

Nonadherence to sublingual immunotherapy in allergic rhinitis: a real-life analysis

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Background: To sustain the long-lasting beneficial effects of allergen-specific sublingual immunotherapy (SLIT), an adequate duration of treatment is required. Nevertheless, many patients discontinue prematurely and therefore fail to obtain satisfactory therapeutic effect in clinical practice. The aim of this study was to analyze the causes leading to premature discontinuation of SLIT in allergic rhinitis (AR), and to provide the corresponding countermeasures for the following SLIT course.

Methods: We performed a retrospective analysis of data from 142 patients with AR who started SLIT during the period from December 2009 to February 2015. Patients were contacted at 1, 3, 6, and 12 months into SLIT as part of our standard of care. The patients who claimed to have stopped treatment were asked to provide a reason during one of the phone calls.

Results: Overall, 76 (54%) patients with AR terminated immunotherapy during the first year of treatment. Among the

76 patients, the following reasons were cited for nonadherence to immunotherapy: patients could not be reached (25%); ineffectiveness (24%); the long course (18%); improvement of symptoms (13%); side effects (4%); lack of confidence in the treatment (4%); or other reasons (12%).

Conclusion: Fifty-four percent of AR patients terminated their treatment within the first year of SLIT. The top reasons for treatment discontinuation included patients not be reached, ineffectiveness, and length of course. © 2017 ARS-AAOA, LLC.

Key Words:

adherence; allergic rhinitis; specific sublingual immunotherapy

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Allergic rhinitis (AR) is a chronic disease with the main pathologic features of nasal congestion, nasal itching, rhinorrhea, and sneezing. According to studies done of 11 major cities in China, the prevalence of AR ranges from 9.6% to 23.9%.¹ Allergen-specific immunotherapy is considered the only treatment currently available that can affect the natural course of allergic disease.^{2,3} Sublingual immunotherapy (SLIT) is an initial approach for treating respiratory allergic disease.³ However, although SLIT is easier and more convenient for patients to use without

supervision, it is difficult to ensure compliance, which influences its therapeutic effect.⁴ Therefore, we analyzed the reasons for termination of SLIT among the 142 AR patients in our department, and we propose some measures to improve adherence and therapeutic effect.

Patients and methods

Participants

The data of 142 AR patients were collected from The First Affiliated Hospital of the People's Liberation Army (PLA) General Hospital, Beijing, China, during the period from December 2009 to February 2015. Mandatory inclusion criteria were as follows: (1) clinical criteria of moderate-to-severe, persistent AR in the past 2 years; (2) sensitization to house dust mites (HDM), including *Dermatophagoides pteronyssinus* and/or *Dermatophagoides farinae* with positive skin prick test (wheal diameter >3 mm) and/or Pharmacia CAP system score >2 (Phadia, Uppsala, Sweden); and (3) forced expiratory volume in 1 second (FEV₁) within normal limits (>79% of predicted value). Exclusion

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criteria were: persistent asthma; anatomic abnormalities of the upper respiratory tract; current long-term treatment with systemic steroids; systemic immunologic disorder; and intercurrent treatment with β -blockers or oral corticosteroids in the previous 6 months.

The pre-therapy counseling routine included: (1) informing patients that immunotherapy is necessary for AR, and SLIT has been proven to be a safe and effective treatment; (2) informing patients that the course of immunotherapy is 3–5 years; and (3) providing details on payment for treatment. Patients who agreed with the treatment and payment would begin SLIT.

Patients were contacted at 1, 3, 6, and 12 months into SLIT as part of our standard of care. Patients who claimed to have stopped the treatment would be asked for a reason during one of those past phone calls. Information regarding patients' demographics, duration of treatment, and diagnosis were obtained from their charts. Reasons for cessation of therapy were grouped into 7 categories: patients could not be reached; ineffectiveness; long course; improvement of symptoms; side effects; lack of confidence in the treatments; or other reasons. Reasons patients *could not be reached* included telephone number error, telephone downtime, or lost contact due to change in private phone number. *Ineffectiveness* included patients who perceived no improvement in symptoms. The *long course* explanation group included patients who cited the high frequency of drug use or long-term inability to persist as their primary reasons. Those citing *improvement of symptoms* believed their symptoms were alleviated and found no reason to continue treatment. *Other* reasons included patients who got pregnant or relocated outside the city or abroad.

