



Internet follow-up can improve the compliance of sublingual immunotherapy in children with allergic rhinitis: a retrospective cohort study

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Background: Sublingual immunotherapy (SLIT) is an effective approach for treating allergic rhinitis in children. Although the curative effect of SLIT is significant, the compliance of patients is poor because of the long treatment time. How to improve patients' compliance with SLIT is an important clinical problem faced by otolaryngology clinicians. At present, there are few studies on SLIT compliance. The present study aimed to analyze the related factors affecting SLIT compliance in children with allergic rhinitis (AR).

Methods: In total, 153 patients with AR who received SLIT were selected as the study objects. Seventeen patients were excluded from this study. The patients' demographic, follow-up methods, complications efficacy, compliance data, etc. were collected, and all patients were followed-up regularly. Patients were considered to have poor compliance when they stop taking medication of SLIT. Univariate and multivariable regression analyses were performed to analyze the independent factors influencing SLIT compliance. The odds ratios (ORs) and 95% confidence intervals (CIs) were computed by logistic regression.

Results: A total of 136 patients were enrolled in this study. The baseline clinical factors of the two groups of follow-up methods were balanced and comparable. Among these, 35 patients (25.7%) ceased SLIT. There was a significant difference in compliance between the Internet follow-up group and the traditional follow-up group ($P < 0.001$). Univariate logistic regression analysis showed that SLIT compliance was significantly related to residence ($P < 0.001$), the caregiver's education level ($P < 0.001$), follow-up methods ($P < 0.001$), and whether the patient also had asthma ($P < 0.002$). In the multivariate regression analysis, it was found that the follow-up methods (OR = 7.60, 95% CI: 2.20–26.21, $P = 0.001$) and caregiver's education level (OR = 8.54, 95% CI: 3.04–23.95, $P < 0.001$) were independent factors influencing SLIT compliance after adjusting for residence and whether the patient also had asthma.

Conclusions: Our study found that the follow-up methods and the education level of caregivers were independent factors affecting SLIT compliance in children with AR. This study suggested that we should use the Internet follow-up method for children treated with SLIT in the future, and provides a basis for how to improve the compliance of SLIT in children with AR.

Keywords: Children; allergic rhinitis; sublingual immunotherapy; internet follow-up

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Introduction

Allergic rhinitis (AR) in children is a non-infectious inflammatory disease of the nasal mucosa mediated by immunoglobulin E (IgE), which occurs following exposure to an allergen. It is one of the common allergic diseases; AR in children has become the main inflammatory respiratory disease in children, with a high incidence rate especially in China (1,2).

The allergic symptoms of children with AR have a significant impact on their quality of life. The main goal of AR treatment in children is to relieve symptoms and improve the quality of life of patients. So far, there is no way to cure AR completely. Compared with symptomatic therapy, allergen-specific immunotherapy (AIT) can fundamentally reduce the body's response to allergens, and its long-term effect is significantly better than that of symptomatic therapy. It is the only treatment that may change the course of allergic diseases (3). Recent advances in AIT include subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). It is generally agreed that SLIT is a safe and consolidated practice, and several studies have demonstrated its efficacy (4-6). Patient compliance is one of the most important factors influencing SLIT efficacy. At present, there are not many articles about SLIT compliance reported, and the non-compliance rate varies greatly, but the overall compliance rate is low. Therefore, how to improve the compliance of children with AR treated with SLIT is an important topic for pediatric

otolaryngologists. The present study aims to clarify the effect of Internet follow-up on patient compliance by conducting a retrospective analysis of pediatric patients with allergic rhinitis treated with SLIT to provide a new method of follow-up for pediatric otolaryngologists, that can ultimately enhance the efficacy of SLIT and benefit more patients. We present the following article in accordance with the STROBE reporting checklist (available at <https://tp.amegroups.com/article/view/10.21037/tp-23-1/rc>).

