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Patient compliance to sublingual immunotherapy for mite-induced allergic rhinitis: A retrospective study

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ABSTRACT

Background: Compliance to sublingual immunotherapy (SLIT) is generally low, resulting in reduced short- and long-term clinical efficacy. Compliance is a critical factor determining the success of allergic rhinitis (AR) treatment.

Objective: To analyze the compliance of patients with house dust mite (HDM)-induced AR to SLIT and the impact of coronavirus disease 2019 (COVID-19) on compliance.

Methods: The clinical data of 3117 patients with HDM-induced AR who started SLIT between July 2018 and April 2022 were retrospectively reviewed. We assessed the reasons for non-compliance and the changes in non-compliance during the COVID-19 pandemic compared to the pre-pandemic period.

Results: Of 3117 patients, 507 (16.27%) patients (ages, 5–67 years) were identified as non-compliant. The most common reason for non-compliance was poor efficacy (27.22%). The non-compliance rate was highest during 24–36 months of SLIT (28.13%, 153/544), followed by 12–24 months (7.02%, 91/1296). Non-compliance was significantly higher in adolescents/adults than in children ($P = 0.000$). Although the generalized linear model analysis indicated that compliance was affected by the COVID-19 pandemic during 3–6 months of SLIT, the overall compliance to SLIT was not significantly affected by the pandemic, according to the Kaplan-Meier survival analysis.

Conclusions: The non-compliance rate of SLIT in this study was low, and poor efficacy was the most common reason for non-compliance. The compliance of adolescents/adults was lower than that of children. The COVID-19 pandemic did not significantly impact compliance to SLIT, which is an appropriate strategy for the home treatment of AR patients during major public health events.

Keywords: Allergic rhinitis, Allergen immunotherapy, Sublingual immunotherapy, Compliance, Patient education

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INTRODUCTION

Allergic rhinitis (AR) is a common non-infectious chronic inflammatory nasal disease that is characterized by the production of specific IgE antibodies and increased eosinophils in the peripheral blood. AR is a global health problem that is estimated to affect 10%–20% of the world population,[1] and is one of the most common diseases encountered in the fields of otorhinolaryngology and allergology. AR patients with house dust mite (HDM) allergy experience symptoms of rhinitis nearly perennially, which seriously affects their quality of life, increases the consumption of medical resources, and places a heavy social and economic burden on patients.

Allergen immunotherapy (AIT) is considered the only treatment that can modify the natural progression of AR. AIT has been confirmed to have both short-term and long-term efficacy in AR, and can prevent the progression of AR to asthma and reduce new sensitization.[2-4] Sublingual immunotherapy (SLIT), a form of AIT, is widely accepted by both specialists and patients due to its efficiency, safety, and convenience. However, the slow onset of action and long duration of SLIT often result in non-compliance with SLIT, which will invariably result in symptom recurrence and worsen patients' quality of life. Therefore, patient compliance with SLIT has become a critical factor for successful treatment outcomes. Studies have estimated that compliance rates to SLIT range from 18% to 45%,[5-7] with some studies reporting that only 7%–13.2% of AR patients complied to SLIT for 3 years.[8-10] Thus, compliance to SLIT is generally low, resulting in reduced short- and long-term clinical efficacy.[10,11] Indeed, patient compliance is a challenge that impacts the treatment of all chronic illnesses, and compliance to SLIT has also been raised as a potential issue.[12] Therefore, assessing the dropout rate during SLIT and analyzing the reasons for dropout are important to improve compliance to SLIT.

Recent studies have revealed a significant impact of the COVID-19 pandemic on compliance to subcutaneous immunotherapy (SCIT).[13,14] However, there are currently no reports on patient compliance to SLIT during the period of the COVID-19 pandemic, and the impact of COVID-19 on patient compliance to SLIT is yet to be determined. We hypothesized that the COVID-19 pandemic had a significant impact on patient compliance to SLIT. Therefore, we conducted a retrospective observational study based on real-world clinical data to summarize the reasons for non-compliance during SLIT for HDM-induced AR, the differences between children and adolescents/adults, and analyzed the impact of COVID-19 on patient compliance. We hope that our findings will provide a basis for the formulation of effective nursing measures and health education strategies during AIT.

METHODS

Study population and design

In this study, we enrolled 3117 AR patients aged 3–67 years who underwent SLIT between July 2018 and April 2022, in the Department of Otorhinolaryngology & Clinical Allergy Center, the First Affiliated Hospital of Nanjing Medical University. The age groups were further divided into 2 categories: children (≤14 years old) and adolescents/adults (>14 years old).[15,16] All the patients in this study were diagnosed with AR according to the clinical guidelines.[17] The patients presented with a medical history consistent with HDM allergy and demonstrated sensitization to *Dermatophagoides farinae* (*Der f*) and/or *Dermatophagoides pteronyssinus* (*Der p*), which was confirmed by positive results from skin-prick tests (≥++) and/or the serological detection of specific IgE antibodies (≥0.7 kU_A/L). Patients with severe or uncontrolled asthma (FEV1 < 70% of predicted value), those who had participated in clinical trials in the past 1 year, those with immunological diseases, and those who were taking β-blockers for any reason were excluded from the study. In addition, patients who could not be reached during follow-up were also excluded. Informed consent was obtained from all the participants and/or their legal guardians. The protocol of this retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2021-SR-565).

