

The effect of the standard length of the first prescription on the adherence to sublingual immunotherapy for patients with allergic rhinitis

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Background: Poor adherence to sublingual immunotherapy (SLIT) has become a major cause of unsatisfactory clinical efficacy for patients with allergic rhinitis (AR). This study was designed to identify the effect of different first prescription lengths on the adherence to SLIT.

Methods: The clinical data of 306 patients with AR who started SLIT between January 2017 and June 2018 were retrospectively reviewed. Patients were divided into 3 groups according to the length of their first prescription (group A: less than 3 months, group B: 3 to 6 months, group C: more than 6 months). The numbers of adherent or nonadherent patients in each group and the main reasons of nonadherence were analyzed.

Results: Groups A, B, and C included 102, 161, and 43 patients, respectively. The average lengths of the first prescription for group A, B, and C were 62.52 ± 17.63 , 102.21 ± 9.22 , and 189.07 ± 17.97 days. There were significance differences among the 3 groups ($p < 0.05$). There were 42 (41.18%), 112 (69.57%), and 37 (86.05%) adherent patients in group A, B, and C. There were 60 (58.82%), 49 (30.43%),

and 6 (13.95%) nonadherent patients in group A, B, and C. There were significant differences in the proportions of adherent and nonadherent patients among the 3 groups ($p < 0.05$). The following reasons were cited for nonadherence to SLIT: the long course of SLIT; inconvenience of getting the prescription; ineffectiveness; side effects; and other reasons.

Conclusion: Under certain conditions, 6 months is recommended as the standard length for the first prescription, which can significantly improve adherence to SLIT in patients with AR. © 2020 ARS-AAOA, LLC.

Key Words:

adherence; allergic rhinitis; evidence-based medicine; standard first prescription; sublingual immunotherapy

How to Cite this Article:

Jin M, Zhang L, Zhou G, Zhang S, Li X, Hu S. The effect of the standard length of the first prescription on the adherence to sublingual immunotherapy for patients with allergic rhinitis. *Int Forum Allergy Rhinol.* 2020;00:1-5.

Allergic rhinitis (AR) is 1 of the most common diseases treated by otolaryngologists. The prevalence of AR in China has increased significantly in recent years.¹ Allergen-specific immunotherapy (AIT) has proven to be a safe and effective treatment for AR,²⁻⁴ and is considered to be the only treatment that can change the natural progression of AR.^{5,6} Many studies have shown that long-term adherence

is necessary to achieve the optimal clinical benefits of AIT in patients with AR.^{7,8} However, poor adherence to AIT, especially to sublingual immunotherapy (SLIT), has become a major cause of poor clinical efficacy,⁹ even though SLIT has become more acceptable to both specialists and patients because of its safety and convenience. Several studies have found that only 7% to 13.2% of patients were adherent to SLIT for 3 years and most patients terminated the treatment before they were expected to.¹⁰⁻¹² Therefore, some researchers believe that the main challenge in the treatment of AR over the next few years will be to improve treatment adherence rather than to introduce new drugs.¹³

In clinical practice, we found there was no recommended length for the first prescription of SLIT in currently available guidelines. The length of the first prescription of SLIT for patients with AR varied for each specialist, ranging from 2 weeks to more than 6 months. During follow-up, we have found that patients with first prescriptions of different lengths may have different adherence to SLIT. Therefore, a retrospective study based on real life clinical

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Funding sources for the study: Department of Health and Family Planning Commission of Zhejiang Province (2017KY407).

Potential conflict of interest: None provided.

Received: 7 November 2019; Revised: 11 February 2020; Accepted: 14 February 2020

DOI: 10.1002/alar.22553

View this article online at wileyonlinelibrary.com.

TABLE 1. The administration method and dose increment plan of the *Dermatophagoides farinae* drops

Time	Specification	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
First week	1	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
Second week	2	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
Third week	3	1 drop	2 drops	3 drops	4 drops	6 drops	8 drops	10 drops
Time	< 14 years old				≥ 14 years old			
Fourth to fifth week	Specification 4, 3 drops/day				Specification 4, 3 drops/day			
Sixth week and later					Specification 5, 2 drops/day			

data was performed to identify the effect of different lengths of the first prescription on adherence to SLIT in AR and to analyze the underlying causes.

