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Subcutaneous immunotherapy with aeroallergens - evaluation of adherence in real life

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Key words

allergy; allergic respiratory diseases; allergen immunotherapy; subcutaneous immunotherapy; adherence

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Summary

Introduction. *Adherence in allergen immunotherapy is crucial for its efficacy. At least 3 years of treatment are recommended for achieving a long-term modifying effect.* **Objectives**. *To assess patient's adherence and to identify determinant factors for allergen subcutaneous immunotherapy (SCIT) suspension in patients with respiratory allergy.* **Methods**. *Retrospective analysis of the medical record of patients submitted to SCIT between January 2013 and December 2016 in our Department.* **Results**. *323 patients were included: 52% female; mean age 30 ± 13 years; average treatment time 19 ± 13 months. 52 patients (16%) stopped SCIT: 54% female; mean age 30 ± 9 years; average treatment time 12 ± 6 months; 67% dropped the treatment during the 1st year, 27% in the 2nd and 6% during the 3rd year of treatment. Adherence rate determined was 77%. The most frequent reasons for withdrawal were due to economic reasons (47.9%), followed by patients' perception of no clinical improvement (23%) and change to sublingual immunotherapy (11.6%).* **Conclusions.** *Adherence rate in our study was 77%. Economic reasons were the main cause of abandonment in the first year, while the perception of non-improvement was the main reason for abandonment in subsequent years. Adequate information on SCIT prescribing and rigorous monitoring of patients during the treatment can improve adherence.*

Introduction

Allergic respiratory diseases, namely rhinitis and asthma, are a major public health problem. Asthma affects an estimated 300 million individuals (1) and allergic rhinitis affects 10 to 40% of the population worldwide (2). These diseases are known to reduce the overall quality of life as well as to increase school and work absenteeism and medical costs (2). Therefore, the correct treatment with adequate control of these diseases is very important.

The key points of the treatment of allergic respiratory diseases are patient education, allergen avoidance and pharmacological therapy (1,2). Allergen immunotherapy has shown to modify the natural history of allergic disease, maintaining beneficial effects even after its cessation and the possibility to prevent the onset of asthma in patients with rhinitis or the appearance of new sensitizations (3). Subcutaneous administration is the main form of immunotherapy with aeroallergens because of its higher effectiveness (4). However, this treatment also has disadvantages: the administration can be painful and it is associated with a higher risk of systemic reactions. Moreover, it is a time-consuming procedure, due to the need for supervised administration by a trained health care professional in a setting with conditions for treating systemic reactions.

Adherence represents the most critical issue and it is essential for achieving good results. Poor adherence to immunotherapy leads to a decrease in treatment benefits that can potentially lead to an increase of morbidity (5). A minimum duration of 3-years of subcutaneous immunotherapy (SCIT), with an optimized

dosing schedule, is required to achieve an adequate clinical and immunological response and long-term efficacy (6).
Adherence can be divided in three different stages: initiation (acceptance), implementation (compliance) and persistence (5). In this study we defined adherence as the accomplishment of at least three complete years of SCIT. Although there is no consensus regarding what an acceptable adherence rate is, most researchers consider an adherence rate greater than 80% to be adequate (5,7). In clinical trials the reported adherence rate is around 80-90% and it is more variable in real-world studies, ranging from 23-88% in adults and 16-89% in children (5).
The reasons for a poor adherence to SCIT may be related to the patient, disease, treatment or healthcare system (5). The identification of these factors can increase the success of immunotherapy. The most common factors associated with a poor adherence to SCIT are: the patient´s knowledge of his/her disease and treatment conditions and benefits, route of administration, treatment inconvenience and costs and side effects (5).
The aim of this study was to evaluate SCIT adherence in patients with allergic rhinitis and/or asthma and to determine the factors that affect adherence to in real-life conditions.