Methods

Patients

This study retrospectively analyzed the clinical data of 153 AR patients who received SLIT in the Department of Otolaryngology, Tianjin Children's Hospital from January 2020 to October 2021. The patients' demographic, follow-up methods, complications efficacy, compliance data, etc. were collected. The enrolled patients were required to fully meet the following conditions: (I) patients diagnosed with AR, with or without other allergic diseases; (II) 3–14 years old, male or female; (III) allergen detection results: dust mites were positive, closely related to clinical symptoms, and were the main allergen; (IV) allergens could be avoided as much as possible during treatment; (V) patients were willing to receive sublingual immunotherapy, and were able to comply with the program and receive follow-up. The exclusion criteria were as follows: patients with infectious rhinitis; patients who could not understand the purpose of this study and refused to cooperate with follow-up; and patients with incomplete data. A total of 136 patients were included in the final statistical analysis and 17 patients were excluded. The flow chart of this study is shown in *Figure 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Children's Hospital (No. KY2020-47) and individual consent for this retrospective analysis was waived.

Diagnostic criteria

AR was diagnosed according to the allergic rhinitis and its impact on asthma (ARIA) guidelines (7), based on the patient's history, symptoms, physical examination, and allergen detection (8). The total serum immunoglobulin E (IgE) and allergen-specific IgE were analyzed using the Fubok Allergen Tester and its allergen diagnostic reagent

Highlight box

Key findings

- Internet follow-up can significantly improve the compliance of sublingual immunotherapy (SLIT) patients with allergic rhinitis in children.

What is known and what is new?

- SLIT is an effective approach for treating allergic rhinitis in children. Although the curative effect of SLIT is significant, the compliance of patients is poor owing to the prolonged treatment time.
- The present study aimed to analyze the related factors affecting SLIT compliance in children with allergic rhinitis and provide a theoretical basis for improving patient compliance.

What are the implications, and what should change now?

- The Internet follow-up method could significantly improve the compliance of SLIT in children with allergic rhinitis. In the future, we will use this method to follow up with patients during SLIT.

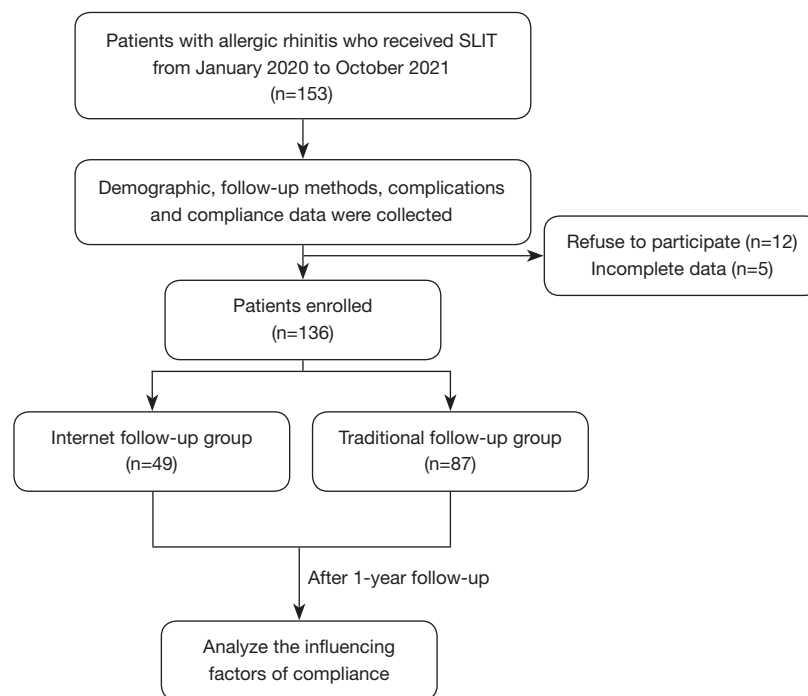


Figure 1 Study flow diagram. SLIT, sublingual immunotherapy.

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Standardized SLIT process

The standardized SLIT process mainly includes the diagnosis of allergic diseases, a standardized prescription, the initial clinical education of patients, an initial medication, and the establishment of patient files and regular follow-up education until the completion of the entire immunotherapy process (9). *Figure 2* shows the simplified flow diagram of standardized SLIT.