Patients and methods

Patients

We retrospectively analyzed 325 patients with AR who started SLIT during the period from January 2017 to June 2018 at the Department of Otolaryngology–Head and Neck Surgery, Sir Run Run Shaw Hospital. AR patients included in the study were diagnosed based on the guidelines for AR published in China. Sensitization to house dust mites (HDM) was confirmed by a positive skin-prick test with *Dermatophagoides farinae* and/or positive serum-specific immunoglobulin E (IgE) detection. Patients with severe or uncontrolled asthma (forced expiratory volume in 1 second [FEV1] <70% of predicted value), systemic immunologic disorder, concomitant treatment with β -blockers, and current long-term treatment with systemic steroids were excluded from the study.

Treatment

Before starting SLIT, patients were informed of its advantages and disadvantages by specialists so that the decision to start SLIT could be performed collaboratively. All patients received pretherapy education lasting approximately 20 to 30 minutes that included information about the administration method, long course of treatment (3 to 5 years), approximate cost, and possible side effects. *D. farinae* drops (Chanllergen; Zhejiang Wolwo Bio-Pharmaceutical Co., Ltd., Wukang, China) were used in this study. Table 1 presents the administration method and dose increment plan of the *D. farinae* drops.

During follow-up, patients were contacted at 1, 3, 6, and 12 months after starting SLIT. Nineteen patients could not be reached during follow-up and were excluded from the study. During follow-up, patients were asked if they had continued the treatment; patients who had terminated the treatment were asked if they had consulted a specialist before termination and for a reason why they terminated the treatment. All patients were followed up for at least 12 months after they started SLIT.

Patients who terminated the treatment for more than 1 week without the approval of a specialist would be recorded as nonadherent patients. Patients who continued the treatment, terminated the treatment with the approval of a specialist, or stopped the treatment for less than 1 week and continued the treatment later would be recorded as adherent patients. The following reasons were cited for nonadherence to SLIT: the long course of SLIT, inconvenience of getting the prescription, ineffectiveness, side effects, and other reasons. Patients could only choose 1 reason as the main reason. Patient age at the time of starting SLIT, sex, length of the first prescription (recorded as the time to use), adherence or nonadherence to SLIT, and the main reason for nonadherence to SLIT were recorded. The data were then statistically analyzed. The research protocol for this clinical study was approved by the ethics committee of Sir Run Run Shaw Hospital.

Patients were divided into 3 groups according to the length of the first prescription. The length of the first prescription for patients in group A was less than 3 months. The length of the first prescription for patients in group B was between 3 and 6 months. The length of the first prescription for patients in group C was more than 6 months.

Statistical analysis

Results for age at the time of starting SLIT and length of the first prescription are presented as mean $\pm$ standard deviation (SD). Results for sex, adherence or nonadherence rate, and main reason for nonadherence are presented as numbers and percentages. Student *t* test and the chi-square test were used for intragroup comparisons. A *p* value <0.05 was considered statistically significant. Prism 5.0 statistical software (GraphPad Software, Inc., La Jolla, CA) was used for the analysis.

