

G. MANZOTTI¹, G.G. RIARIO-SFORZA², M. DIMATTEO³, C. SCOLARI³, E. MAKRI², C. INCORVAIA²

Comparing the compliance to a short schedule of subcutaneous immunotherapy and to sublingual immunotherapy during three years of treatment

¹Allergy Outpatients Service, Treviglio-Caravaggio General Hospital, Treviglio, Italy

²Allergy/Pulmonary rehabilitation, ICP Hospital, Milan, Italy

³Pharmacy Unit, General Hospital, Treviglio, Italy

KEY WORDS

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Corresponding author

Giuseppina Manzotti
Allergy Outpatients Service
Treviglio-Caravaggio General Hospital
Piazza Ospedale, 1
24047 Treviglio, Italy
Phone: +39 0363 424 383
E-mail: giusimanzotti@gmail.com

Summary

Background. Allergen immunotherapy (AIT) in its two forms of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT) is an effective treatment of respiratory allergy, but is particularly concerned by the issue of compliance. **Objective.** We aimed a real-life study at evaluating the compliance to SLIT and to SCIT administered by a short-course of four injections during a 3-year period of observation. **Methods.** A group of 145 patients (79 males, 66 females, age ranging from 14 to 69 years), suffering from pollen-induced rhino-conjunctivitis with or without asthma, were included in the study. Following adequate education on AIT and according to patient's preference, 72 patients chose to be treated with short-course SCIT and 73 chose to be treated with SLIT. The latter was performed by allergen extracts from different manufacturers according to the suggested schedules. **Results.** The rate of withdrawal was as follows: after one year, 15.6% for SCIT and 33.4 for SLIT; after two years, 25.6% for SCIT and 44.8% for SLIT; after three years, 26.7 for SCIT and 46% for SLIT. There was no significant difference in the rate of withdrawal between males and females. Regarding the safety, no systemic reaction requiring medical treatment was observed either in SCIT or SLIT group. **Conclusion.** The findings of this study confirm that involving the patient in the choice of the route of administration is associated to a satisfactory compliance to AIT. In particular, more than 70% of patients treated with a short schedule of SCIT completed the three-years course of treatment that is recommended for AIT, while this goal was reached by 54% of SLIT treated patients.

Introduction

Allergen immunotherapy (AIT) is an effective treatment of respiratory allergy, but is affected, as any other medical treatment, by the issue of compliance. The early studies were performed when only subcutaneous immunotherapy (SCIT) was available, detecting a low compliance, that ranged from 45% to 60%. The demanding schedules used, with very frequent injections, accounted for this outcome, as shown by patients' recognition of inconvenience as the major cause of noncompliance (1). Sublingual immunotherapy (SLIT), that is administered at home by patients themselves, is free from such problem and should have compliance characteristics similar to drug treatment. In fact, first studies

on SLIT reported very good compliance, ranging from 79% to 97% (1). A study compared the compliance with SCIT and SLIT administered in hospital or in private office settings in a large group of children (2). With SCIT, applied on 1886 subjects, 207 (10.9%) were noncompliant, with no significant difference between the two settings. The major reasons for withdrawing were the cost (35%), family problems (21%), inconvenience (20%), lack of efficacy (16%), and adverse reactions (7%). SLIT was used in 806 patients, 173 of whom (21.4%) were noncompliant, with a highly significant difference for a better compliance in hospital setting (90.5%) compared to private office setting (61.2%); the most common reasons of withdrawal were the cost of treatment, reported globally in 36.4% of cases, inconvenience, feeling of in-

efficacy, and side effects. Still, the good compliance to SLIT was not confirmed when the data from manufactures were analyzed. In fact, calculating the rate of spontaneous discontinuations by the sales data of two large manufacturers in Italy over a 3-year period, a decrease from 100% to 43.7% in the first year, to 27.7% in the second year, and to 13.2% in the third year, was found (3). We aimed the present real-life study at evaluating the compliance to SLIT and to SCIT administered by a short-course of four injections during a 3-year period of observation.