Follow-up

All patients were followed-up regularly. The baseline clinical factors of the two groups of follow-up methods were balanced and comparable. The traditional follow-up group was followed up by telephone interviews and outpatient visits, and the Internet follow-up group was followed up using the mobile medical applications (APP) and WeChat applications. Patients in the traditional follow-up group were followed up by telephone once a month. Follow-up included answering the patients' questions about SLIT

medication, reminding them to take the medication, and asking them about their symptomatic drug use and rhinitis symptoms. Outpatient follow-up was carried out every 3 months. The contents of the follow-up were the same as above, and patients were given renewed prescriptions. In the Internet follow-up group, the Mobile Medical APP was used to publish popular science about AR, distribute and recover questionnaires, remind patients to take the drugs and return to visit and guide patients to evaluate their own efficacy and adjust symptomatic drugs. WeChat was used to push popular health science knowledge, conduct regular live lectures, and facilitate doctor-patient interactions. The details of the follow-up plan are shown in *Figure 3*. Patients were considered to have poor compliance when they stop taking medication of SLIT.

Statistical analysis

Continuous variables were tested for normality and transformed into categorical variables for statistical analysis. The Chi-square test was used to compare the categorical variables between groups. Univariate and multivariable regression analyses were performed to analyze the independent factors influencing SLIT

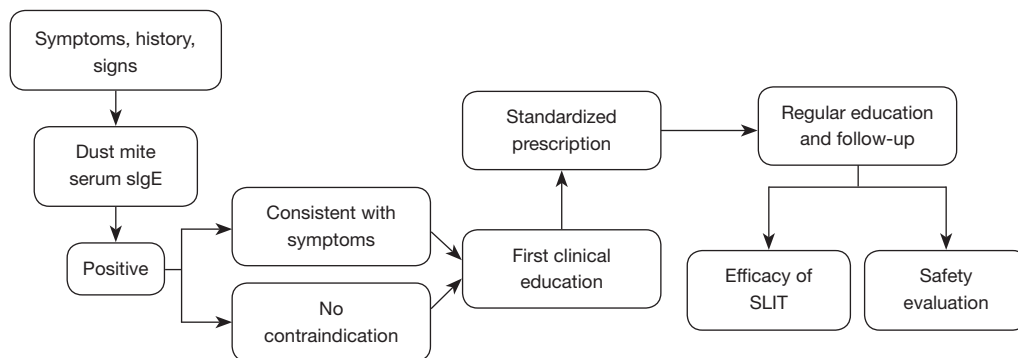


Figure 2 A schematic view showing the concise process of standardized SLIT. SLIT, sublingual immunotherapy.

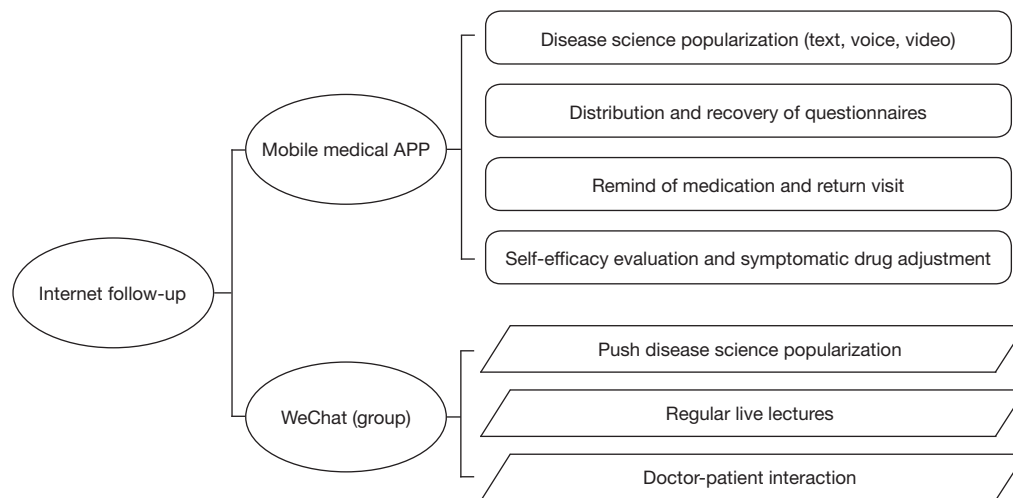


Figure 3 The Internet follow-up plan.