Treatment

The HDM allergen extract for SLIT (*Dermatophagoides farinae* drops; Wolwopharma Biotechnology, Zhejiang, China). The biologically standardized extracts were labeled in concentrations of total protein and used in the form of drops (No. 1: 1 $\mu\text{g/mL}$; No. 2: 10 $\mu\text{g/mL}$; No. 3: 100 $\mu\text{g/mL}$; No. 4: 333 $\mu\text{g/mL}$; No. 5: 1000 $\mu\text{g/mL}$), as determined by bicinchoninic acid (BCA) protein assay. The biologic activity of the allergen extracts was determined by indirect enzyme-linked immunoassay (ELISA), as approved by the China Food and Drug Administration. As described elsewhere,⁵ patients <14 years old were asked to take daily increasing doses (from No. 1 to No. 3), according to the manufacturer's instructions, during the 3-week up-dosing phase, and were then instructed to take 3 drops of No. 4 solution once daily during the maintenance phase. For patients >14 years old, increasing doses from No. 1 to No. 4 were taken during the 5-week up-dosing phase. The patients were then instructed to take 2 drops of No. 5 solution once daily during the maintenance phase. Drops were instructed to be kept under the tongue for 2–3 minutes before being swallowed.

TABLE 1. Demographics and adherence*

	Subjects	Age (years)	Men	Women
Adherence ^a	66 (46)	22.8 $\pm$ 13.2	39 (27)	27 (19)
Nonadherence ^b	76 (54)	28.3 $\pm$ 18.3	44 (31)	32 (23)
Total	142	25.0 $\pm$ 15.4	83 (58)	59 (42)

*Data expressed as number (%) or as mean $\pm$ standard deviation.

^aPatients who continued sublingual immunotherapy in the first year.

^bPatients who discontinued sublingual immunotherapy in the first year.

This was a retrospective study and was approved by the local ethics committee.

Results

Demographics and adherence

One hundred forty-two patients were enrolled, 83 (58%) males and 59 (42%) females, with an age range of 6–60 years. Seventy-six of them discontinued SLIT prematurely, accounting for 54% of those initially enrolled (Table 1).

Reasons for premature cessation

The most commonly cited reason cited for premature cessation of SLIT was that patients could not be reached (25%). The remaining reasons leading to poor compliance were ineffectiveness (24%), the long course (18%), improvement of symptoms (13%), side effects (4%), lack of confidence in the treatments (4%), and other reasons (12%) (Figure 1).

Discussion

SLIT has been proven to safe and effective for treatment of AR.^{6–10} Its advantages include high level of safety and good efficacy, and patients can utilize the therapy at home. However, with this therapy there may be decreased interaction between patient and doctor, which weakens the management and education of patients. In clinical practice, studies have identified poor patient compliance with SLIT,^{11–16} but few have focused on the reasons for dropout in the first year. Most of the studies did, however, highlight the importance of pretreatment education and patient management. Thus, there is an urgent need for identification of potential barriers and measures that will lead to enhanced persistence and compliance.

Sales data from 2 large drug manufacturers in Italy demonstrated a 56.3% rate of spontaneous discontinuations in the first year.¹⁴ Similarly, in our investigation, the dropout rate was 53.5% in the initial 1-year stage of SLIT.

The most common reason cited for the dropout in our study was that patients could not be reached. This highlights the great importance of recording more complete and accurate personal information on the first visit. In addition, it is important to inform patients about the significance of follow-up and the need to save the hospital's contact number so information can be kept up to date. Another leading