Treatment schedule

We prescribed standardized *Der f* drops (Zhejiang Wolwo Biopharmaceutical Co., Ltd, Zhejiang, China) to AR patients with HDM allergy; the whole treatment course was recommended to last for 3–5

years. The administration and dose-increment schedule of the *Der f* drops are shown in Table 1. All patients received health education before starting SLIT, and were provided information regarding the treatment course, approximate cost, precautions, possible efficacy, and potential adverse reactions of SLIT. According to the clinical symptoms and signs of the patients, the doctor may also prescribe anti-allergic drugs for symptomatic relief.

Follow-up

Medical files containing patient information, including age, gender, and date of starting treatment, were established at the beginning of the treatment. Nurses set up and sustained communications with the patients via WeChat, a free messaging and calling application available on smartphones. The patients were followed up from July 2018 to April 2022. During follow-up, patients were instructed to visit the outpatient clinic for the evaluation of symptoms and signs at 1, 3, 6, 12, 18, 24, 30, and 36 months after starting SLIT. After each follow-up visit, nurses reminded the patients, via WeChat, to take the medicines prescribed by the specialists. If the patient refused to continue the treatment, the nurses confirmed the main reason for the termination of the treatment and recorded the information in the patient's file.

Patient compliance and the COVID-19 pandemic

Patients who refused to visit the outpatient clinic and terminated the treatment on their own or with their guardian's wishes for more than 1 week were recorded as non-compliant patients. Patients who terminated the treatment on the recommendation of the medical specialists, or resumed the treatment within 1 week of discontinuing it were recorded as compliant patients.

The COVID-19 pandemic is a major public health emergency due to its wide spread and high incidence. China officially implemented a nationwide lockdown on January 24, 2020, and initiated a first-level public health emergency response. For the analysis of the compliance of AR patients to SLIT during the COVID-19 pandemic in Nanjing, China, the pandemic period was defined as the 28-month period starting from the first confirmed case in January 2020.

Statistical analysis

Categorical variables were evaluated using the χ^2 test or Fisher exact test, which were conducted using SPSS version 26.0 (IBM SPSS, Chicago, IL, USA). Generalized linear models (GLMs) were used to quantify the impact of the COVID-19 pandemic on patient compliance during different stages of the follow-up period. We reported exponentiated regression coefficients as adjusted odds ratios (ORs). GLM analyses were conducted using the R software version 4.0.3 (https://www.r-project.org/, R Foundation for Statistical Computing, Vienna, Austria). We estimated survival curves using the Kaplan–Meier method and compared them using log-rank tests. Statistical significance was evaluated with two-sided *P*-values at the level of $\alpha = 5\%$.

RESULTS

Compliance and non-compliance rates

Overall, 3117 patients who underwent SLIT for the management of HDM-induced AR were

Time	Prescription[a]	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Week 1	No. 1 (1 µg/mL)	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
Week 2	No. 2 (10 µg/mL)	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
Week 3	No. 3 (100 µg/mL)	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
Weeks 4 and 5	No. 4 (333 µg/mL)	3 drops per day						
Weeks 6 and later	No. 5 (1000 µg/mL)	2 drops per day						

Table 1. Administration and dose-increment schedule of *Dermatophagoides farinae* drops. [a]*The schedule shown is for patients aged ≥14 years. Patients aged <14 years used bottles No. 1, 2, and 3 in the dosing build-up phase, and bottle No. 4 in the maintenance phase.*

enrolled in our study (Fig. 1). Of them, 2610 (83.73%) patients had good compliance, and 507 (16.27%) patients were identified as having non-compliance. Among these 507 patients (aged 5–67 years), 268 (52.86%) were male and 239 (47.14%) were female. The dropout times of the non-compliant patients ranged from 1 week to 36 months from the start of SLIT. The non-compliance rates in children and adolescents/adults were 12.59% (123/977) and 17.94% (384/2140), respectively. A total of 42 patients who had their treatment terminated by attending doctors due to adverse reactions or poor efficacy were classified as compliant patients during the entire study period.

Reasons for non-compliance and non-compliance rates across different stages of the follow-up period

In this study, the most common reason for non-compliance to SLIT was poor efficacy, and a total of 138 (27.22%) patients terminated treatment for this reason (Fig. 2). Other common reasons for non-compliance were excessive treatment time (22.09%), improved symptoms (16.77%), impact of COVID-19 (13.21%), adverse reactions (12.23%), economic difficulty (3.94%), pregnancy (1.58%), and other incidents (2.96%). A total of 15 patients terminated the treatment due to "other incidents": 3 patients terminated SLIT because they travelled abroad, and 12 patients terminated SLIT because of another serious condition, such as cancer, heart disease, depression, surgery, and respiratory infection.

