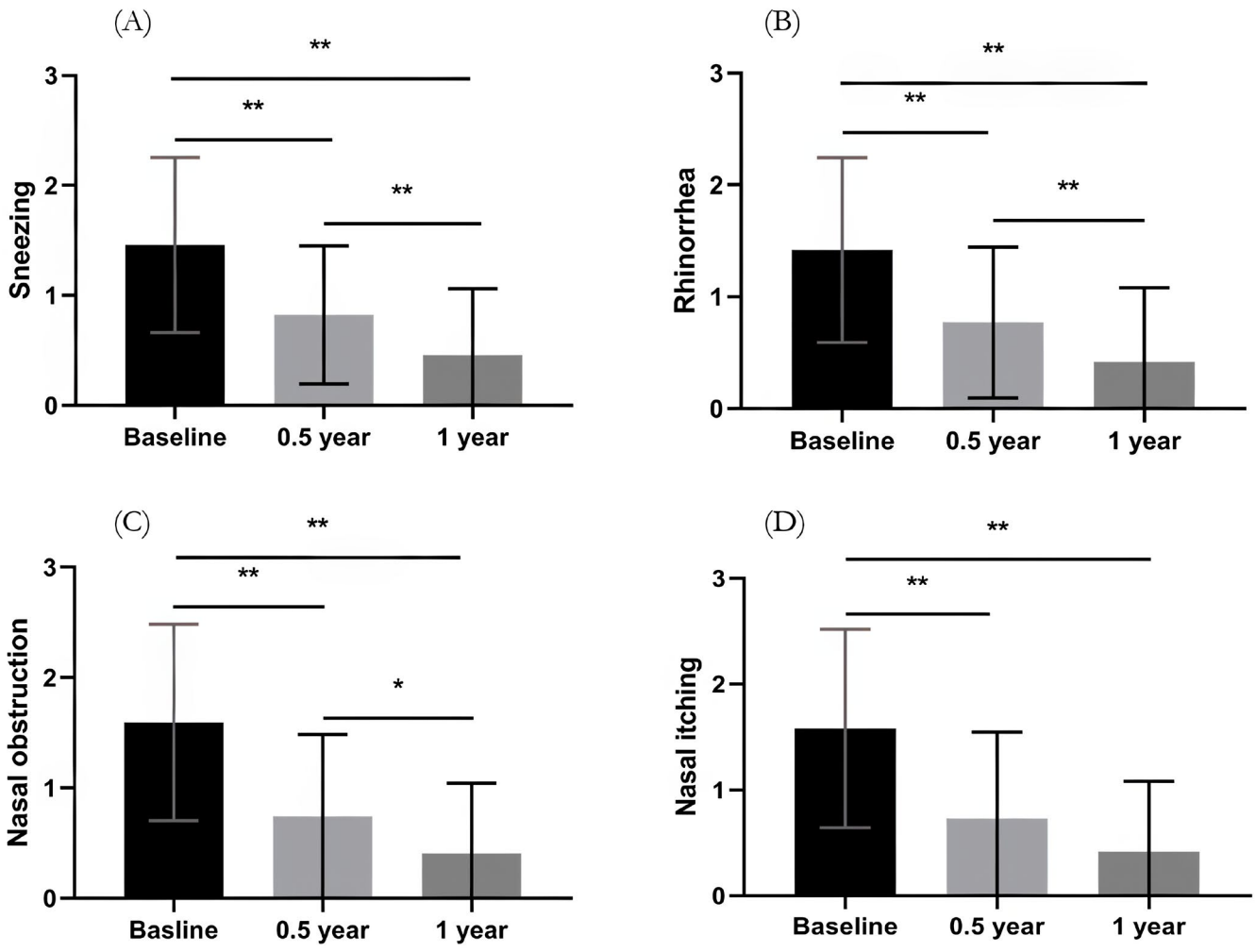
All of the AEs, based on five levels (0-4 scale) according to the grading system proposed by World Allergy Organization (WAO) immunotherapy committee (24), were promptly addressed under

the instruction of the physician. No severe systemic AEs, anaphylaxis, acute attack of asthma, or use of adrenaline were reported. Seven patients reported 7 local AEs, including 3 skin local rash, 1 hypoglossal edema, and 3 symptom aggravation. All AEs in this study were grade 1 and relieved within a week without medication.