Material and methods

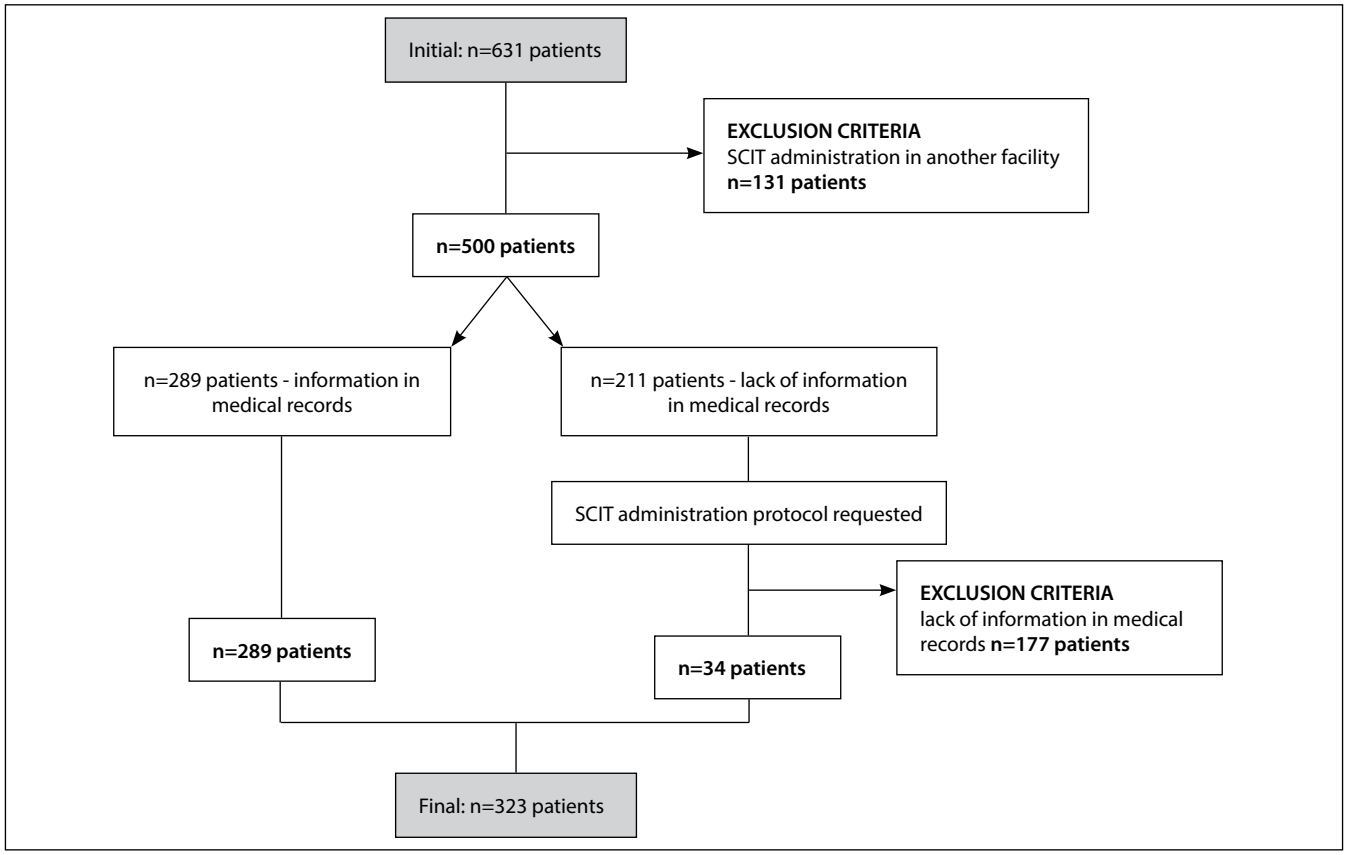
Population and study design

A retrospective analysis of the medical and nursing records of 631 patients submitted to SCIT between January 2013 and December 2016 in our Immunotherapy Center, Allergy and Clinical Immunology Outpatient Clinic of Hospital de Santa Maria, Centro Hospitalar Universitário de Lisboa Norte, was performed. Patients' age, gender, allergic disease diagnosis (rhinitis and/or asthma; eczema; conjunctivitis; food allergy), SCIT composition, date of initiation and SCIT administration schedule were registered and evaluated. The reasons to stop SCIT were also analyzed and evaluated. Switching to sublingual route of immunotherapy was considered a reason of SCIT dropout, once the aim of this study was to specifically evaluate adherence to the subcutaneous route and determine the factors that affect it.
Patients who lacked clinical information about SCIT composition or administration (n = 211), were contacted by letter requesting SCIT administration protocol information**,** with very poor response (response rate 16%). Patients that sent the SCIT administration protocol and had dropout SCIT were contacted again, by call and were asked about dropout reasons.
Patients were excluded from the study if SCIT was administered in another facility (n = 131) or if there was missing information in their medical records concerning SCIT administration, namely SCIT composition, date of initiation and SCIT administration schedule (n = 177) (**figure 1**). This lack of parameters is due to absence of electronic clinical records before 2012/2013 and the impossibility to get access to written medical information.
The diagnosis and treatment of allergic rhinitis and asthma were appropriate according to current guidelines, Allergic Rhinitis and its Impact on Asthma (ARIA) (8) and Global Initiative for Asthma (GINA) (1). Skin prick tests with Roxall® extracts and/or serum specific IgE tests using ImmunoCAP system® (TermoFisher scientific; Uppsala, Sweden) were conducted. All patients had positive skin prick tests and/or specific IgE tests > 0.70 kU/L, and a correlation between these results and their symptoms was found. SCIT was initiated in patients with allergic symptoms despite being under medical treatment. SCIT was chosen considering the results of skin prick tests and/or specific IgE tests to house dust mites, storage mites, pollens (grass, *Parietaria*, olive tree and *Artemisia*) and cat epithelium or extract associations (mites and pollens). The route of therapy (subcutaneous) was prescribed taking into consideration the patient's preference, allergic symptoms and personal concerns.
A written informed consent was obtained from all patients and/or their legal representatives before initiating SCIT.
The maintenance dose was administered at 4-6-week intervals over a period of 3 to 5 years. All injections were administered by trained nurses with supervision of the allergist in the Immunotherapy Center, equipped with material for treating systemic reactions. All patients were evaluated before and 30 minutes after the SCIT administration.