The rates of non-compliance during 4 distinct stages of the follow-up period are illustrated in Fig. 3. The compliance rate was highest in the period of 3–6 months (96.92%, 2703/2789). The non-compliance rate was highest in the period of 24–36 months (28.13%, 153/544), followed by the periods of 12–24 months (7.02%, 91/1296) and 6–12 months (3.55%, 76/2142). The non-compliance rates in periods of 24–36 months and 12–24 months significantly differed from those in the periods of 0–3 months, 3–6 months, and 6–12 months, respectively ($P < 0.05$). In addition, the non-compliance rate was significantly higher in the period of 24–36 months than in the period of 12–24 months ($P < 0.05$). The rates in the other periods showed no statistically significant differences ($P > 0.05$, all). It is worth mentioning that the non-compliance rate in the initial one year of SLIT was 8.44% (263/3117). Of the 123 patients enrolled between July 2018 and April 2019, all were followed-up for over 36 months by the study's endpoint, with 72 (58.54%) were still undergoing SLIT.

Non-compliance rates across different age groups

As shown in Table 2, a difference of 5.35% was observed in the non-compliance rates of children and adolescents/adults, with the non-compliance rate being significantly higher in adolescents/
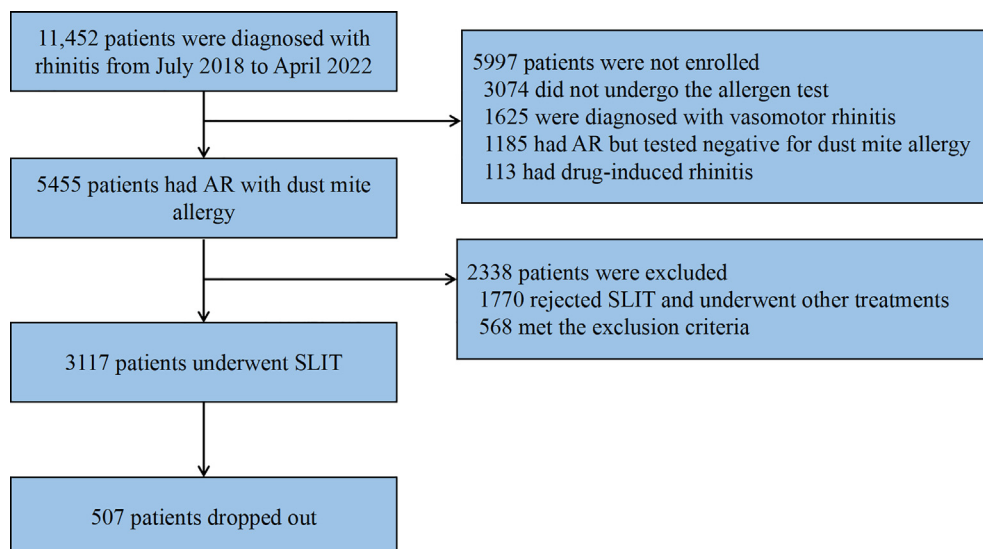

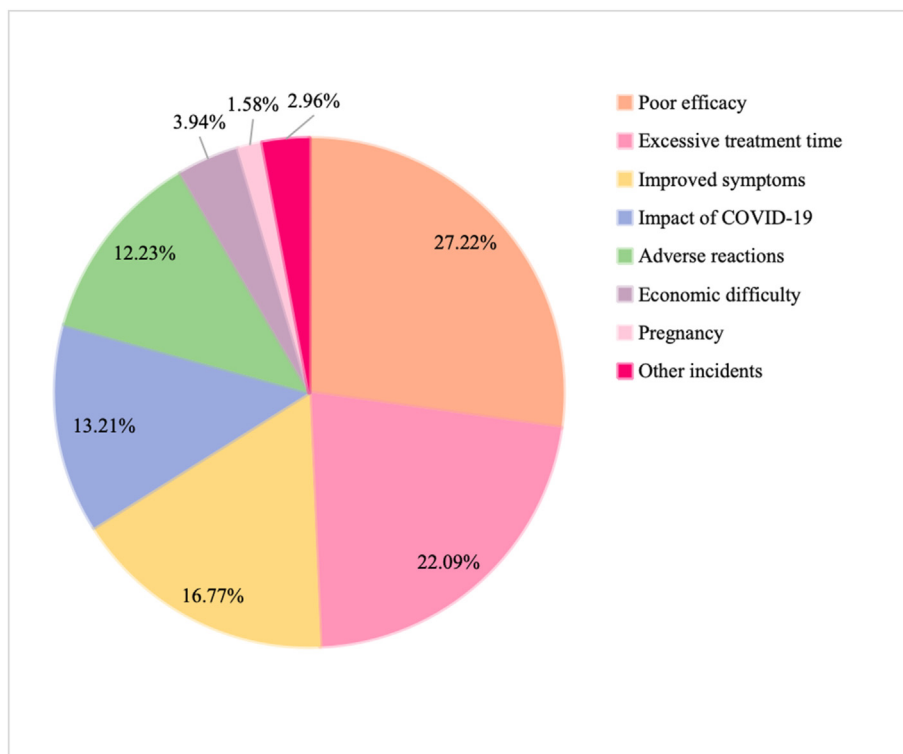**Fig. 1** Flow chart of patient enrollment