Patients and methods

Patients

During the pollen season 2010-2011, 145 patients (79 males, 66 females, age ranging from 14 to 69 years), suffering from pollen-induced moderate to severe rhino-conjunctivitis with or without mild asthma were enrolled in the study. To be included, patients must have homogeneous characteristics according to allergic disease severity. As reported in a previous article (4), we proposed either SCIT with Pollinex 4 (Allergy Therapeutics, Worthing, UK), a product based on a short administration in 4 injections, or SLIT with extracts from different manufacturers, namely Allergy Therapeutics, ALK Abellø (Horsholm, Denmark), Stallergenes (Antony, France), Allergopharma (Reinbek, Germany) and Lofarma (Milan, Italy). For each kind of SIT, the major practical advantages or burdens were highlighted. Of 145 patients, 72 chose Pollinex 4 SCIT and 73 chose SLIT. SCIT-treated patients received a total of 90 treatments (18 patients had double course of SCIT). SLIT-treated patients received a total of 87 treatments (14 patients had double course of SLIT). The pollens used for AIT were as follows: birch pollen or tree mix pollens, 28 SLIT and 20 SLIT; grass pollen, 56 SCIT and 47 SLIT; *Parietaria* pollen, 3 SCIT and 2 SLIT; ragweed pollen, 2 SCIT and 0 SLIT; mixed birch and grass pollen, 0 SCIT and 10 SLIT; mixed grass and *Parietaria* pollen, 1 SCIT and 4 SLIT; mixed grass and ragweed pollen, 0 SCIT and 4 SLIT. In the SCIT group, there were 49 males and 23 females; in the SLIT group, there were 30 males and 43 females. Mean age was 36.5 years in SCIT group and 28.5 years in SLIT group. Here we present the data from three years of follow-up in patients treated with SCIT or SLIT. All patients received written information and had to refer every year to the Allergy service to renew the prescription of SCIT or SLIT; during this visit, the data regarding safety and tolerability of the treatments were obtained. All patients were instructed to contact us in case of problems with the treatment.

Educational forms

Two kinds of written forms were given to patients, concerning SLIT and SCIT, respectively. The SLIT form reported:

1. How to take the treatment (number of days per week, time to assume SLIT during the day, up-dosing modality, how to storage the AIT).
2. The possible local adverse event (oral or gastro-enteric) and how to deal with them.
3. The outpatient clinic phone number to call if the patient needed explanation from doctor or nurse or to inform the doctor in case of interruption.
4. The remind to schedule another visit to order the allergen extracts for AIT at the 2nd and 3rd year. The form indicated the month of the year the patient had to visit the clinic to be in time for the re-order.

The SCIT form reported:

1. The number, date and time of visits to perform the injections course.
2. The possible local adverse event after the injection and how to deal with them.
3. The outpatient clinic phone number to call if the patient needed explanation from doctor or nurse or to inform the doctor in case of interruption or troubles with the injection visits.
4. The remind to schedule another visit to order the allergen extracts for AIT at the 2nd and 3rd year, with the same instructions as for the SLIT form

The objective was to educate the patient to have an active role in the AIT process and to increase the compliance.

All data from the two groups of patients were compared by the chi square test, a significant difference being stated at a p value < 0.05.

Results

SCIT was chosen by a number significantly higher ($p < 0.05$) of males, this significant difference was confirmed after 1, 2 and 3 years of treatment (**table 1**). SLIT was chosen by more females than males, but the difference was not significant. No patient discontinued SCIT or SLIT during the first cycle of treatment. **Table 1** shows the number of patients continuing the treatment after 1, 2, and 3 years. The withdrawal after 1 year concerned 11 grass pollen and 3 birch pollen SCIT treatments, and 19 grass pollen and 7 birch pollen SLIT treatments (including one double treatment with both pollens). After 2 years it concerned 7 grass pollen and 2 *Parietaria* pollen SCIT treatments, 7 grass pollen and 3 birch pollen SLIT treatments and 2 *Parietaria* pollen SCIT treatment (including 2 double treatments, one grass / birch and the other grass / *Parietaria*). After 3 years, it concerned one grass pollen treatment both for SCIT and SLIT. There was no significant difference in the rate of withdrawal between males and females, while the mean age of patients who

Table 1 - Number of SCIT and SLIT treatments continued during the follow-up.

	After 1 year (%)	After 2 years (%)	After 3 years (%)
SCIT (90)	76 (84.4)	67 (74.4)	66 (73.3)
59 males, 31 females	50 males, 26 females	44 males, 23 females	43 males, 22 females
SLIT (87)	58 (66.6)	48 (55.2)	47 (54)
35 males, 52 females	23 males, 35 females	17 males, 31 females	16 males, 31 females

withdrew was 40 years after one year (higher than the mean age of 36.5 years in SCIT group and 28.5 years in SLIT group at baseline), this higher age being confirmed for SCIT at the study end for females (mean 40 years compared to 35 years at baseline) but not for males (mean age 33 years compared to 35 years at baseline). All these differences were not significant. The reasons for withdrawal were missed visits for all patients interrupting SCIT, while were local reactions for 20 patients (8 males and 12 females) and missed visits in the other patients. Regarding the safety, no systemic reaction requiring medical treatment was observed either in SCIT or SLIT group.