Discussion and conclusions

AR is a highly prevalent chronic disease that limits the self-image and psychosocial interaction of patients (2). Until now, the clinical effect of SLIT on HDM-induced AR had been proven by plenty of clinical trials (15, 16, 25-27). A previous study showed that the early effect of SLIT was generally observed in 3 to 6 months (28). Similarly, the individual nasal symptom scores, TMS, CSMS, and VAS signally declined after 0.5 year of SLIT in this study. Besides, these clinical scores continued decreasing with prolonged treatment when compared with 0.5 year. Our results further substantiated the previous findings that the longer duration of SLIT treatment contributes to the better efficacy

Figure 1 *- Analysis of four individual AR typical symptoms* ***(A)*** *sneezing,* ***(B)*** *rhinorrhea,* ***(C)*** *nasal obstruction, and* ***(D)*** *nasal itching at the baseline, 0.5 year, and 1 year of SLIT treatment.*



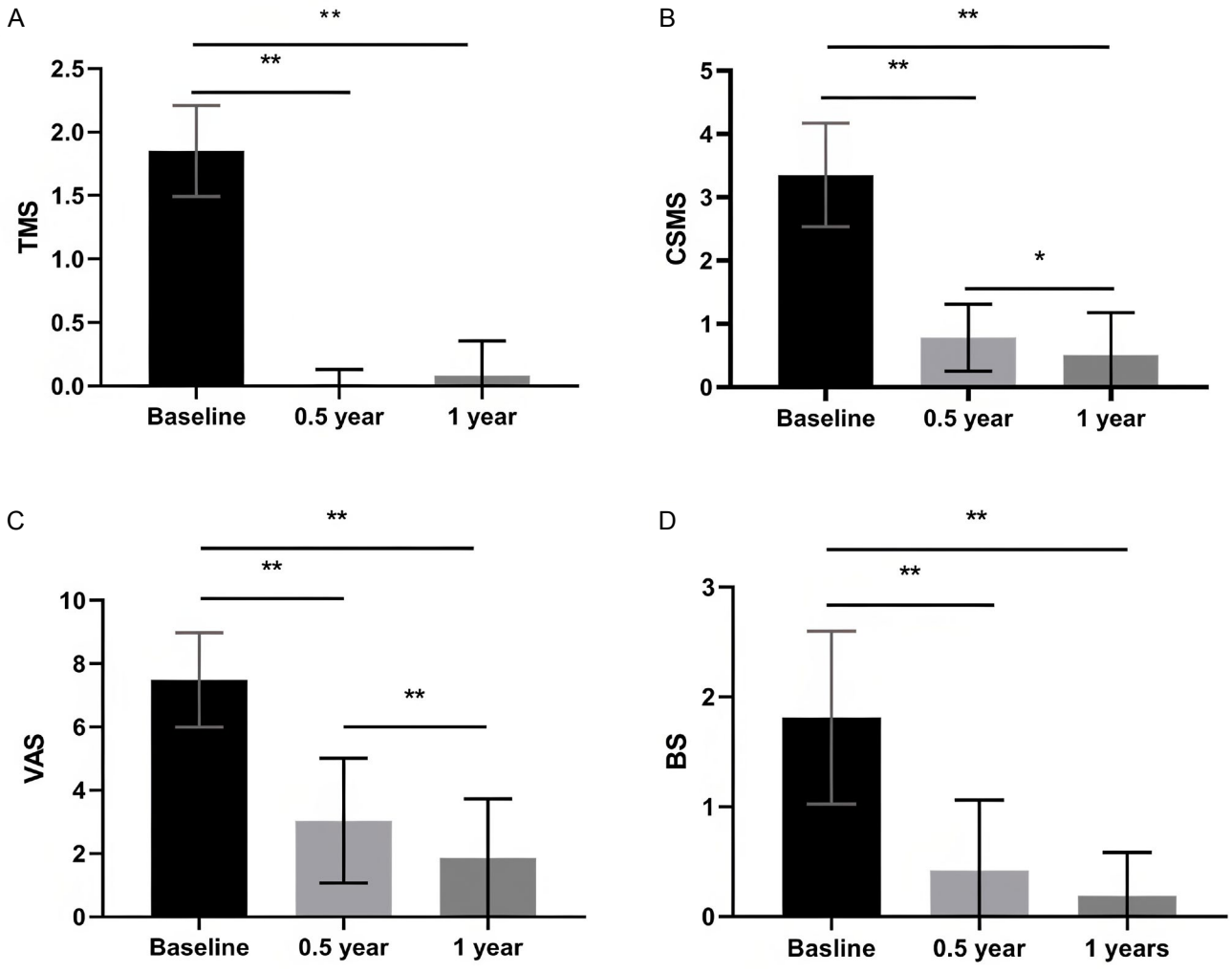
*p < 0.05; **p < 0.01, significant difference between different time points; AR: allergic rhinitis.