compliance. Statistically significant variables in univariate logistic regression analysis were included in multivariate regression analysis (using Enter method). Two-tailed P values <0.05 were considered statistically significant. All statistical analyses were performed using SPSSv26.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

A total of 136 patients were enrolled in this study. All patients were followed up for at least 1 year. Among them, 104 (76.5%) were males; 83 (61.0%) were 6–14 years old and the remaining patients were 3–6 years old; 69 (50.7%) patients lived in cities and towns; 97 (71.3%) patients had single allergies and the rest had multiple allergens; the

primary caregivers of 62 (45.6%) patients were highly educated; and 55 (40.4%) patients were complicated with asthma. Also, 35 patients (25.7%) ceased SLIT, and the remaining patients insisted on taking drugs. The baseline clinical features of the patients are shown in *Table 1*. Through the Chi-square test, it was found that there was no significant difference in age, sex, residence, type of allergen, education level of caregivers, whether the patient also had asthma, etc. between the Internet follow-up group and the traditional follow-up group ($P>0.05$). However, there were significant differences in compliance between the two groups ($P<0.001$).

Analysis of the causes of non-compliance in SLIT

The reasons for non-adherence in SLIT patients included poor efficacy in 18 cases (51.4%), familial factors in seven

Table 1 Baseline clinical characteristics of the included patients

Characteristics	Total, n (%)	Follow-up methods		P value
		Internet, n (%)	Traditional, n (%)	
Total	136 (100.0)	49 (36.0)	87 (64.0)	
Sex				0.287
Male	104 (76.5)	40 (81.6)	64 (73.6)	
Female	32 (23.5)	9 (18.4)	23 (26.4)	
Age, years				0.153
≤6	53 (39.0)	23 (46.9)	30 (34.5)	
>6	83 (61.0)	26 (53.1)	57 (65.5)	
Permanent residence				0.307
In cities or towns	69 (50.7)	22 (44.9)	47 (54.0)	
In the countryside	67 (49.3)	27 (55.1)	40 (46.0)	
Allergen type				0.678
Single allergen	97 (71.3)	36 (73.5)	61 (70.1)	
Multiple allergens	39 (28.7)	13 (26.5)	26 (29.9)	
Education level of caregivers				0.631
Higher education	62 (45.6)	21 (42.9)	41 (47.1)	
Not receiving higher education	74 (54.4)	28 (57.1)	46 (52.9)	
Whether the patient also had asthma				0.247
No	81 (59.6)	26 (53.1)	55 (63.2)	
Yes	55 (40.4)	23 (46.9)	32 (36.8)	
Compliance				<0.001
Continue medication	101 (74.3)	45 (91.8)	56 (64.4)	
Give up medication	35 (25.7)	4 (8.2)	31 (35.6)	

cases (20.0%), unable to renew the prescription in five cases (14.3%), children-specific factors in three cases (8.6%), and incidence of adverse reactions in two cases (5.7%). Since the sample size was too small for statistical analysis, please refer to *Table 2* for more specific reasons.

Logistic regression analysis

In this study, univariate logistic regression analysis showed that SLIT compliance was related to residence ($P<0.001$), the caregiver's education level ($P<0.001$), follow-up methods ($P<0.001$), and whether the patient also had asthma ($P<0.002$), and the differences were statistically significant. Variables with statistically significant differences

in the univariate logical regression were included in the multivariate regression analysis. After adjusting for the residence and whether the patient also had asthma, we found that the follow-up methods (OR =7.60, 95% CI: 2.20–26.21, $P=0.001$) and caregiver's education level (OR =8.54, 95% CI: 3.04–23.95, $P<0.001$) were independent factors influencing SLIT compliance. The specific logistic regression results of SLIT compliance are detailed in *Table 3*.