Discussion

A poor compliance is a general issue for prolonged medical treatments, but is particularly detrimental for AIT, because an insufficient duration prevents the occurrence of the immunological changes that underlie the clinical efficacy and, especially, the persistence of the clinical effects after stopping AIT (5), that must be administered for at least three years (6). This makes the achievement of a good compliance of critical importance. Actually, in the rigid organization of controlled trials, the compliance to both SCIT and SLIT was good in most cases (7), and also the first real-life studies reported, particularly for SLIT, compliance and adherence rates often higher than 80% (1). However, the data based on manufacturers sales reported by Senna et al (3) changed the landscape and were confirmed by recent surveys. For example, in a recent retrospective analysis by Dutch authors of data from 6486 patients starting immunotherapy between 1994 and 2009, 2796 patients receiving SCIT and 3690 received SLIT, only 18% reached the minimally required duration of treatment of 3 years (SCIT, 23%; SLIT, 7%). Median durations for SCIT and SLIT users were 1.7 and 0.6 years, respectively. These findings were, according to the authors' suggestion, a sign for "an urgent need for further identification of potential barriers and measures that will enhance persistence and compliance" (8). In another study, German sales data for different preparations of a single allergen manufacturer were retrospectively evaluated for 5 consecutive years, based on prescriptions per patient. Pollen SLIT and high-dose hypoallergenic (allergoid or unmodified depot pollen and mite preparations for SCIT) were used, 85,241 patients receiving pollen or mite SCIT and

706 patients receiving pollen SLIT. Prescriptions for at least 3 years were done for 42% of patients with pollen SCIT and for 45% of patients with mite SCIT. Compliance with SLIT concerned only 16% of patients receiving prescriptions for at least 3 treatment years (9). The approaches to improve compliance to AIT, and particularly to SLIT, that were proposed when the available data were more positive, remain valid. They include patients' education and appropriate timing of control visits. Concerning education, a better compliance was reported in patients receiving a complete educational program on SLIT with written instructions compared with patients receiving verbal standard information (10). This was confirmed in a study based on an educational / follow-up plan applied on 149 patients treated with SLIT compared to 90 patients not participating to the plan. In the first group, discontinuations at 4 months were 5% vs. 18% in the controls and after one year they concerned 12% of patients in the first group and 35% in the control group. The authors concluded that "An adequate education and a strict follow-up can significantly reduce SLIT discontinuations" (11). Regarding the timing, Vita et al. performed a study on three groups of SLIT treated patients, the first with a control visit scheduled at 3-months interval, the second at 6-months interval, and the third with only one visit / year. The best compliance was found in patients called for visits four times per year (18.5% of withdrawals), while children of other two groups abandoned SLIT with a rate of 32.3% in patients with two visits and 70.4% in patients with one visit / year, respectively (12).

In the present study we used the innovative approach to involve the patient in the treatment choice. Following extensive information and written instructions on the two treatments for seasonal allergy, 49.6% of patients chose SCIT and 50.3% chose SLIT (4). This suggests that when the SCIT schedule is short (only 4 injections / year with the product we employed) choosing SLIT is not so obvious. Sixty-eight per cent of male patients preferred SCIT (a rate significantly higher than females), while 58.9% of female patients preferred SLIT, this difference being not significant compared with males). The results of the follow-up showed that the higher rate of withdrawal occurred at the first year (15.6% and 33.4% for SCIT and SLIT, respectively), with a rate increase at the second year of 10% for SCIT and 11.4% for SLIT, and a further but small increase of withdrawal of about 1% at the

third year. Very recently, a study based on the same approach was published. Patients underwent to SLIT or SCIT according to their preference (active group) or to physician's choice (control group). After 6 months, there was no difference in adherence to SLIT or SCIT in the active group, while a significant difference was detected between the rate of non-adherence in the active group (11%) compared with the control group (21%), this being a good outcome, though limited by the short follow-up duration (13). In a recent review, Antico discussed the large differences of compliance and adherence observed in the available studies. He suggested that the better outcome in placebo-controlled studies may depend on the patient's motivation, and particularly on the patient's decision to participate in the trial and to meet the researcher's expectations, defining a condition conceptually similar to concordance, that is a consultation process, based on the patient's belief and needs, that tends to establish a therapeutic alliance between the physician and patient (14). This is in agreement with the role of patient's values and preferences in the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to medical treatments (15). Our study, as well as the study by Sanchez discussed above, supports the importance of this concept.

In conclusion, the findings from this real-life study show that when patients are involved in the choice of the kind of AIT, a satisfactory compliance to the treatment is observed. In particular, more than 70% of patients treated with a short schedule of SCIT completed the three-years course of treatment that is recommended for AIT, while this goal was reached by 54% of SLIT treated patients. This rate of compliance to SLIT, though lower than to SCIT, is much better than those reported in recent studies (3,7,8) and is comparable to the compliance commonly observed with prolonged drug treatments by oral administration (16).

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