Fig. 2 Distribution of reasons for non-compliance with treatment

adults than in children (*P* = 0.000). The following reasons for non-compliance were more common in adolescents/adults than in children: excessive treatment time (4.21% *vs*. 2.25%), improved symptoms (3.04% *vs*. 2.0%), impact of COVID-19 (2.62% *vs*. 1.13%), economic difficulty (0.89% *vs*. 0.10%), pregnancy (0.37% *vs*. 0.00%), and other incidents (0.56% *vs*. 0.31%). The difference between the 2 groups was statistically significant only for the reasons of excessive treatment time (*P* = 0.007), impact of COVID-19 (*P* = 0.008), and economic difficulty (*P* = 0.007). To our surprise, the probability of non-compliance due to adverse reactions was lower in adolescents/adults than in children (1.82% *vs*. 2.35%) although the difference was not statistically significant (*P* = 0.324).
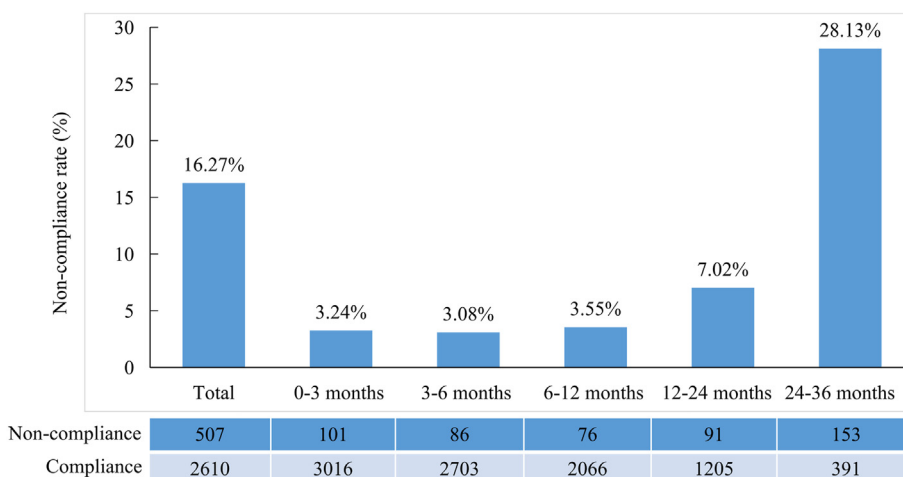

	Total	0-3 months	3-6 months	6-12 months	12-24 months	24-36 months
Non-compliance	507	101	86	76	91	153
Compliance	2610	3016	2703	2066	1205	391

Fig. 3 Compliance rates during sublingual immunotherapy for house dust mite-induced allergic rhinitis

Reason for non-compliance	Children, n (%) [n = 977]	Adolescents/adults, n (%) [n = 2140]	Difference[a]	P-value
Poor efficacy	43 (4.40%)	95 (4.44%)	0.04%	0.962
Excessive treatment time	22 (2.25%)	90 (4.21%)	1.96%	0.007
Improved symptoms	20 (2.05%)	65 (3.04%)	0.99%	0.115
Impact of COVID-19	11 (1.13%)	56 (2.62%)	1.49%	0.008
Adverse reactions	23 (2.35%)	39 (1.82%)	0.53%	0.324
Economic difficulty	1 (0.10%)	19 (0.89%)	0.79%	0.007
Pregnancy	0 (0.00%)	8 (0.37%)	0.37%	0.114
Other incidents	3 (0.31%)	12 (0.56%)	0.25%	0.342
Total	123 (12.59%)	384 (17.94%)	5.35%	0.000

Table 2. Comparison of reasons for non-compliance across age groups. *COVID-19, coronavirus disease 2019. [a]Difference in the percentage incidence between children and adolescents/adults.*

Impact of the COVID-19 pandemic on compliance to SLIT

During the COVID-19 pandemic, 3085 AR patients were in the first 3 years of SLIT (32 AR patients were identified as having non-compliance to SLIT before the epidemic of COVID-19). In total, 475 patients with non-compliance during the COVID-19 pandemic were distributed across the 5 stages of the follow-up period. Of these, 67 (14.11%) patients discontinued treatment due to the impact of the COVID-19 pandemic, which was the third major reason for non-compliance during the COVID-19 pandemic, with the first 2 reasons being perceptions of clinical efficacy (ie, poor efficacy or improved symptoms) and excessive treatment time. In addition, non-compliance due

to the impact of the COVID-19 pandemic mainly occurred in the first year of the pandemic in 2020, which accounted for 86.57% (58/67) of cases.

