Adv Ther
DOI 10.1007/s12325-016-0347-0

ORIGINAL RESEARCH

Comprehensive Study of Patients' Compliance with Sublingual Immunotherapy in House Dust Mite Perennial Allergic Rhinitis

Alfonso Malet · Angel Azpeitia · Diego Gutiérrez · Francisco Moreno · María del Mar San Miguel Moncín · José Angel Cumplido · Magdalena Lluch · Eva Baró · Albert Roger

Received: April 27, 2016
© Springer Healthcare 2016

ABSTRACT

Introduction: Allergen immunotherapy is a long-term treatment that has been associated with patient adherence issues. The aim of the study was to increase the knowledge on compliance of patients allergic to house dust mites, receiving sublingual immunotherapy (SLIT).

Methods: A retrospective observational study was performed in 53 Spanish allergy units. We enrolled patients undergoing the SLIT treatment for house dust mites including a scheduled control visit 12 months after initiating the therapy. We conducted a comprehensive assessment of compliance using three methods. In the first step, an allergist evaluated the patients according to the results of an interview and the existing medical records. The subjects taking more than 80% of the overall prescription were defined as compliant. The remaining noncompliant patients were divided into groups taking less than 25%, 25–50%, and 50–80% of the prescribed SLIT. In the second stage, we conducted the Morisky–Green test. Finally, the noncompliant patients were asked to fill a

Enhanced content To view enhanced content for this article go to http://www.medengine.com/Redeem/13D4F06010476126.

A. Malet · M. Lluch
Al.lergo Centre, Barcelona, Spain

A. Azpeitia
Medical Department, Stallergenes Iberica, Barcelona, Spain

D. Gutiérrez
Servicio Neumologia-Alergia, Puerta del Mar Hospital, Cádiz, Spain

F. Moreno
Doctor Lobatón Clinic, Cádiz, Spain

M. M. San Miguel Moncín
Allergy Unit, Pius Hospital de Valls, Xarxa Santa Tecla, Tarragona, Spain

J. A. Cumplido
Doctor Negrín University Hospital, Gran Canaria, Spain

E. Baró (✉)
Health Outcomes Research Department, 3D Health, Barcelona, Spain
e-mail: ebaro@3dhealth.es

A. Roger
Allergy Unit, Germans Trias i Pujol Hospital, Badalona, Spain

Published online: 16 June 2016

self-report assessment form. Data were stratified into age groups. The potential factors affecting compliance were also investigated.

Results: Overall, 380 subjects participated in the study. The compliance rate was 79.7%, and the treatment discontinuation rate was 22.5%, while 66.8% of patients were adherent (both compliant and continuing with the treatment). The results showed that children were the most compliant and adolescents the least compliant (86.6% and 60.9%, respectively). The main reason for noncompliance was "forgetting some doses" in 31.0% of the children, 48.0% of the adolescents, and 53.2% of the adults. Compliance was associated with the following factors: age, number of annual control visits, and reduction in symptomatic medication.

Conclusion: Our results showed that two out of three patients with house dust mite-induced allergic rhinitis adhered to the SLIT treatment. Multidisciplinary and integral solutions are needed to improve the compliance, with special attention paid to adolescents.

Funding: Stallergenes Greer Spain.

Keywords: Allergy; Adherence; Allergen immunotherapy; Pulmonary; Respiratory; Treatment interruption; Sublingual immunotherapy

INTRODUCTION

The allergen-specific immunotherapy is currently the closest approach to curing allergic rhinitis. The treatment alters the underlying immune inflammatory response, thereby preventing renewed sensitization. It is recommended for patients with well-identified allergens, insufficiently controlled by the symptomatic medication. The treatment has been traditionally performed by the health-care providers, in the form of subcutaneous injections. However, this method is associated with several problems, such as inconvenience, invasiveness, and moderate-to-severe adverse effects [1]. Thus, there is a growing interest in sublingual administration as an effective alternative [1, 2]. One of the advantages of sublingual immunotherapy (SLIT) is that, as an oral drug, it can be administered at home. However, the physicians cannot effectively supervise the drug administration at home, which has resulted in a surge in compliance issues [3]. Regardless of the route of administration, the perennial allergic rhinitis (PAR) as a chronic condition requires long-term treatment of over 3 years [4–7]. Therefore, adherence problems can be expected a priori [8]. Chronic patients often have other associated comorbidities and follow complex medical regimens; the adherence is frequently compromised [9]. Young patients might not have different comorbidities but face different challenges to compliance. A lack of compliance is a common multifactorial problem, which arises not only from treatment-related factors but also due to the condition itself and the societal and health-care system factors [10]. The available data on the patient adherence to allergen-specific immunotherapy are often conflicting [11, 12]. In particular, in allergic rhinitis, compliance rates for sublingual administration range between 70% and 97% [10, 13–22]. This wide variation might be explained by differences in the characteristics and methodology of the studies, such as the population profiles and the definition of compliance [23].