Discussion

SLIT for allergic rhinitis is a type of causative therapy that has been widely used in the clinic. In China, SLIT has been listed as a first-line treatment for AR in children, and

Table 2 Analysis of the causes of non-compliance with sublingual immunotherapy

Causes of non-compliance	n	Constituent ratio (%)
Poor efficacy	18	51.4
Reasons for children's families	7	20.0
Temporary improvement of symptoms	2	
Insufficient confidence in efficacy	2	
Worry about side effects of long-term medication	2	
Family contradiction	1	
Unable to renew the prescription	5	14.3
Go abroad	1	
Move to another city	1	
Government control measures for COVID-19	3	
Reasons for children	3	8.6
Resistance to long-term medication	2	
High learning pressure (entering a higher school)	1	
Adverse reactions	2	5.7
Acute asthma attack	2	

Chinese guidelines for SLIT have been developed. Although the curative effect of SLIT is significantly better than that of symptomatic treatment, patient compliance is still an important factor restricting the efficacy of SLIT. Korean scholars investigated the clinical results of SLIT using two kinds of SLIT drugs (LAIS and Staloral) for the treatment of AR patients with house dust mites and *Dermatophagoides farinae*. The results showed that LAIS had higher compliance and fewer side effects, while Staloral had higher satisfaction and immunoglobulin G4 (IgG4) levels (10). Italian scholars demonstrated that there is a significant difference in the understanding of the disease between patients with AR alone and those with asthma; thus, it is necessary to establish a different approach to management. Proactive and ongoing interventions that support patient needs and preferences have proven effective in ensuring long-term, good adherence to SLIT in real life (11).

A systematic review of SLIT compliance showed that the reported real-world SLIT persistence and compliance rates vary greatly due to research methods, and studies with long follow-up periods usually report low compliance rates (12). The main endpoint of this study was the compliance of SLIT patients. Consistent with previous reports, we found that 35 of the 136 patients ceased SLIT, accounting for 25.7% of the total number of included patients (13-16).

Table 3 Regression analysis of compliance with sublingual immunotherapy

Variables	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Sex	1.67	0.63–4.49	0.305			
Age	0.64	0.26–1.47	0.290			
Permanent residence	5.85	2.34–14.67	<0.001	6.57	0.68–63.32	0.103
Allergen type	1.50	0.61–3.66	0.379			
Education level of caregivers	7.88	3.13–19.89	<0.001	8.54	3.04–23.95	<0.001
Follow-up methods	6.23	2.05–18.95	0.001	7.60	2.20–26.21	0.001
Whether the patient also had asthma	4.55	1.74–11.92	0.002	0.81	0.08–8.69	0.859

OR, odds ratio; CI, confidence interval.

Thus, it can be seen that the non-compliance rate of SLIT is too high, which is a very important clinical problem facing clinicians, and an overall solution that improves patient compliance is needed. A previous study showed that timely telephone follow-up education and guidance for patients can improve their SLIT compliance (17). With the advent of the Internet era, the mobile medical APP has played an increasingly important role in the follow-up of chronic diseases. In recent years, a study showed that self-media management can markedly improve the compliance of SLIT patients (18). At the same time, some studies illustrated that Internet-based interactive and mobile platforms can improve compliance with subcutaneous immunotherapy (19,20). Therefore, our team decided to use the mobile medical APP and WeChat to follow-up SLIT patients; compared with patients who received telephone follow-up in the past, we found that Internet follow-up can significantly improve the compliance of SLIT patients.

A previous study showed that providing patients with treatment-related Internet health information will not harm the doctor-patient relationship. On the contrary, encouraging patients to seek treatment-related health information online can improve their compliance (21). We applied the Internet follow-up method, and published science popularization knowledge about SLIT using the mobile medical APP, which could also be disseminated through WeChat, so that more family members of similar patients could receive professional guidance, and thus, significantly improve the compliance of SLIT patients. From the patients' perspective, the quality of Internet health information plays a greater role in affecting their trust in doctors and their subsequent compliance (22). Therefore, strengthening the quality management of Internet health information can improve the compliance of patients. We used the mobile medical APP to publish authoritative and professional SLIT-related health information, and its quality was significantly higher than that which could be obtained from general comprehensive search engines. Thus, the Internet follow-up method can significantly improve patients' compliance.