Results

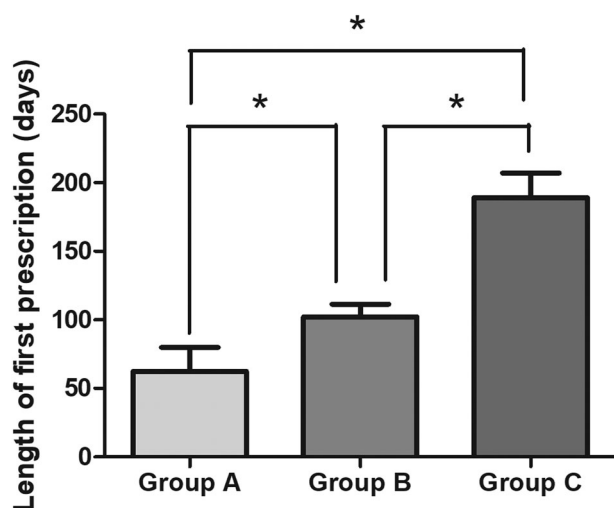
General patient information

A total of 306 patients with AR who agreed to SLIT were included in the study. There were 155 male (50.65%) and 151 female (49.35%) patients. Patient age ranged from 7 to 70 years old (age, mean $\pm$ SD, 30.54 $\pm$ 11.71 years). A total of 102 patients (33.33%) were categorized into group

TABLE 2. General information for patients with AR in each group

Group	Gender (n)		Age (years)	
	Male	Female	Mean $\pm$ SD	Range
A	56	46	31.82 $\pm$ 11.51	14–61
B	77	84	30.19 $\pm$ 11.20	8–62
C	22	21	28.53 $\pm$ 13.80	7–70
Total	155	151	30.54 $\pm$ 11.71	7–70

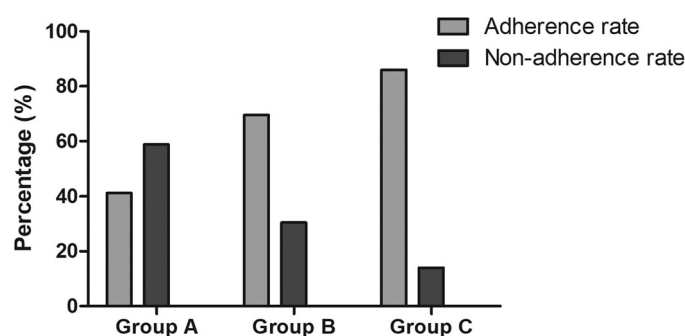
AR = allergic rhinitis; SD = standard deviation.

**FIGURE 1.** Length of first prescription for groups A, B, and C, respectively. There were significant differences among the 3 groups.

A, 161 patients (52.62%) into group B, and 43 patients (14.05%) into group C. There was no significant difference in age or sex distribution among groups A, B, and C. The characteristics of patients in each group are shown in Table 2.

Effect of length of first prescription

The average length of the first prescription in group A (62.52 ± 17.63 days) was less than that of group B (102.21 ± 9.22 days); both were less than that of group C (189.07 ± 17.97 days). The difference in average length of the first prescription was significantly different among the 3 groups ($p < 0.05$). The length of the first prescription in 3 groups is shown in Figure 1. In group A, there were 60 nonadherent patients (58.82%) and 42 adherent patients (41.18%). In group B, there were 49 nonadherent patients (30.43%) and 112 adherent patients (69.57%). In group C, there were 6 nonadherent patients (13.95%) and 37 adherent patients (86.05%). There were significant differences between the 3 groups ($p < 0.05$). The adherence/non-adherence rates in the 3 groups are shown in Figure 2.

**FIGURE 2.** Adherence and nonadherence rates for groups A, B, and C, respectively. There were significant differences among the 3 groups.

Reasons for nonadherence

The main reasons for nonadherence in group A were the long course of SLIT (12 cases), inconvenience of getting the prescription (12 cases), ineffectiveness (11 cases), side effects (2 cases), and other reasons (23 cases). The main reasons for nonadherence in group B were the long course of SLIT (13 cases), inconvenience of getting the prescription (6 cases), ineffectiveness (4 cases), side effects (5 cases), and other reasons (21 cases). The main reasons for nonadherence in group C were the long course of SLIT (1 case), side effects (3 cases), and other reasons (2 cases). The main reasons for nonadherence in the 3 groups are shown in Table 3.