Adherence was determined as the accomplishment of three years of SCIT. The patients who dropped SCIT before this time were considered as non-adherent; the patients that continued the treatment were considered as adherent. To calculate adherence rate, only patients who started SCIT in 2013 were considered in order to have completed the recommended three years of treatment, since it is the minimum to be considered compliant.
Data were anonymized, and their confidentiality guaranteed, and this study protocol was approved by the Ethical Board of Centro Hospitalar Universitário de Lisboa Norte.

Descriptive and statistical analysis

As previously mentioned, the main objective of this study was to assess and identify the main causes behind treatment discontinuation. According to our objectives, we analyzed the group of patients who stopped SCIT and evaluated the causes that contributed to the suspension of SCIT using descriptive statistics. For the descriptive analysis, categorical variables were given as numbers and percentages, and continuous variables were presented using mean, standard deviation, median, interquartile range (IQR) and minimum and maximum values.
Statistical analyses were performed using version 24 of SPSS software for Windows (SPSS Inc., Chicago, Ill). Mann-Whitney U and Kruskal-Wallis tests were used to compare differ-

***Figure 1** - Study design and flow chart.*



ences between groups and p value < 0.05 was considered statistically significant.

Results

From a total of 631 patients under SCIT during the study period, 323 patients met the inclusion criteria and 308 were excluded due to data unavailability.

According to the demographic data (**table I**), there was a predominance of female gender (167, 52%), mean age of the patients was 30 ± 13 years (minimum 7, maximum 65, median 27). The age group of 18 to 30 years was the most prevalent with 45% (n = 145) and the group older than 50 years was the least prevalent with 7.1% (n = 23).

Regarding the allergen used in SCIT, we observed a predominance of mite allergen (233, 72%). More information about SCIT composition is detailed in **table I**.

The diagnosis of patients submitted to SCIT was also evaluated and is provided in **table I**. All patients had allergic respiratory disease, with rhinitis being the most frequent diagnosis (313, 97%) followed by asthma (145, 45%), about 40% of patients had concomitant asthma and rhinitis. The average treatment duration was 19 ± 13 months (maximum 58 months; minimum 1 month). Most patients (70.8%) were in the first 2 years of SCIT and 17.7% completed at least 3 years of treatment. We also evaluated the number of patients by year of treatment: first year 132, 40.8%; second year 97, 30%; third year 37, 11.5%; fourth year 38, 11.8%; fifth year 19, 5.9%.

When comparing the patients who dropped SCIT without medical indication with those who completed the treatment (i.e. adherent group), no statistical differences were found regarding age, gender, clinical diagnosis and allergen extract (**table I**). **Table I** shows the clinical and demographic comparison between the 2 groups (adherent and non-adherent patients).

Adherence was determined at the end of 3 years of SCIT treatment. Fifty-two patients (16%) stopped SCIT without medical indication before the recommended time. In the group of patients who abandoned SCIT (i.e. non-adherent patients), there was a slight predominance of female gender (28, 54%), mean age 30 ± 9 years (minimum 14, maximum 48, median 28).