Since the included patients were followed up for a maximum of 18 months in the period before the COVID-19 pandemic, the patients enrolled during the COVID-19 pandemic were also followed up for 18 months after starting SLIT to evaluate the impact of the COVID-19 pandemic on non-compliance rates. The GLM analysis presented in Table 3 revealed a significant impact of the COVID-19 pandemic on patient compliance with AR during the 3–6-month period after initiating SLIT (OR = 2.69, 95% CI = 1.20–7.69, $P = 0.033$). However, the compliance of AR patients during the follow-up periods of 0–3 months, 6–12 months, and

Treatment period	Phase I[a]		Phase II[b]		OR (95% CI)	P-value
	n	Non-compliance	n	Non-compliance		
0–3 months	541	22 (4.07%)	2576	79 (3.07%)	0.75 (0.47–1.24)	0.234
3–6 months	368	5 (1.36%)	2266	81 (3.57%)	2.69 (1.20–7.69)	0.033
6–12 months	101	3 (2.97%)	1705	73 (4.28%)	1.46 (0.53–6.04)	0.526
12–18 months	32	2 (6.25%)	874	28 (3.20%)	0.50 (0.14–3.16)	0.354

Table 3. GLM-estimated odds ratios for the impact of the COVID-19 pandemic on patient compliance. *Notes: In phase I, the data shown are from patients enrolled before 1st January 2020, and the follow-up results of these patients during the COVID-19 epidemic are not included. In phase II, the data shown are from patients enrolled after 1st January 2020, and only the follow-up results of the first 18 months of the treatment are included. COVID-19, coronavirus disease 2019; GLM, generalized linear model; OR, odds ratio; CI, confidence interval. [a]From July 2018 to December 2019. [b]From January 2020 to April 2022.*
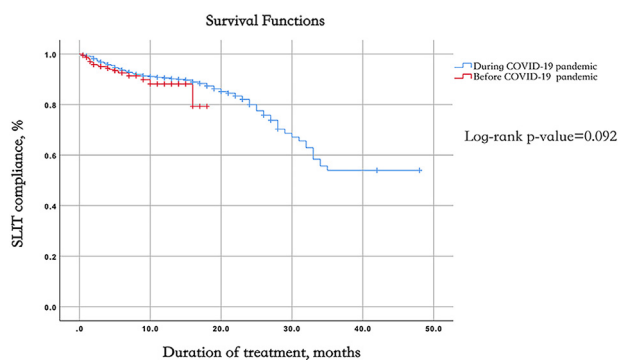
Fig. 4 Kaplan-Meier curves for SLIT compliance over time before and after the COVID-19 pandemic, and the results of comparison of the curves using the log-rank test. COVID-19, coronavirus disease 2019; SLIT, sublingual immunotherapy

12–18 months was not significantly affected by the COVID-19 pandemic ($P > 0.05$, all).

We further analyzed the changes in the compliance of cumulative proportions of patients undergoing SLIT before and after the COVID-19 pandemic over time, by using Kaplan-Meier curves. As shown in Fig. 4, the overall compliance of the 2 groups was not significantly affected by the COVID-19 pandemic (log-rank $P = 0.092$).

DISCUSSION

Compliance to AIT has received increasing attention in recent years and has become a research "hot spot". Clinicians have recognized compliance as a critical and essential factor affecting the efficacy of SLIT for managing AR patients. In this study, we analyzed non-compliance in 507 AR patients undergoing SLIT between July 2018 and April 2022, including the causes of non-compliance, the impact of the COVID-19 pandemic on non-compliance, and differences in non-compliance between children and adolescents/adults. The non-compliance rate in AR patients undergoing SLIT was 16.27%. Poor efficacy reported by patients or guardians was the most common cause of terminating SLIT, followed by excessive treatment time, improvement of symptoms, the impact of the COVID-19 pandemic, and adverse reactions. Compliance was highest in 0–12 months after starting SLIT, especially in the 3–6-month period of SLIT, while non-compliance was highest in the 24–36-month period. The COVID-19 pandemic had no significant impact on overall compliance. Non-compliance was higher in

adolescents/adults than in children, and the main reasons accounting for this difference were excessive treatment time, impact of COVID-19, and economic difficulty. Therefore, analyzing the reasons for non-compliance and the impact of the COVID-19 pandemic can help clinicians reasonably educate and manage patients in daily clinical practice to improve compliance and increase the efficacy of SLIT.

