

BRIEF COMMUNICATION

Causes of SLIT discontinuation and strategies to improve the adherence: a pragmatic approach

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Abstract

Sublingual immunotherapy (SLIT) is often discontinued, and many patients do not renew the prescription. We evaluated the reasons for discontinuation and set up an educational/follow-up plan to improve the adherence. In a first phase, the adherence at 4 months was directly assessed. Based on those results, an action plan (education, frequent contacts, and strictly scheduled visits) was developed and tested in other patients. A group of matched patients did not undergo the follow-up plan (controls). In the first phase, involving 252 subjects, at 4 months, there were 30% dropouts, mainly due to side-effects. In the second phase, 149 patients underwent education/follow-up and 90 received no intervention. In the first group, discontinuations at 4 months were 5%, vs 18% in the controls ($P = 0.01$). After one year, 12% of patients were lost in the first group and 35% in the control group ($P < 0.001$). An adequate education and a strict follow-up can significantly reduce SLIT's discontinuations.

Sublingual immunotherapy (SLIT) is a viable alternative to the traditional subcutaneous administration (1), and it is routinely used in many countries (2). The main advantages of SLIT are the self-administration, the safety, and the convenience. Nevertheless, these advantages are counterbalanced by adherence problems, as often happens with long-lasting treatments (3). According to the data provided by manufacturers, 56% of patients discontinue SLIT during the first year, and at the third year, only 15% are still on therapy (4). Some questionnaire-based surveys have shown that the most important reasons for discontinuation are side-effects and nonperception of efficacy (5, 6). On the other hand, adequate information and strict follow-up of patients seem able to improve the adherence (7).

Efficient strategies to improve the adherence with SLIT are needed, provided that the relevant causes of nonadherence are identified. Thus, we performed a two-phase study, to assess the reasons for nonadherence and to test the effects of a specifically designed educational/follow-up program.

Methods

This study involved patients receiving SLIT for pollen-induced allergic rhinitis/asthma (1). In all patients, SLIT was

started approximately 2 months before the expected beginning of the pollen season, according to the local pollen calendar.

In a first phase, consecutive patients receiving pre-seasonal SLIT were evaluated by telephone calls and/or direct interviews to assess the number and reasons for permanent/temporary discontinuations. Based on these results, an educational/follow-up program (see details in Table 1) was specifically designed to improve the adherence. In a second phase, other patients were allocated, according to their choice, to either the educational program (Table 1) or no intervention. All patients' characteristics including dropouts were managed through a dedicated database. Specifically trained nurses were in charge of the first-line contacts. Patients signed an informed consent, and the study was approved by the local ethical committee.

The diagnosis of pollen-induced rhinitis/asthma was based on clinical history, matching between symptoms and pollen seasons, and positive result of skin prick test/specific IgE assay, according to guidelines (8, 9). Skin prick test was performed using a standard panel including grass, Parietaria, olive, birch, hazelnut, house dust mite, ragweed, alternaria, and cat/dog dander. The first SLIT dose was administered under medical supervision, and a physician was always

Table 1 Educational and follow-up programs

Action taken	Time
Educational session (about 30 min) at the first dose administration. Information about effects of sublingual immunotherapy (SLIT), what to expect, when to expect improvement, possible side-effects and their management, duration, how to store the product.	Time 0 First dose
Collection of contact details.	
Phone/e-mail contact for a possible early discontinuation. In the case of mild side-effects, nurse counseling, else an extra visit, is scheduled.	Time + 7–10 days
Phone/e-mail contact to fix the next follow-up visit	Time + 3 months
Follow-up visit for SLIT refill, dropout evaluation	Time 4 months (± 10 days)
Phone/e-mail contact for the visit to prescribe a new SLIT course for the second season	Time + 12 months

available for information/advice. Percentages of dropout in the enrolled populations were compared by the chi-square test.

Results

In the first phase, starting in 2010, 252 patients (145 male, age range 5–58 years) received SLIT for pollen allergens. A routine follow-up visit was scheduled at the beginning of the pollen season (2011), about 4 months after prescription. Those patients who did not come to the visit were contacted by phone call or e-mail to assess whether they had continued treatment and if not for which reasons. Of 252 patients, 76 (30%) had discontinued SLIT at 4 months. Of them, 20 (8%) patients stopped SLIT during the first 10 days, due to local side-effects (oral itching, swelling, burning) and 2% stopped after 10 days, again for side-effects. Finally, 20% of patients forgot the scheduled control visit and spontaneously discontinued but without side-effects reported.