Table I *- Demographic and clinical data of the patients under subcutaneous immunotherapy.*

Variables	Patients			p-value
	total (n = 323; 100%)	adherent (n = 271; 84%)	non-adherent (n = 52; 16%)	
Age (median; IQR) years	27; 21	26; 20	28; 19	0.073
Age groups				
7 - 17 n (%)	53 (16.4)	49 (18)	4 (7.7)	
18 - 30 n (%)	145 (45)	117 (43)	28 (54)	
31 - 50 n (%)	102 (31.5)	90 (33)	12 (23)	
51 - 65 n (%)	23 (7.1)	15 (6)	8 (15.3)	
Gender				0.525
female n (%)	167 (52)	139 (51)	28 (54)	
male n (%)	156 (48)	132 (49)	24 (46)	
Clinical diagnosis				0.449
rhinitis n (%)	313 (97)	263 (97)	50 (96)	
asthma n (%)	145 (45)	121 (44)	24 (46)	
rhinitis and asthma n (%)	129 (40)	100 (37)	17 (33)	
conjunctivitis n (%)	92 (28.5)	70 (25)	13 (25)	
eczema n (%)	52 (16)	40 (15)	12 (23)	
food allergy n (%)	30 (9)	23 (8)	7 (13)	
Type of allergen extract				0.423
Dermatophagoides (*pteronyssinus* and/or *farinae*) n (%)	172 (53.4)	148 (54.5)	24 (46.2)	
Dermatophagoides + another mite n (%)	41 (12.7)	33 (12.2)	8 (15.4)	
storage mites n (%)	7 (2.2)	4 (1.5)	3 (5.8)	
Dermatophagoides + pollen n (%)	13 (4)	10 (3.7)	3 (5.8)	
grass pollen n (%)	66 (20.4)	56 (20.7)	10 (19.2)	
Parietaria n (%)	10 (3.1)	8 (3)	2 (3.8)	
grass pollen + olive tree n (%) grass pollen + *Parietaria*	5 (1.5)	5 (1.8)	0 (0)	
n (%)	4 (1.2)	3 (1.1)	1 (1.9)	
grass pollen + *Artemisia* n (%)	2 (0.6)	1 (0.4)	1 (1.9)	
olive tree n (%)	2 (0.6)	2 (0.7)	0 (0)	
cat epithelium n (%)	1 (0.3)	1 (0.4)	0 (0)	

The most prevalent age group was from 18 to 30 years old (54%) and the least prevalent age group was from 7 to 17 years old (7.7%). Regarding the immunotherapy composition, SCIT suspension for mites was predominant (73%, 16.3% of total SCIT for mites) followed by pollens (32.6%, 13.6% of total SCIT for pollens). The average treatment duration was 12 ± 6 months (maximum 27 months; minimum 4 months).

In order to calculate adherence rate, only patients who started SCIT in 2013 were considered in order to have completed the recommended three years of treatment, since it is the minimum to be considered compliant. Fifty-seven patients started SCIT in this year and 13 stopped it before completing 3 years of treatment, corresponding to an adherence rate of 77%.

Most patients (67%) abandoned SCIT during the first year, 27% in the second and 6% during the third year of treatment. The main reasons for abandoning SCIT without medical indication are presented in **table II**.

Economic reasons were the most frequent factor reported, accounting for almost half of the treatment abandonment (47.9%). Twenty-three percent referred the absence of clinical improvement and around 12% switched to sublingual immunotherapy. Personal issues such as relocation, support to family and professional reasons resulted in 7.7% of suspensions; adverse reactions, namely large recurrent local reactions motivated 3.9% of the SCIT suspension. Two patients (3.9%) stopped SCIT because they were diagnosed with other medical conditions (neoplasm). Pregnancy was the reason behind the withdrawal of 2% of patients; in this case, SCIT abandonment was a patient's choice.

When analyzed the main causes by year, results have shown that the most frequent cause of suspension in the first year was due to economic reasons (21/35, 60%), and the perception of no improvement was the most frequent reason in the following years (7/17, 41%).