Treatment adherence in patients with AR poses a significant challenge. The compliance with AIT is essential for the effective treatment of AR, whereas adherence to SLIT is generally poor, resulting in diminished clinical efficacy in both short- and long-term outcomes.[10,11] A meta-analysis of 81 articles with 9998 patients showed that a composite non-compliance percentage of 14% was observed in AR patients undergoing SLIT,[12] which is similar to the 16.27% in our study. However, a study in Beijing, China reported that the non-compliance rate of AR patients undergoing SLIT was as high as 53.5% in the initial one year of SLIT.[7] In a recent systematic review comprising 32 articles and 63,683 patients, a longer follow-up duration was associated with decreased rates of compliance and persistence.[18] Specifically, in patients followed up for less than 1 year, persistence rates ranged from 69.05% to 88.7%, whereas in those followed up for 3 years, persistence rates varied from 7% to 59%, and compliance rates from 9.6% to 49.0%. In the present study, the non-compliance rate was only 8.44% in the initial 1 year of SLIT, which is significantly lower than the rates reported in previous studies.[7,10] This difference may be mainly attributed to the health education delivered to patients during their first consultation. Before initiating SLIT for AR patients who meet the indications, our medical specialists always provide detailed explanations regarding the advantages and disadvantages of SLIT, expected efficacy, treatment duration, potential adverse reactions, etc. Once the patients decide to undergo SLIT, professional nurses create a file for each patient, and establish contact with the patient through WeChat to confirm the next visit time and arrange regular follow-up visits. During SLIT, if the patients have any questions, they can consult with healthcare staff and get timely replies through WeChat. In addition, differences in study design and subjects may partly explain the

heterogeneity of outcomes. Similar to the results of other studies,[9,19] the present study found that the non-compliance rate in the late stage of SLIT increased significantly, especially in the third year, when the non-compliance rate reached 28.13%. The perceptions of clinical efficacy (ie, poor efficacy or improved symptoms) in the period of 24–36 month, especially poor efficacy, were the most important factors that positively affected compliance. These factors were even more important than excessive treatment time, which is similar to the results of some other studies.[20,21] Additionally, inadequate reinforcement of education during biannual follow-ups could further contribute to premature discontinuation of SLIT. Patients always have high expectations regarding the effects of SLIT, but a 3-year course of SLIT is very lengthy, and the onset of effects is relatively slow. The failure to meet patients' expectations is a critical reason for the termination of SLIT. In another review, only 13% of patients treated with SLIT adhered to the recommended 3-year treatment according to the manufacturer's data.[6] However, our study found that out of the 123 patients we followed for more than 36 months, 72 (58.54%) were still undergoing SLIT. The compliance rate was higher than that reported in literature,[5,18,22] possibly due to the fact that our study patients were more carefully selected, closely observed and followed. Studies have shown that in AR patients, 3-year SLIT could significantly relieve the clinical symptoms of AR,[19,23] and was more effective than 1- or 2-year courses.[23] Therefore, the importance of long-term treatment should be emphasized to patients. Patients should be told that early efficacy is not equal to the final efficacy. For patients who receive standardized immunotherapy, the decision to discontinue SLIT should be made based on a comprehensive evaluation of the clinical benefits. In recent years, an increasing number of researchers have focused on enhancing compliance to SLIT in patients with AR. They have recognized that patient education, effective communication, standardized follow-up protocols, the provision of comprehensive information, and technology-based tools such as online platforms, social media, email, and short message service by phone can improve compliance.[5,6] These strategies align with those implemented in our ongoing investigation.

The COVID-19 pandemic has had a dramatic impact on clinical practice. The prevention and control of emerging viral transmission can effectively reduce the occurrence of infectious diseases; however, it presents novel challenges in managing chronic airway inflammatory conditions like AR. In our study, the impact of COVID-19, either throughout the study period or during the COVID-19 pandemic, was one of the most common reasons for non-compliance, second only to perceptions of clinical efficacy and excessive treatment time. A recent study of patient compliance to SCIT showed that the COVID-19 pandemic was an independent factor for dropout, with approximately 25% of patients giving up the treatment due to fear of hospital-acquired COVID-19.[13] In the present study, during the COVID-19 pandemic, 14.11% of patients stopped treatment due to the impact of COVID-19, mainly due to the prevention and control measures for COVID-19, which restricted daily life activities and mandated social distancing, resulting in AR patients possibly not being able to revisit the outpatient clinic in a timely manner and having to terminate SLIT due to the unavailability of medicines. Therefore, the implementation of internet hospitals enhanced the follow-up and management of patients during the pandemic. The concept of an internet hospital involves utilizing internet information technology to facilitate connections among hospitals, doctors, and patients. Its primary objective is to improve the efficiency of medical services by optimizing resource allocation. This internet hospital allows for large-scale online diagnosis and treatment, share of electronic medical records, conduction of online medical consultations, and proposal of electronic prescriptions. The ultimate goal is to integrate online and offline medical service systems to cater the entire treatment. On the other hand, for the convenience of patients, *Der f* drops for SLIT can be sent home by express delivery to offset the increased non-compliance due to the impact of COVID-19, although the non-compliance rate for the period of 3–6 months of SLIT was still significantly higher during the COVID-19 pandemic than before the pandemic. For this point, SLIT may be a more appropriate strategy than SCIT during public health emergencies.