When we first planned our study in 2009, a few trials that had attempted to assess compliance to allergen immunotherapy were mainly exploratory, with limited sample sizes and short- to medium-term follow-up. No

significant progress has been made since, and the identification of the reasons for noncompliance remains a challenge. Our study attempted to broaden the current knowledge of compliance of patients undergoing SLIT for house dust mite-caused PAR. The results were stratified by age, and a comprehensive evaluation of the factors that determine noncompliance was performed.

METHODS

This multicenter observational study was conducted in 53 allergy units throughout Spain between September and December 2009. All procedures were in accordance with the ethical standards of the Committee on Human Experimentation of the Consorci Sanitari Integral de l'Hospitalet (Barcelona) and with the Helsinki Declaration of 1964 (as revised in 2013). Informed consent was obtained from all patients included in the study.

Study Design

The study was divided into two phases. During the prescreening stage, the clinicians identified 8–10 consecutive outpatients with a confirmed diagnosis of PAR caused by house dust mites. The patients had symptoms for more than 12 months, started the SLIT between September and December 2008, and had a scheduled control appointment during the period of data collection (September–December 2009), 12 months after initiating the SLIT (Fig. 1). The diagnosis of PAR was performed according to the common practice of the centers. This is currently based on the clinical history of symptoms, the positivity of skin prick tests, and spirometry with methacholine challenge when indicated. Asthma and rhinitis were graded according to GINA [24] and ARIA guidelines [25], respectively. The severity was classified following the method of Valero et al. [26]. In the second phase, the prescreened patients or their caregivers were asked to sign an informed consent form to participate in the study. Sociodemographic and pathology data and the retrospective information on the clinical management of PAR were gathered in a single visit (the routine yearly visit to the clinic). The specialist involved and the type of center were also registered.