Table II *- Reasons for subcutaneous immunotherapy withdrawal.*

Reasons for SCIT withdrawal	**Non-adherent patients (n = 52)**			
	1st year n = 35	2nd year n = 14	3rd year n = 3	total n (%)
economic reasons	21	4	0	25 (47.9)
no clinical improvement	5	7	0	12 (23)
switch to sublingual immunotherapy	4	2	0	6 (11.6)
personal issues	2	0	2	4 (7.7)
adverse reactions	2	0	0	2 (3.9)
medical illness	0	1	1	2 (3.9)
pregnancy	1	0	0	1 (2)

Discussion

In our real-life study, the adherence rate was 77%. In total, 52 (16%) patients dropped out: 35 patients (67.3%) in year 1, 14 (27%) in year 2, and 3 (5.7%) in year 3. Reviewing the literature, we find that reported SCIT adherence rates are very variable, both in percentage as follow up duration (3 and 4 years). The adherence rate of previous studies is summarized in **table III** and ranges between 23-88%. In most studies, the adherence rate is < 70%, lower than the rate shown in our work.

The heterogeneity of the results found in literature can be explained by the differences existing between the studies methodologies, populations, countries, allergen composition vaccines, treatment schedules, immunotherapy cost and funding. The concept of adherence is also variable; in some studies it is defined as missed doses of SCIT, while in others as stopping SCIT without medical approval.

When compared with previous published data, and according with the definition of good adherence, our adherence rate can be considered as acceptable. These good results can be explained by the existence of an Immunotherapy Center in our Outpatient Clinic where we try to promote a close and genuine patient-physician relation. There is always a support physician for SCIT administration that facilitates physician-patient communication, helping with any problem or doubt, namely addressing questions about the treatment itself, adverse reactions or any other patient's doubt. We provide a weekly schedule with extended hours in order to offer several options to SCIT administration and try not to interfere with regular working hours. We also have a direct phone number that patients can call and contact us easily. Frequent visits at our Center permit that our professionals (nurses and physicians) can enhance adherence during the visits, offering a continuous education on SCIT principles.

No statistical differences were found in our study between adherent and non-adherent groups in what concerns age, gender, clinical diagnosis or allergenic composition of the SCIT. Although it was not significant, we observed a decrease of SCIT

Table III *- Adherence to treatment in subcutaneous immunotherapy studies.*

Study	**sample (n)**	**age group**	**study duration (follow-up)**	**adherence rate (%)**
Cohn et al., 1993 (9)	217	adults	4 years	50
Lower et al., 1993 (10)	315	children	4 years	56
Donahue et al., 1999(11)	603	children and adults	4 years	33
Rhodes, 1999 (12)	1033	adults	3 years	88
More et al., 2002 (13)	381	children and adults	3 years	77
Pajno et al., 2005 (14)	1886	children	3 years	89
Hankin et al., 2008 (15)	520	children	3 years	47 (1st year) 16 (3rd year)
Hsu et al., 2012 (16)	139	adults	4 years	55
Guedechea-Sola et al., 2013 (17)	156	adults	5 years	63
Kiel et al., 2013 (18)	2796	adults	3 years	23
Silva et al., 2014 (19)	122	children and adults	4 years	54
Gelincik et al., 2017 (20)	204	adults	3 years	73
Lemberg et al., 2017 (21)	207	children and adults	3 years	68
Yang et al., 2018 (22)	311	children and adults	3 years	64.6
Tat, 2018 (23)	95	adults	3 years	65
Lee et al., 2019 (24)	1162	children and adults	3 years	80

suspension in younger patients. In literature, results regarding demographic and clinical data are also very variable. Tat also has not found differences in age or gender between the two groups (23). Rhodes found a significant correlation between age and gender: non-adherent patients were younger than adherent and males were more frequently non-adherents than females (12). More et al. confirmed Rhodes findings in what concerns age (13). On the other hand, Yang et al. concluded that children had higher adherence to SCIT than adults and did not found any other correlation with gender (22). Gelincik et al. concluded that adherence was higher in female patients. Age, clinical diagnosis and the type of allergen extract used for SCIT did not influence the adherence rate (20). Donahue et al. reported a higher adherence in patients with both asthma and rhinitis then in those with either of them (11). However, More et al. and Yang et al. have not found a correlation between adherence and kind of respiratory disease (13, 22).

Lemberg et al. concluded that patients who adhere to immunotherapy in the first year of the treatment are more likely to complete it (21). Their conclusion is in agreement with our data, where more than half of the non-adherent patients discontinued the treatment during the first year.

In order to improve adherence to treatment, it becomes particularly important to identify patients who are likely to be non-adherent and find out the reasons for stopping the treatment. The reasons for SCIT suspension are also variable among the literature; there is a lot of heterogeneity and the identified factors vary depending on the countries and populations involved.