In this study, we also found that the compliance of adolescents/adults was significantly lower than

that of children, which is consistent with previous studies.[24,25] As there are many one-child families in modern society, the child usually gets all the attention from the family members. Parents' concerns about childhood allergies make communication between family and medical staff more harmonious and meaningful. In contrast, adults have high life pressure, no regular rest time, and difficulty in adhering to a prolonged treatment duration, which makes it more difficult for them to comply with AIT than it is for children.

SLIT is an effective, safe, and convenient treatment that makes community AIT possible, and is widely accepted by specialists and patients.[26-28] Compliance is the most important factor affecting the efficacy of SLIT. We have comprehensively analyzed the reasons for non-compliance to SLIT during different time periods as well as the impact of the COVID-19 pandemic and patient age on compliance, in order to improve compliance and therefore treatment efficacy. Studies have shown that adequate patient education, optimized management plans, and a balance between dose effect and cost can improve patients' compliance with treatment.[11,29] Therefore, in the environment of the COVID-19 pandemic, firstly, medical staff, as the front line of the medical service, should have sufficient knowledge of health and positive attitudes, which may directly affect patients. Secondly, a peer-to-peer connection was established between the patient and the healthcare team (including doctors and nurses) through online platforms such as WeChat. Throughout the treatment process, patients had access to the healthcare team for guidance on optimizing SLIT effectiveness and adherence. The following measures may help establish a good relationship with patients: patient education, visits to collect information, weekend and holiday intervention visits, answering patients' questions, providing prevention tips at the peak of mite reproduction, and reminding patients to avoid allergen exposure. Thirdly, effective psychological counseling provided by our medical professionals can help improve patients' adherence and compliance to the treatment.[5,25,28-31] Finally, the internet hospitals in China have grown significantly in recent years, with unprecedented development during the COVID-19 pandemic. The establishment of internet hospitals can add more convenient ways for patients to consult with healthcare staff and purchase medicines to offset the impact of the COVID-19 pandemic. Even after the pandemic, these internet hospitals are still helping doctors to deliver online diagnosis, treatment, follow-up suggestions, and e-prescription services for patients with common and chronic conditions.

Our study has several potential limitations. First, the clinical data in this study were retrospective in nature, and thus might have an inherent bias. Second, due to the limited study duration, the follow-up periods of the enrolled patients were different, and the results of this study may have slight deviations. Third, data related to patients' occupation, income, education level, permanent residence area, mode of transportation for medical treatment, and family support were not collected. Therefore, we plan to conduct a prospective cohort study to further research the effects of more potential factors on the nature of non-compliance to SLIT.

In conclusion, our findings suggest that the non-compliance rate of patients receiving SLIT for the treatment of HDM-induced AR was low, and the highest non-compliance rate during SLIT was in the third year of SLIT. The compliance of adolescents/adults was lower than that of children for the main reason of excessive treatment time. The effect of the COVID-19 pandemic on compliance was not significant. During periods of public health emergencies, like the COVID-19 pandemic, SLIT may be a more appropriate strategy than SCIT. Nevertheless, it is necessary to further strengthen patient education and patient management, and timely communication with patients through internet hospitals and electronic devices, such as smartphone apps, increases the convenience of treatment and helps patients better comprehend the medical benefits of SLIT in treating AR.

Abbreviations

AIT, allergen immunotherapy; AR, allergic rhinitis; CI, confidence interval; COVID-19, coronavirus disease 2019; *Der f, Dermatophagoides farina; Der p, Dermatophagoides pteronyssinus*; FEV1, forced expiratory volume in one second; HDM, house dust mite; GLM, generalized linear model; OR, odds ratio; SCIT, subcutaneous immunotherapy; SLIT, sublingual immunotherapy.

Availability of data and materials

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

Author contributions

L.C., W.-J.W. and Q.-Y.X. contributed to the conception and design of the study. Q.-Y.X. and Z.-J.G. performed statistical analyses. M.-P.L., Q.L., J.Y., X.-J.Z., and X.-Y.C. collected the patient data. W.-J.W., Q.-Y.X. and M.-P.L. wrote the manuscript. Q.X. and L.C. revised the manuscript. All authors participated in the interpretation of the data, provided critical feedback, and approved the final manuscript for submission.

Ethics statement

The protocol of this retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2021-SR-565). Informed consent was obtained from all the participants and/or their legal guardians.

Consent for publication

All authors have approved the manuscript for submission. The participants and/or their legal guardians understand that their personal information will not be published.

Declaration of competing interest

The authors declare that they conducted the research without any potential conflict of interest arising from commercial or financial relationships.

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REFERENCES

1. Brozek JL, Bousquet J, Baena-Cagnani CE, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol*. 2010;126(3):466–476.

2. Alvarez-Cuesta E, Bousquet J, Canonica GW, et al. Standards for practical allergen-specific immunotherapy. *Allergy*. 2006;61(Suppl 82):1–20.

3. Jutel M, Agache I, Bonini S, et al. International consensus on allergy immunotherapy. *J Allergy Clin Immunol*. 2015;136(3): 556–568.