(29, 30). Also, our findings manifested that SLIT performed a significant efficacy on AR patients.

In outpatient practice, epistaxis is frequently observed in AR patients (7-9, 31). A few literatures confirmed the improvement of nasal symptoms and nasal bleeding after the treatment of AIT in AR patients co-existing with epistaxis (18, 32, 33). Shao *et al.* (18) focused on the efficacy of SLIT with *D. farinae* drops on pediatric patients by evaluating the score of epistaxis symptoms. In our study, the same criteria was used to assess the improvements of epistaxis. Our results exhibited significantly declined in BS scores after 0.5 year and 1 year SLIT treatment, which is consistent with the conclusions of the previous published study (18). Our study also first analyzed that BS was positively correlated with CSMS and VAS.

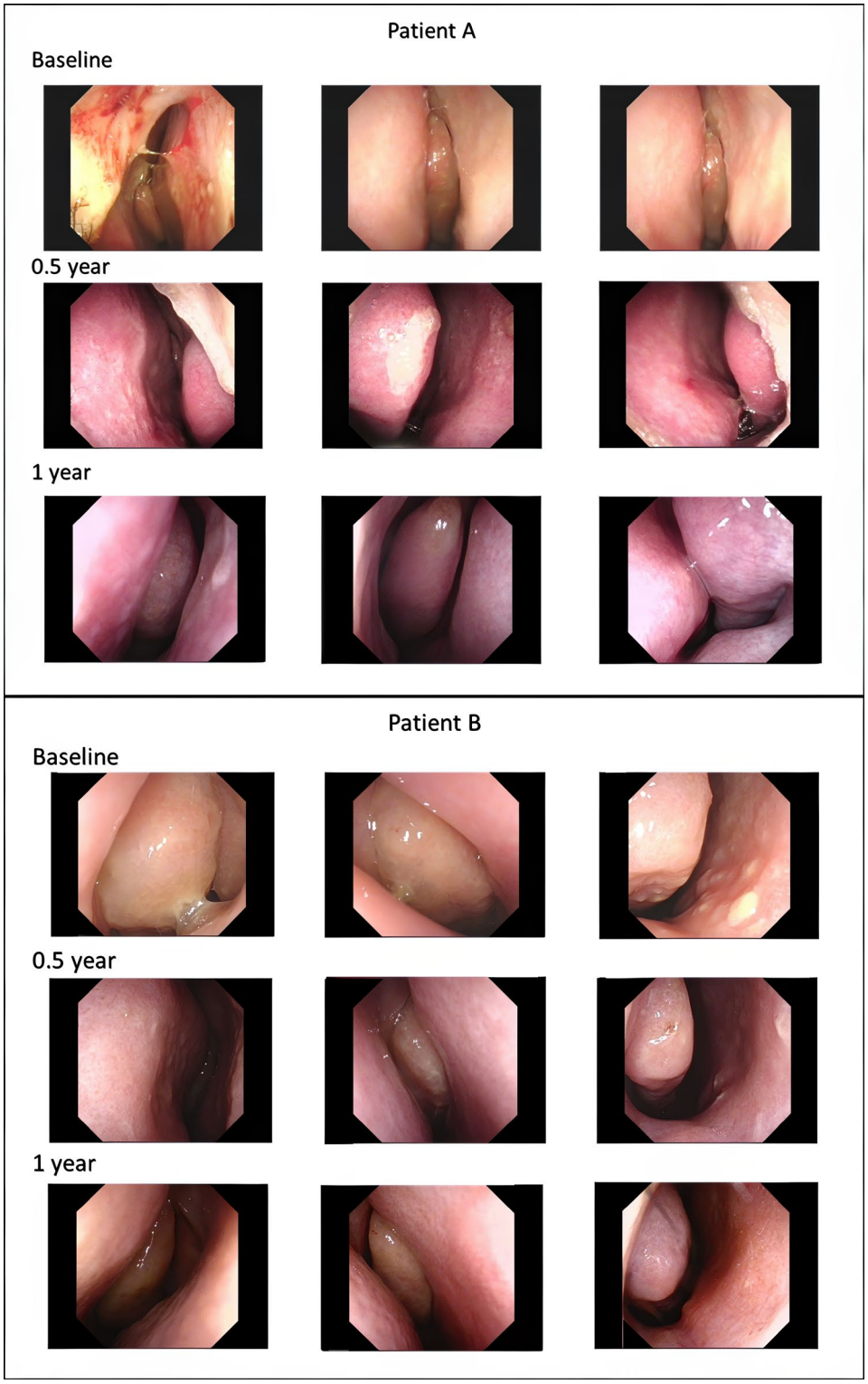
In addition, the changes of patients' nasal signs were observed using nasal endoscopy. After treatment, the nasal mucosa returned to