Discussion

In recent years, how to improve the adherence to AIT for patients with AR has become a hot topic. Many studies have focused on improving patient adherence through better patient education and/or more rigorous follow-up.¹⁴⁻¹⁷ In our daily practice, a specific patient education program and rigorous follow-up plan have been provided to all patients who accepted SLIT. If necessary, all patients can contact our medical center via telephone or WeChat (<https://web.wechat.com/>) during working hours. However, the total adherence rate at the 1-year follow-up in our study was 62.42%, which was lower than expected. In our study we found that the patients in group C had the best adherence rate. Patients should be evaluated after 6 months of SLIT to decide whether to continue treatment and whether to adjust the dose. Therefore, 6 months is recommended as the standard length of the first prescription of SLIT for patients with AR.

However, the factors that determine the length of the first prescription are very complex. Different laws and government regulations, doctors' experience and different understandings of the disease and treatment, patients' awareness of the disease, and patients' education and economic situation may influence the length of the first prescription. Therefore, the standard length of the first prescription is not suitable for all specialists and patients. The standard length of the first prescription may even cause some waste

TABLE 3. Reasons for nonadherence in each group

Group	Long course (n)	Inconvenient (n)	Ineffectiveness (n)	Side effect (n)	Other reasons (n)
A	12	12	11	2	23
B	13	6	4	5	21
C	1	0	0	3	2
Total	26	18	15	10	46

in those patients who terminate treatment early because of side effects. However, in our opinion, the low adherence rate for SLIT may cause much more waste. Therefore, under certain conditions, 6 months is still recommended as the standard length of the first prescription of SLIT for patients with AR. For those specialists who have difficulty prescribing for 6 months, we recommend that the length of first prescription should not be too short (eg, less than 3 months or 1 month). At the same time, better patient education, more rigorous follow-up plan as well as a better patient management system are all effective and necessary actions to help improve patient adherence.

There are many reasons for terminating SLIT treatment, including subjective and objective reasons. Some scholars believe that the desire for using the lowest possible dosing, the best patient-appreciated effects, and the easiest administration for patients with chronic disease are the major factors related to the burden of therapy.¹⁸ In our study, the long course of SLIT, inconvenience of getting the prescription, ineffectiveness, side effects, and other reasons were identified as the main reasons for nonadherence according to the results of the follow-up. In our study, there were 18 patients who discontinued treatment because of the inconvenience of getting the prescription. The most reasonable explanation might be that many patients could only come to our hospital to get prescription refills, but not from their family doctors or nearby local medical center. The greatly increased time and economic costs are too much to afford. Forty-six patients were found to have discontinued their treatment for other reasons. Four of the 46 terminated SLIT treatment after being told by other people that SLIT treatment was ineffective and harmful; 2 of the 46 stopped without consulting a specialist because of getting pregnant during the treatment; 2 of the 46 just forgot to take the medication for more than 1 week; the remaining patients of the 46 terminated SLIT treatment and switched to other treatments that they thought were better (such as changing a job, using air purifiers, wearing face masks,

taking traditional Chinese medicine, accepting acupuncture or surgical treatment, etc.). All these reasons were classified as “other reasons.” We also found that there were no patients in group C who discontinued treatment due to the inconvenience of getting the prescription or ineffectiveness and there was only 1 patient who discontinued treatment due to the long course of SLIT. Therefore, for patients with a longer first prescription, the improvement in adherence to SLIT may be due to better understanding of the long course, increased convenience of the treatment, and better patient appreciation of medical effects. Moreover, we believe that the standard length of the first prescription (6 months) actually forms a long-term agreement with patients at the start of SLIT, which helps to select those patients who are more willing to comply with long-term treatment, and those patients always have better adherence.

There are some limitations to this study. The clinical data in this study were retrospective in nature and thus have an inherent bias. The length of the first prescription was not randomly allocated to patients. Until now, the follow-up time is only 1 year. We should continue follow-up until the end of SLIT treatment.

Conclusion

Extending the length of the first prescription can significantly improve adherence to SLIT for patients with AR. Under certain conditions, 6 months is recommended as the standard length for the first prescription. The reasons for the improvement may be attributed to better understanding of the long-term course, increased convenience of the treatment, and better patient appreciation of the treatment's medical effects. ④

Acknowledgment

We are very grateful to Mr. Shenzhi Yu for his work on language modification.

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