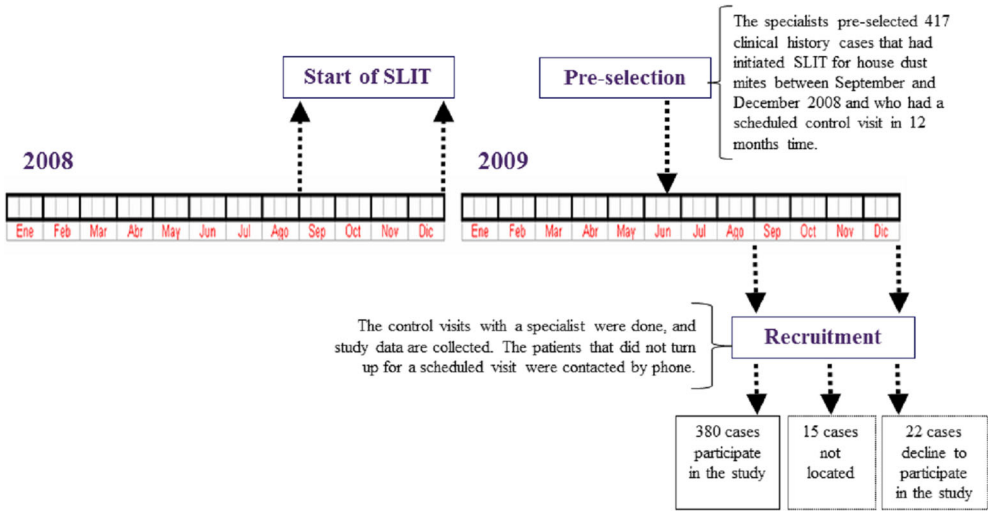

Fig. 1 Study flowchart. *SLIT* sublingual immunotherapy

Compliance and Discontinuation Measurements

The main variable of the study was the rate of compliance. This information was obtained using three different methods. The first was based on the allergist assessment of the proportion of patients completing the recommended SLIT treatment after 12 months. The data were obtained by interviewing the patients and/or caregivers how often they took their medication and by the retrospective evaluation of the medical records. Compliant subjects took ≥80% of the overall prescription, while noncompliants were divided into groups taking <25%, 25–50%, and 50–80% of the prescribed SLIT. Second, the results of the Morisky–Green test, a structured four-item self-reported adherence measurement tool (validated in Spain by Val et al. [27, 28]), were used. Patients who answered all questions correctly were identified as complaints. Noncompliant subjects were classified according to the item failed of the Morisky–Green test: Do you ever forget to take your medicine? Are you careless at times about taking your medicine? When you feel better, do you sometimes stop taking your medicine? If you feel worse when you take your medicine, do you stop taking it? Finally, noncompliant patients and/or their caregivers were given a questionnaire to assess their compliance and discontinuation of the SLIT treatment. The questionnaire collected the socioeconomic information, such as sex, age, educational level, marital status, and employment status. It also contained questions regarding SLIT treatment. These were "Did you administer all the doses?", "Had you terminated the treatment before you were instructed by the doctor?", and "Reasons for not following the treatment." Patients who permanently discontinued the SLIT treatment, regardless of the degree of compliance, were considered "treatment discontinuation" cases. Patients were considered adherent when they were both compliant and continued the treatment throughout the study. The questions could be answered not only by the patient (>15 years), but also by the caregiver or both the patient and caregiver.

Given the multifactorial nature of the compliance, reasons for noncompliance were self-registered by the patients according to the five dimensions suggested by the World Health Organization (WHO): socioeconomic, health-care system-, condition-, therapy-, and patient-related factors [29].

Statistical Analysis

The sample size was calculated assuming a 95% confidence level and considering a proportion of 50%, 385 cases would be recommended for the study. However, considering an estimated 15% dropout or loss to follow-up rate, a sample of 453 patients would be required. Therefore, the initial number of pre-selected individuals per participating site was 10. The categorical variables were described according to the number and percentage of subjects in each category. The Kolmogorov–Smirnov bilateral test with a confidence level of 95% was performed to assess normal distribution. The descriptive analysis was stratified by age groups: children (<15 years), adolescents (15–18 years), and adults (>18 years).

To evaluate the effect of the five evaluated dimensions on the compliance, a bivariate analysis was performed using the nonparametric Mann–Whitney bilateral test, with a confidence level of 95%, and Pearson's Chi-square test. Multivariate analysis was conducted using a logistic regression model.

The analyses were performed to explore and identify the factors associated with SLIT compliance.

Statistical analysis was carried out using the SPSS software, version 13.0 (IBM, New York, USA) [30].

RESULTS

Of the 417 prescreened patients, 22 withdrew their informed consent, and 15 were lost to follow-up, leaving 380 evaluable patients. Sociodemographic and clinical characteristics of the participants are shown in Table 1. The overall mean age was 19.8 ± 14.8 years, and patients suffered from PAR for a mean duration of 5.9 years, mostly from persistent and moderate/severe rhinitis (73.4% and 88.9%, respectively). Before initiating SLIT, most of the patients received antihistamine medications (87.1%) and corticosteroids (67.4%). The subjects had attended a mean of 2.4 control appointments with the allergist during the previous year. The main characteristics of the 53 allergists participating in the study are shown in Table 2.

The overall compliance rate was 79.7%, and SLIT discontinuation was 22.5%, according to the allergist evaluation (Figs. 2, 3, respectively). The rate of adherent patients, defined as being compliant and without discontinuing the therapy, was 66.8%. The analysis per age showed that most of the compliants were children (86.6%), with few treatment discontinuations (12.3%), followed by the adult group (78.1% and 27.5%, respectively; Figs. 2, 3). Finally, the adolescents showed the lowest compliance and the highest SLIT discontinuation rates in comparison with the overall rates (60.9% and 42.6%, respectively; Figs. 2, 3). When the overall compliance rate was calculated using the Morisky–Green test, the rates decreased considerably (50.9%; Fig. 4). Patients who were initially considered noncompliant responded to the patient questionnaire and 31.7% rejected nonadherence to SLIT (Fig. 5). The mean time for PAR-specific immunotreatment cessation was 5.3 ± 3.6 months for the global study sample: 3.8 ± 4.4 months for adolescents, 5.5 ± 2.9 for adults, and 6.5 ± 4.4 months for children.

The most commonly reported causes of noncompliance are shown in Table 3. The principal reason for not complying with the prescribed SLIT was “forgetting some doses” in all age groups (children 31.0%, adolescents 48.0%, and adults 53.2%; Table 3). The “intolerance or adverse effects” was the second most frequently mentioned cause among the children (27.6%) followed by “complexity and prolonged duration of treatment” (20.7%). “Complexity and prolonged duration of treatment” was mentioned in the noncompliant adolescent and adult groups. Finally, the second and third cause most common reasons given by adolescents were “perception of illness improvement” and “intolerance or adverse effects” (16.0% each). In the adult group, 27.7% admitted to having “difficulty in taking the medication within the timetable or schedule.”