Figure 2 - *The comparison at the baseline, 0.5 year, and 1 year of SLIT treatment of* ***(A)*** *TMS;* ***(B)*** *CSMS;* ***(C)*** *VAS;* ***(D)*** *BS.*



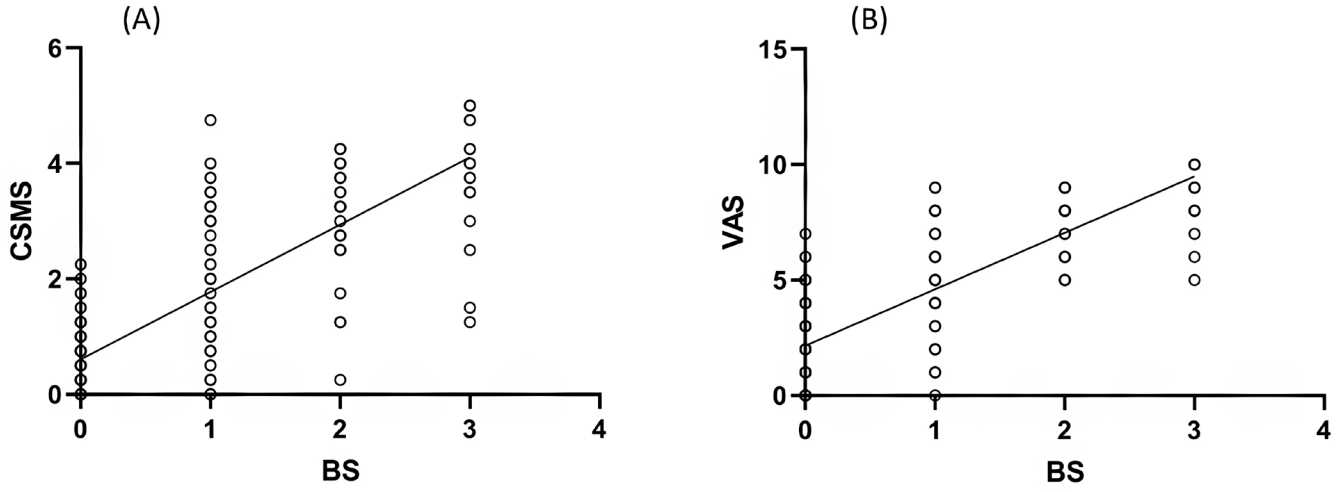
**p < 0.01, *p < 0.05: significant difference between different time points; TMS: total medication score; CSMS: combined symptom and medication score; VAS: visual analogue scale; BS: bleeding score.