The present study found that the main reasons for non-compliance were as follows: poor efficacy, familial factors, unable to renew the prescription, children-specific factors, and adverse reactions. Poor efficacy was the main reason for patients to cease treatment, and thus, there is a pressing need for clinicians to identify the factors affecting SLIT efficacy. Our team found that vitamin D₃ is an independent factor affecting the efficacy of SLIT, which

provides a potential target for further enhancing SLIT efficacy. At present, related articles are being summarized for publication. The familial factors of the children include temporary improvement of symptoms, the lack of confidence in efficacy, concern regarding the side effects of long-term medication, and family conflicts. These factors are mainly related to inadequate communication between doctors and patients. Internet follow-up can effectively enhance the interaction between doctors and patients, and help eliminate family concerns in all aspects, thereby improving the compliance of patients in terms of taking their medication.

Five patients were unable to renew their prescriptions; one was due to going abroad, one moved to another city, and three were unable to come to the hospital to take the medicine due to the government's control policy regarding the Corona Virus Disease 2019 (COVID-19) epidemic. For these reasons, the online prescription and distribution of drugs can be achieved through the mobile medical APP function of the Internet follow-up method, which is valuable for reducing patient dropouts. The considerable learning pressure on children and their resistance to long-term medications were also reasons for drug withdrawal. Three patients were going through puberty and had a rebellious mentality toward their parents, which led to non-compliance with treatment. The parents of such children should pay more attention to their children, assist them in terms of psychological counseling, and help them to face and cope with the situation together. Some scholars have reported that teenagers are the most disobedient in SLIT compliance studies, and emphasized that special attention should be paid to adolescents during treatment (14). Two patients stopped taking medicine temporarily due to acute asthma attacks. However, with the help of respiratory doctors, and after communicating with the family members of the children, they expressed understanding and agreed to reschedule SLIT.

Some research results indicate that patients with characteristics such as bronchial asthma or mild symptoms have a higher probability of non-compliance (16), which is inconsistent with our research conclusions. Through univariate logistic regression analysis, we found that there were statistical differences between residence and whether the patient also had asthma. After multivariate logistic regression analysis, we found that these two variables were confounding factors of patient compliance. This indicates that the compliance of SLIT patients will not be affected regardless of whether the patients have asthma or not and

whether or not they live in the countryside. After adjusting for these two variables, multivariate logistic regression analysis found that the follow-up methods and education level of caregivers were independent factors influencing the compliance of SLIT patients, suggesting that the Internet follow-up method could significantly improve the compliance of patients. At the same time, these findings also remind us that families whose caregivers have not received higher education should pay sufficient attention to their children, communicate with them more, and eliminate all kinds of doubts to ensure that the children can adhere to treatment.

There are also some limitations in this study that should be considered. Firstly, this is an observational study, and thus, there is inevitably a certain bias in the data collection. Also, the statistical analysis was relatively simple, and the small sample size and short follow-up time also limit the conclusions of this study. In the future, we will design prospective clinical trials to further confirm the reliability of our conclusions.

Conclusions

Our study found that the follow-up methods and education level of caregivers were independent factors affecting SLIT compliance in children with AR. Internet follow-up can significantly improve the SLIT compliance of children with AR.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://tp.amegroups.com/article/view/10.21037/tp-23-1/rc>

Data Sharing Statement: Available at <https://tp.amegroups.com/article/view/10.21037/tp-23-1/dss>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tp.amegroups.com/article/view/10.21037/tp-23-1/coif>). LL serves as an unpaid editorial board member of *Translational Pediatrics*

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Tianjin Children's Hospital (No. KY2020-47) and individual consent for this retrospective analysis was waived.

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