The bivariate analysis (Table 4) identified the factors associated with high SLIT compliance rates after 12 months. These were age, length of medical consultation, frequency of specialist appointments, using the educational material or participating in activities concerning allergen immunotherapy, lack of corticosteroid treatment, self-perception of PAR improvement (in particular, a reduction in PAR severity) [26], and the reduction of medication after 12 months (Table 4). The

Table 1 Patient sociodemographic characteristics and clinical characteristics of PAR by age groups

Characteristics	Children (*N* = 180)	Adolescents (*N* = 48)	Adults (*N* = 151)	Overall (*N* = 380)
Sex, female, *N* (%)	95 (52.8)	22 (45.8)	67 (44.4)	185 (48.7)
Age, years, mean ± SD	8.4 ± 3.0	16.5 ± 1.3	34.5 ± 12.7	19.8 ± 14.8
Time since diagnosis, years, mean ± SD	3.5 ± 2.1	6.4 ± 3.2	8.6 ± 6.8	5.9 ± 5.2
Comorbidities[a], *N* (%)				
Asthma	132 (73.3)	24 (50)	60 (39.7)	216 (56.8)
Dermatitis	55 (30.6)	8 (16.7)	14 (9.3)	77 (20.3)
Other	71 (39.4)	19 (39.6)	73 (48.3)	163 (43)
Type of asthma[b], *N* (%)				
Intermittent	64 (48.5)	10 (41.7)	38 (63.3)	112 (51.9)
Mild/persistent	34 (25.8)	13 (54.2)	20 (33.3)	67 (31)
Moderate/persistent	27 (20.5)	1 (4.2)	1 (1.7)	29 (13.4)
Severe/persistent	1 (0.8)	0	0	1 (0.5)
Type of allergic rhinitis[c], *N* (%)				
Intermittent	54 (30)	10 (20.8)	29 (19.2)	93 (24.5)
Persistent	121 (67.2)	37 (77.1)	120 (79.5)	279 (73.4)
Severity of allergic rhinitis[d], *N* (%)				
Mild	20 (11.1)	2 (4.2)	6 (4)	28 (7.4)
Moderate	131 (72.8)	38 (79.2)	112 (74.2)	281 (73.9)
Severe	21 (11.7)	7 (14.6)	29 (19.2)	57 (15)
Treatment before allergen immunotherapy, *N* (%)				
Nasal corticosteroids	105 (58.3)	31 (64.6)	119 (78.8)	256 (67.4)
Antihistamines	145 (80.6)	43 (89.6)	142 (94)	331 (87.1)
Others	47 (26.1)	7 (14.6)	19 (12.6)	73 (19.2)

Participants were stratified by age groups: children (<15 years), adolescents (15–18 years), and adults (>18 years)
Due to some missing cases, some percentages do not add up to 100
PAR perennial allergic rhinitis, *SD* standard deviation
[a] A patient could respond to more than one option
[b] According to GINA classification [21]
[c] According to ARIA classification [22]
[d] According to Valero et al. work [23]

subsequent logistic regression analysis allowed the identification of covariates independently associated with compliance, and in particular, age, the number of control visits with allergist per year, and a reduction in PAR medication (Table 4).

Table 2 Professional profile of investigators participating in the study ($N = 53$)

Characteristics	$N = 53$
Sex, male, *N* (%)	37 (69.8)
Age, mean ± SD	49.9 ± 9.1
Type of health-care center, *N* (%)	
Public	25 (47.2)
Private	27 (50.9)
Years practicing as specialist, *N* (%)	
<5 years	3 (5.6)
5–20 years	25 (47.2)
≥20 years	25 (47.2)
Time with each patient, *N* (%)	
<10 min	0 (0)
10–15 min	28 (52.8)
15–30 min	23 (43.4)
>30 min	2 (3.8)
Educational approach[a], *N* (%)	
Classroom training courses	20 (37.7)
Informative leaflets	44 (83)
Oral explanation	5 (9.4)
Other measures	18 (33.9)

Due to some missing cases, some percentages do not add up to 100
SD standard deviation
[a] A patient could respond to more than one option

DISCUSSION

The treatment of allergic rhinitis is based on environmental allergen avoidance, symptomatic pharmacotherapy, and allergen-specific immunotherapy [5]. These treatments are effective; however, there are some serious compliance issues [31]. There is little information on adherence to educational strategies of dust mite avoidance or treatment with antihistamines and nasal corticosteroids [11]. Several studies have attempted the evaluation of the real compliance to SLIT, without clear-cut results. Therefore, we designed a comprehensive assessment of compliance of patients suffering from PAR caused by house dust mite, including an assessment of the most probable causes for noncompliance and, importantly, stratifying the population into age groups.