Figure 3 *- Representative endoscopy findings in 2 cases of AR patients at baseline, 0.5 year, and 1 year after treatment.*



AR: allergic rhinitis.

Figure 4 *- Correlation between different clinical outcomes:* ***(A)*** *CSMS and BS;* ***(B)*** *VAS and BS (95% CI).*



CSMS: combined symptom and medication score; BS: bleeding score; VAS: visual analogue scale; CI: confidence interval.

a healthy state with nasal secretions, hyperaemia, and inflammation alleviated. Overall, the alleviated or even disappeared symptoms of AR and epistaxis might be probably due to the improvement of nasal signs.

The safety of SLIT has been demonstrated in multiple articles of numerous clinical trials (34-37). The incidence of AEs in Chinese AR patients undergoing SLIT ranged from 8.4% to 27.7% according to the summarized results of several preceding reports (2, 35-37). In our study, the AE rate of SLIT in AR patients with epistaxis was 9.5%, suggesting that the concomitant disease such as epistaxis did not increase the occurrence of AEs. Meanwhile, the main AEs were local AEs such as transient oral swelling and skin local rash. These results identified that SLIT was generally safe and could be well tolerated in AR patients with epistaxis.

Some limitations of this study should be acknowledged. First, the number of patients was small. Second, the impact of HDM level in the environment which might be variable in different seasons wasn't considered. Thirdly, the course of treatment was short, the long-term efficacy of SLIT for AR with epistaxis was not investigated. In the future, studies with larger sample sizes, larger geographical areas, and longer treatment duration would be researched to further provide more evidence on the short-term and long-term efficacy of SLIT in AR patients with epistaxis.

In conclusion, our study preliminary confirmed the efficacy and safety of SLIT on HDM-induced AR patients accompanied by epistaxis. There was clinical improvement of epistaxis after SLIT treatment of AR with *D. farinae* drops in this study.

Fundings

None.

Contributions

JP, CQH, YJT: conceptualization, writing – original draft. ZRD: methodology, writing – review & editing. LC: methodology, data curation. HFY formal analysis.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgements

We thank the patients for their availability in taking part in this study and for the excellent cooperation they have shown.

References

1. Wise SK, Damask C, Roland LT, Ebert C, Levy JM, Lin S, et al. International consensus statement on allergy and rhinology: Allergic rhinitis - 2023. Int Forum Allergy Rhinol. 2023;13(4):293-859. doi: 10.1002/alr.23090.