According to those results, an action plan was established (Table 1) and applied in 2011 to another group of 239 SLIT patients (well matched with those of the first phase) (Table 2) and allocated to either the educational/follow-up plan (149 patients, 88 male, mean age 26 years) or no intervention (90 subjects, 53 male, mean age 31 years). In the intervention group, 20 patients (13%) had discontinued SLIT at the first phase (10 days), but 17 of them had resumed after our phone contact. Thus, after 10 days, only 3 (2%) had permanently discontinued SLIT. At the 4-month visit, a further six patients had stopped, but two had resumed after the visit. Thus, at 4 months, there were only seven dropouts (5%). In the control group, there were 16 dropouts at 4 months (17%), 12 due to side-effects occurring in the first 10 days and four lost to follow-up or for the onset of other diseases. No difference was seen between children and adults. Three

Table 2 Characteristics of the patient populations

	First phase	Second phase	
		Intervention	Control
Pats, <i>N</i>	252	149	90
M/F	145/107	88/61	53/37
Age range, years	5–58	5–53	6–57
Age 5–14 years	83 (33%)	54 (36%)	32 (35%)
Sublingual immunotherapy (SLIT)			
Birch	39	26	15
Grass	190	107	60
Cypress	7	5	3
Grass + birch	16	11	12
Monosensitized, <i>N</i> (%)	236 (94%)	138 (93%)	78 (87%)
Rhinitis only, <i>N</i> (%)	10 (4%)	8 (5%)	9 (10%)
Asthma + Rhinitis, <i>N</i> (%)	242 (96%)	141 (95%)	81 (90%)
Discontinued at 4 months, <i>N</i> (%)			
Early side-effects (<10 days)	20 (8%)	3 (2%)	13 (14%)
Late side-effects (>10 days)	6 (2%)	4 (3%)	4 (4%)
Forgot the visit	50 (20%)	11 (7%)	15 (17%)
Lost at the subsequent season, <i>N</i> (%)	76 (30%)	18 (12%)	32 (35%)

<14-year patients in the intervention group and five in the control group forgot the scheduled visit. At the time of the scheduled visit for the second SLIT course (1 year), 18 of 149 (12%) of the patients in the intervention group were lost, vs 32 of 90 (35%) of the controls, with a *P* value <0.001% (Table 2). The rate of discontinuations in the control group in the second phase was comparable with that detected in the first-phase population (35% vs 30%, respectively, *P* = NS).

Discussion

Sublingual immunotherapy is considered convenient for patients, due to the self-administration and to the safety profile (2, 10), but it suffers from important adherence problems. The data from postmarketing surveys are encouraging (adherence rates of 70–100%) (4), but the manufacturers' data are alarming, with the percentage of sold refills dropping to <15% at the third year of treatment (5). Several attempts have been made to identify the reasons for SLIT discontinuation. A low-efficacy perception is reported by specialists as the main reason (6, 11), and it is also true that SLIT is more effective in highly symptomatic patients (12). Also the economic aspect (13) may affect the adherence, whereas under the age of 4, local side-effects are the main responsible for stopping (14). Some studies focused on how to maintain a satisfactory adherence. Incorvaia et al. (15) showed that detailed information on the methods and scopes of SLIT can improve the compliance. Vita et al. (16) showed that the adherence is positively correlated with the frequency of visits. In the present study, we identified the major causes of nonadherence and tried to correct them by an appropriate educational/follow-up plan. As side-effects

and failure to attend the visits appeared to be critical, in the intervention plan, we introduced an early phone contact (within 10 days) and a prescheduled visit at the beginning of the pollen season. In addition, an educational training was applied, and the visits for the prescription of the second course of SLIT were strictly monitored. As observed in the second phase, the intervention significantly reduced the discontinuations due to side-effects and, more importantly, maintained 80% of patients on therapy at the second course, as compared to 65% in the control group. The main limit of this study is its open fashion, but a randomization in real life is difficult to do, without affecting the objective observation of adherence.

In conclusion, more educational and strict follow-up effort is needed to increase patients' knowledge (17) about aeroallergen immunotherapy to improve the compliance and the success and safety of this therapeutic modality. A simple

educational plan, early and late contacts to assess/discuss side-effects, and a strict visit scheduling allow a satisfactory adherence to be maintained and the number of discontinuations to decrease.

Author contributions

All coauthors equally contributed to the clinical work, collection and analysis of the data, and preparation of the MS.

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Conflict of interest

None to disclose.

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