4. Zuberbier T, Bachert C, Bousquet PJ, et al. GA^{2}LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy*. 2010;65(12):1525–1530.

5. Bender BG, Oppenheimer J. The special challenge of nonadherence with sublingual immunotherapy. *J Allergy Clin Immunol Pract*. 2014;2(2):152–155.

6. Incorvaia C, Mauro M, Leo G, Ridolo E. Adherence to sublingual immunotherapy. *Curr Allergy Asthma Rep*. 2016;16(2):12.

7. Wang T, Li Y, Wang F, Zhou C. Nonadherence to sublingual immunotherapy in allergic rhinitis: a real-life analysis. *Int Forum Allergy Rhinol*. 2017;7(4):389–392.

8. Kiel MA, Roder E, Gerth van Wijk R, Al MJ, Hop WC, Rutten-van Molken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. *J Allergy Clin Immunol*. 2013;132(2):353–360 e352.

9. Musa F, Al-Ahmad M, Arifhodzic N, Al-Herz W. Compliance with allergen immunotherapy and factors affecting compliance among patients with respiratory allergies. *Hum Vaccines Immunother*. 2017;13(3):514–517.

10. Senna G, Lombardi C, Canonica GW, Passalacqua G. How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' viewpoint. *J Allergy Clin Immunol*. 2010;126(3):668–669.

11. 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(6): 544–548.

12. Makatsori M, Scadding GW, Lombardo C, et al. Dropouts in sublingual allergen immunotherapy trials - a systematic review. *Allergy*. 2014;69(5):571–580.

13. Koca Kalkan I, Ates H, Aksu K, et al. Real-life adherence to subcutaneous immunotherapy: what has changed in the era of the COVID-19 pandemic. *World Allergy Organ J*. 2021;14(7), 100558.

14. Aytekin ES, Soyer O, Sekerel BE, Sahiner UM. Subcutaneous allergen immunotherapy in children: real life compliance and effect of COVID-19 pandemic on compliance. *Int Arch Allergy Immunol*. 2021;182(7):631–636.

15. Elliott IS, Groen RS, Kamara TB, et al. The burden of musculoskeletal disease in Sierra Leone. *Clin Orthop Relat Res*. 2015;473(1):380–389.

16. Katayama Y, Kitamura T, Nakao S, et al. Telephone triage for emergency patients reduces unnecessary ambulance use: a propensity score analysis with population-based data in Osaka City, Japan. *Front Public Health*. 2022;10, 896506.

17. 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(4):300–353.

18. Park M, Kapoor S, Yi J, Hura N, Lin SY. Sublingual immunotherapy persistence and adherence in real-world settings: a systematic review. *Int Forum Allergy Rhinol*. 2023;13(5):924–941.

19. Valovirta E, Petersen TH, Piotrowska T, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. *J Allergy Clin Immunol*. 2018;141(2):529–538 e513.

20. Scurati S, Frati F, Passalacqua G, et al. Adherence issues related to sublingual immunotherapy as perceived by allergists. *Patient Prefer Adherence*. 2010;4:141–145.

21. Passalacqua G, Frati F, Puccinelli P, et al. Adherence to sublingual immunotherapy: the allergists' viewpoint. *Allergy*. 2009;64(12):1796–1797.

22. Borg M, Lokke A, Hilberg O. Compliance in subcutaneous and sublingual allergen immunotherapy: a nationwide study. *Respir Med*. 2020;170, 106039.

23. 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(1):82–87.

24. Pajno GB, Vita D, Caminiti L, et al. Children's compliance with allergen immunotherapy according to administration routes. *J Allergy Clin Immunol*. 2005;116(6):1380–1381.

25. Egert-Schmidt AM, Kolbe JM, Mussler S, Thum-Oltmer S. Patients' compliance with different administration routes for allergen immunotherapy in Germany. *Patient Prefer Adherence*. 2014;8:1475–1481.

26. Nolte H, Maloney J. The global development and clinical efficacy of sublingual tablet immunotherapy for allergic diseases. *Allergol Int*. 2018;67(3):301–308.

27. Kucuksezer UC, Ozdemir C, Cevhertas L, Ogulur I, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and allergen tolerance. *Allergol Int*. 2020;69(4):549–560.

28. Li H, Chen S, Cheng L, et al. Chinese guideline on sublingual immunotherapy for allergic rhinitis and asthma. *J Thorac Dis*. 2019;11(12):4936–4950.

29. Incorvaia C, Mauro M, Ridolo E, et al. Patient's compliance with allergen immunotherapy. *Patient Prefer Adherence*. 2008;2:247–251.

30. Lemberg ML, Berk T, Shah-Hosseini K, Kasche EM, Mosges R. Sublingual versus subcutaneous immunotherapy: patient adherence at a large German allergy center. *Patient Prefer Adherence*. 2017;11:63–70.

31. Nam YH, Lee SK. Physician's recommendation and explanation is important in the initiation and maintenance of allergen immunotherapy. *Patient Prefer Adherence*. 2017;11:381–387.