2. Li H, Chen S, Cheng L, Guo Y, Lai H, Li Y, et al. Chinese guideline on sublingual immunotherapy for allergic rhinitis and asthma. J Thorac Dis. 2019;11(12):4936-50. doi: 10.21037/jtd.2019.12.37.
3. Cheng L, Chen J, Fu Q, He S, Li H, Liu Z, et al. Chinese Society of Allergy Guidelines for Diagnosis and Treatment of Allergic Rhinitis. Allergy Asthma Immunol Res. 2018;10(4):300-53. doi: 10.4168/aair.2018.10.4.300.
4. Li X, Xu X, Li J, Huang Y, Wang C, Zhang Y, et al. Direct and indirect costs of allergic and non-allergic rhinitis to adults in Beijing, China. Clin Transl Allergy. 2022;12(4):e12148. doi: 10.1002/clt2.12148.
5. Qing J, Cai Y, Tang S, Wang Y. Clinical Characteristics and Risk Factors for Allergic Rhinitis in Children with Epistaxis. Int J Clin Pract. 2023;2023:6731414. doi: 10.1155/2023/6731414.
6. Yang L, Hur K, Koempel J, Ference EH. Epistaxis health disparities in the United States pediatric population. Int J Pediatr Otorhinolaryngol. 2018;114:20-5. doi: 10.1016/j.ijporl.2018.08.025.
7. Murray AB, Milner RA. Allergic rhinitis and recurrent epistaxis in children. Ann Allergy Asthma Immunol. 1995;74(1):30-3.
8. GIRSH LS. Allergic rhinitis, a common cause of recurrent epistaxis in children. AMA J Dis Child. 1960;99:819-21. doi: 10.1001/archpedi.1960.02070030821017.
9. Teo WY, Wong HB, Hwarng GYH, Tan HKK. Outcome of childhood epistaxis with treatment of allergic rhinitis: a randomized controlled study. Eur J Pediatr. 2023;182(3):1127-35. doi: 10.1007/s00431-022-04701-7.
10. Cheng L, Zhou WC. Sublingual immunotherapy of house dust mite respiratory allergy in China. Allergol Immunopathol (Madr). 2019;47(1):85-9. doi: 10.1016/j.aller.2018.02.008.
11. Liu X, Ng CL, Wang Y. The efficacy of sublingual immunotherapy for allergic diseases in Asia. Allergol Int. 2018;67(3):309-19. doi: 10.1016/j.alit.2018.02.007.
12. Ma D, Zheng Q, Sun J, Tang S, He W. Efficacy of Sublingual Immunotherapy in Allergic Rhinitis Patients with Asthma: A Systematic Review and Meta-Analysis. Am J Rhinol Allergy. 2023;37(6):766-76. doi: 10.1177/19458924231193528.
13. Patel K, Gupta N, Prajapati BJ, Prajapati A, Sharma S, Rathava D. Study on Effects of Sublingual Immunotherapy in Allergic Rhinitis Patients. Indian J Otolaryngol Head Neck Surg. 2023;75(Suppl 1):804-8. doi: 10.1007/s12070-022-03366-w.
14. Liu B, Feng J, Hu S. The Role of Nasal Endoscopy in Allergic Rhinitis and House Dust Mite Sublingual Immunotherapy. Int Arch Allergy Immunol. 2021;182(8):690-6. doi: 10.1159/000513810.
15. Chen WB, Shen XF, Li Q, Zhou WC, Cheng L. Efficacy of a 3-year course of sublingual immunotherapy for mite-induced allergic rhinitis with a 3-year follow-up. Immunotherapy. 2020;12(12):891-901. doi: 10.2217/imt-2020-0006.
16. Yang J, Zheng J, Zhou Y, Qiu Q, Zhan J, Wei X. Short-term and long-term efficacy of sublingual immunotherapy in different courses for house dust mite-induced allergic rhinitis. Am J Otolaryngol. 2023;45(2):104118. doi: 10.1016/j.amjoto.2023.104118.
17. Wu EL, Harris WC, Babcock CM, Alexander BH, Riley CA, McCoul ED. Epistaxis Risk Associated with Intranasal Corticosteroid Sprays: A Systematic Review and Meta-analysis. Otolaryngol Head Neck Surg. 2019;161(1):18-27. doi: 10.1177/0194599819832277.
18. Shao J, Feng S, Liu S. *Dermatophagoides Farinae* Drops in Treating Children with Allergic Rhinitis and Recurrent Epistaxis (Chinese). China Pharmaceuticals. 2016;25(21):55-7.
19. Pfaar O, Demoly P, Gerth van Wijk R, Bonini S, Bousquet J, Canonica GW, et al. Recommendations for the standardization of clinical outcomes used in allergen immunotherapy trials for allergic rhinoconjunctivitis: an EAACI Position Paper. Allergy. 2014;69(7):854-67. doi: 10.1111/all.12383.