In our study, we evaluated not only the main reasons for SCIT suspension, but we also evaluated it in separate years since the beginning of SCIT. Economic reasons were the main cause of drop-outs, responsible for 47.9% of immunotherapy suspension in a global way and for 60% of SCIT suspension in the first year. These results are in agreement with another study conducted in the north of Portugal in 2014, which reported the treatment cost as the main reason for abandoning SCIT in 59% of participants (19). To our knowledge, these are the only studies evaluating the reasons for SCIT non-adherence in Portugal, where SCIT cost ranges from 250 - 350 €/year, without reimbursement in most cases. This amount does not include the expenses related to the administration of the treatment and transportation to the hospital. Similarly, an Italian study conducted in 2005 also concluded that the cost of SCIT was the most common cause of treatment withdrawal, responsible for 39.6% of SCIT drop-outs (14). In 2011, Vaswani et al. reported a rate of 40% of suspension due to SCIT costs, especially inadequate or nonexistent insurance coverage (25). In his study, Tat also concluded that a main reason for SCIT suspension was the delayed reimbursement by health insurance (23).

Another important adherence factor is the patient's perception of clinical improvement. It is associated with his/her knowledge of treatment and the expectation of the time from initiation to symptom relief and the degree of improvement to be achieved. In our study, individual perception of absence of clinical improvement was the second leading cause of treatment withdrawal, resulting in approximately 23% of treatment discontinuation and being the main reason of suspension during the second and third year of SCIT. Gelincik et al. in their study referred the lack of efficacy as a major cause of SCIT cessation with a percentage of 66.7% (20). Silva et al. found a percentage of almost 27% due to lack of efficacy (19). Yang et al. described a discontinuation rate of 25.5% secondary to treatment inefficacy (second more frequent cause in their study) (19). Tat described a withdrawal of 14.8% of patients secondary to lack of efficacy (23).

In our study, 11.6% of patients preferred a change to sublingual immunotherapy due to SCIT inconvenience, namely, route of administration and need of monthly hospital visits. Although it was not the main reason for suspension of SCIT in the present study, treatment inconvenience is described in many studies as the main reason for treatment abandonment (9,12,16) with proportions ranging from 35 to 65%. Tat described a percentage similar to ours: 14.8% (23).

It is crucial to ensure a high adherence rate to SCIT, prior to its prescription, to inform patients about goals, risks, duration of treatment, direct and indirect costs and potential inconvenience related with the treatment (travel to appointments, skipping work). These aspects are crucial for patient's involvement in the decision to initiate SCIT. Frequently, the patient's expectations do not coincide with those of the physician. Sade et al. concluded that 39% of patients under SCIT expected full recovery, 35% expected some improvement, 16% expected prevention of the development of new allergies and 10% expected protection against the onset of asthma. In what concerns the patient's knowledge about the duration of treatment, 60% were unaware of the optimal duration and only 10% were expecting several years of therapy. These data indicate that patients were not informed about the principles of treatment with SCIT. Another conclusion was that patients who initiated treatment within the previous 6 months were more informed about it that patients receiving therapy for a longer period of time (26), reinforcing the necessity to evaluate these patients periodically.

To our knowledge, this is the second study made in Portugal on SCIT adherence, namely determination of the adherence rate and the reasons responsible for its suspension. Our study has a large sample with 323 patients. Concerning suspension factors, we evaluated these factors in a global manner and also performed an individualized analysis per year, aiming to identify and group the main causes of SCIT withdrawal and trying to be more attentive in these aspects, preventing SCIT suspension.

Limitations

The study design may limit the results: it is a retrospective study performed in one center; there was an exclusion of al-

most half of the total population due to lack of clinical information about SCIT administration. Moreover, our definition of adherence may differ from those of other studies, which can lead to some difficulty in comparing factors associated with immunotherapy adherence between the reported results. Also, this study does not consider failures / inadequate doses of allergen in SCIT administration as non-compliance of treatment.

More evidence is needed from larger samples in prospective studies, where we can get more detailed information addressing all dimensions of adherence. In addition, the definition of adherence and non-adherence to immunotherapy should be addressed in future immunotherapy guidelines.

Conclusions

The adherence rate in our study can be considered high when compared with other real-world rates, while economic reasons, followed by lack of efficacy and SCIT inconvenience were the main causes for patient's non-adherence. Informing the patients about the progress of the allergic disease and immunotherapy program may help to improve compliance. Well-informed patients are less likely to drop SCIT, once they can follow a long-lasting treatment which takes to a gradual symptom improvement.

Conflict of interests

The authors declare that they have no conflict of interest.

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