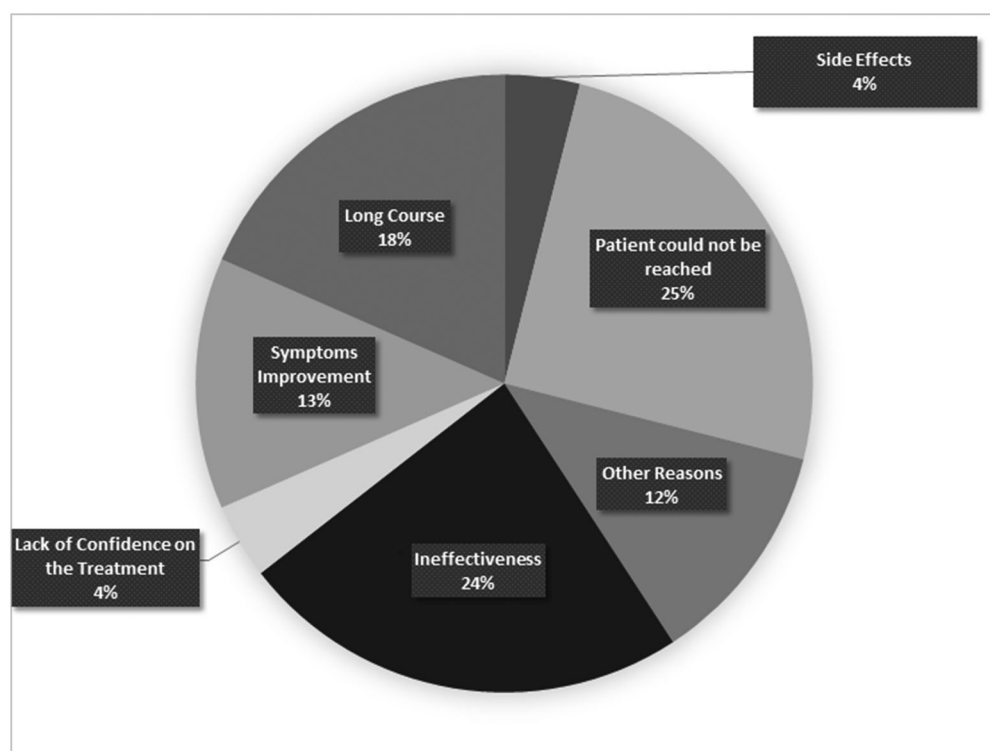


FIGURE 1. Reasons for premature discontinuation of immunotherapy.

reason for dropout in this survey was ineffectiveness. An Italian study investigated the causes for SLIT nonadherence, citing lack of perceived efficacy as the most common motive for patient discontinuation of treatment,^{17,18} yet other studies reported its effectiveness. For SLIT, the onset time is up to several months.¹⁹ However, during telephone follow-up, we found that patients were still unsure. Health care workers should provide full details to patients at the beginning of the treatment to avoid premature withdrawal. Further, some patients discontinued when symptoms improved, with the assumption that treatment was no longer needed. Lin et al²⁰ showed that SLIT could generate different efficacy levels with varying durations. Thus, we emphasize to patients that the initial effect is not equivalent to the final outcome. Moreover, several postmarketing surveys and clinical trials have concluded that the one of causes for patients' nonadherence to SLIT is side effects.^{14,21,22} Herein we found that side effects accounted for 4% of the reasons for nonadherence, possibly related to drug and dose.

In studies assessing compliance, the reasons for dropout in the first year have rarely been analyzed, and most studies made no mention of the pretreatment education. An extensive investigation from the United States disclosed the immense financial burden of AR in children as the most common reason for nonadherence in child and adult populations.²³ However, we found that discussions regarding costs in advance of treatment can lead to a decreased dropout rate, further emphasizing the importance of pretreatment education. With regard to the long treatment

course, even when patients were informed with regard to the multiyear therapy, when they actually began to take medicine daily they indicated difficulty in staying with the treatment course. For these patients, adherence may be improved by management and supervision provided by medical workers.

In view of some controllable elements influencing compliance, and in the light of clinical management experience with SLIT,^{12,24} we must take measures to reduce the dropout rate and improve treatment compliance. First, doctors and nurses need to help patients improve their awareness before treatment, including providing information on significance of SLIT, onset time, cost, side effects, and duration. Second, it is necessary to establish good doctor-patient communication channels. To remove doubts and to correct inappropriate usage, regular telephone interviews every 3 months could be implemented for SLIT patients. Third, we can use WeChat and Microblog to establish a public platform to disseminate knowledge and improve public understanding of allergic disease, and also to carry out patient health education lectures. Fourth, family members of patients could be enlisted to help patients complete their immunotherapy. Studies have shown that adherence can be improved if patients perceive a good quality of life.²⁵ Beyond 3–5 years, efficacy can be maintained for a long time.²⁶ Moreover, immunotherapy can also prevent progression of rhinitis to asthma and production of new allergy.²⁷ The successful completion of treatment can establish a good foundation for subsequent therapeutic efficacy.

Conclusion

The dropout rate in the first year of sublingual specific immunotherapy among AR patients was found to be 54%. The inability to reach patients, ineffectiveness, and the long course of treatment were the main impact factors, all of which could be improved through better patient

management and education. Furthermore, with proper pre-therapy counseling, patients rarely drop out due to payment issues. 

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