20. Gao Y, Lin X, Ma J, Wei X, Wang Q, Wang M. Enhanced Efficacy of Dust Mite Sublingual Immunotherapy in Low-Response Allergic Rhinitis Patients after Dose Increment at 6 Months: A Prospective Study. Int Arch Allergy Immunol. 2020;181(4):311-9. doi: 10.1159/000505746.
21. Li L, Cui X, Zhang X, Zheng L, Sun X, Yang C, et al. Serum vitamin D3 deficiency can affect the efficacy of sublingual immunotherapy in children with allergic rhinitis: a retrospective cohort study. J Thorac Dis. 2023;28;15(2):649-57. doi: 10.21037/jtd-22-1883.
22. Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Chinese Otorhinolaryngology Society of Chinese Medical Association. [Diagnostic and treatment principle for allergic rhinitis and a recommended scheme]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2005 Mar;40(3):166-7. Chinese.
23. Rodeghiero F, Tosetto A, Abshire T, Arnold DM, Coller B, James P, et al. ISTH/SSC bleeding assessment tool: a standardized questionnaire and a proposal for a new bleeding score for inherited bleeding disorders. J Thromb Haemost. 2010;8(9):2063-5. doi: 10.1111/j.1538-7836.2010.03975.x.
24. Passalacqua G, Baena-Cagnani CE, Bousquet J, Canonica GW, Casale TB, Cox L, et al. Grading local side effects of sublingual immunotherapy for respiratory allergy: speaking the same language. J Allergy Clin Immunol. 2013;132(1):93-8. doi: 10.1016/j.jaci.2013.03.03.
25. Han M, Chen Y, Wang M. Sublingual immunotherapy for treating adult patients with allergic rhinitis induced by house dust mite among Chinese Han population: A retrospective study. Medicine (Baltimore). 2018;97(30):e11705. doi: 10.1097/MD.0000000000011705.
26. Zhang AZ, Liang ME, Chen XX, Wang YF, Ma K, Lin Z, et al. Clinical Evaluation for Sublingual Immunotherapy with *Dermatophagoides farinae* in Polysensitized Allergic Asthma Patients. Front Med (Lausanne). 2021;8:645356. doi: 10.3389/fmed.2021.645356.
27. Chen H, Chen Y, Lin B, Huang S, Liu Q, Zheng H, et al. Efficacy and adherence of sublingual immunotherapy in patients aged 60 to 75 years old with house dust mite-induced allergic rhinitis. Am J Otolaryngol. 2020;41(4):102538. doi: 10.1016/j.amjoto.2020.102538.
28. Wang DH, Chen L, Cheng L, Li KN, Yuan H, Lu JH, 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(6):1334-40. doi: 10.1002/lary.23935.
29. Zeng Y, Xiao H, Gao S, Li J, Yang C, Zeng Q, et al. Efficacy and immunological changes of sublingual immunotherapy in pediatric allergic rhinitis. World Allergy Organ J. 2023;16(7):100803. doi: 10.1016/j.waojou.2023.100803.
30. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. J Allergy Clin Immunol. 2010;126(5):969-75. doi: 10.1016/j.jaci.2010.08.030.
31. Purkey MR, Seeskin Z, Chandra R. Seasonal variation and predictors of epistaxis. Laryngoscope. 2014;124(9):2028-33. doi: 10.1002/lary.24679.
32. Li X, Sheng X, Huang J. Clinical effect of allergic rhinitis caused by nasal bleeding in patients with different treatment options (Chinese). Hainan Med J, 2015;26(01):27-30.
33. Feng Y. Observation on the therapeutic effect of impulse immunotherapy on epistaxis caused by allergic rhinitis (Chinese). J Clin Med Pract. 2015;(23):210-211,216.

34. Chen M, Lin L, Yan M, Xu C, Chai R. Characteristics of dust mite sublingual immunotherapy-associated adverse events in the early phase. Front Med (Lausanne). 2022;9:1015032. doi: 10.3389/fmed.2022.1015032.
35. 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 (Madr). 2017;45(5):457-62. doi: 10.1016/j.aller.2016.10.016.
36. Shao J, Cui YX, Zheng YF, Peng HF, Zheng ZL, Chen JY, et al. Efficacy and safety of sublingual immunotherapy in children aged 3-13 years with allergic rhinitis. Am J Rhinol Allergy. 2014;28(2):131-9. doi: 10.2500/ajra.2014.28.4006.
37. 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. doi: 10.1016/j.ijporl.2015.12.001.