The results of this study showed that two-thirds (66.8%) of the population under study were adherent (taking ≥80% of the indicated doses, without abandoning the treatment during the 12 months of study). The overall compliance rate was 79.7% and the discontinuation rate, 22.5%. These compliance data are in agreement with several previously published studies of patients with PAR, which have reported the rates of around 70–80% [10, 15, 17–22]. Another study has reported a higher compliance of approximately 97% [20]. However, in that study, the patients counted the pills themselves and reported via a telephone interview, which could be inaccurate and susceptible to misrepresentation. Variations caused by the method of compliance measurement were apparent in our study. The results of the Morisky–Green test gave lower rates of compliance (50.9%), even to be also a self-reported method that may trend to overestimate compliance. However, the Morisky–Green test contains a too broadly phrased question: "do you ever forget to take your medicine?" which makes the responders frequently being classified as noncompliants, because forgetting one dose might be very common. The choice of a method for an accurate measurement of compliance is always under discussion, as both the subjective and objective techniques suffer from important limitations. Compliance has frequently been

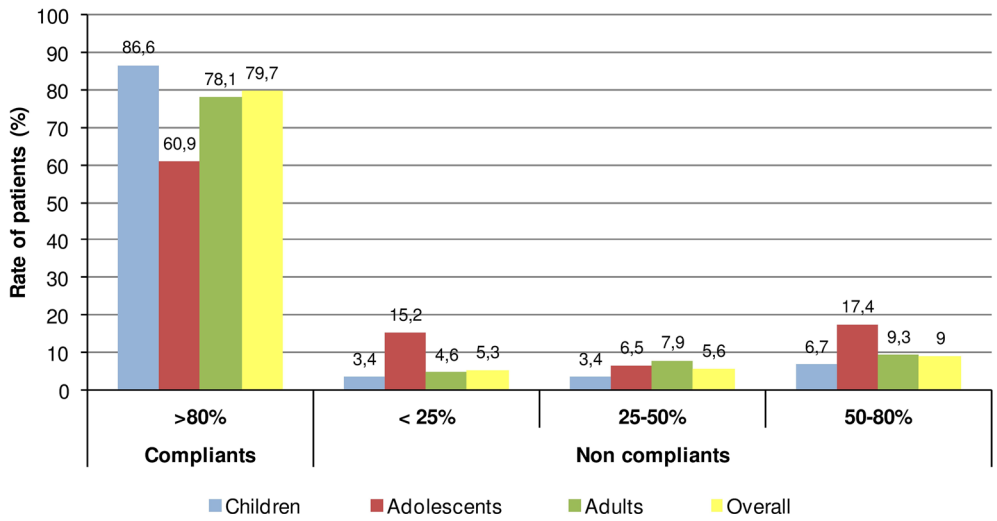

Fig. 2 Information on compliance with sublingual immunotherapy based on the allergist assessment $N = 376$. The allergist assessment of the proportion of patients completing the recommended sublingual immunotherapy (SLIT) doses after 12 months was obtained both by interviewing the patients and/or caregivers how often they took their medication and by the retrospective evaluation of the medical records. Compliant subjects were defined as those taking more than 80% of all prescribed doses. The noncompliants were divided into groups taking <25%, 25–50%, and 50–80% of the prescribed medication. Participants were stratified by age groups: children (<15 years), adolescents (15–18 years), and adults (>18 years). *Chi-square test, $P < 0.0001$ for adolescents in comparison with the overall rate

assessed using self-reporting. This is a feasible method for observational studies conducted according to the standard clinical practice and simple enough for the patients. However, it can be inaccurate, with a tendency to overestimate compliance [32, 33]. In the present study, when a potential noncompliant case was detected based on patient response and the retrospective evaluation of the medical records, the patient and/or the caregiver was invited to answer specific questions to assess the compliance in greater depth. Overall, 31.7% of the subjects who were initially identified as noncompliant by the investigators reported themselves as compliant. It is not clear whether this figure reflects the extent to which the patients overestimate their compliance. Certainly, this is not a perfect tool to measure the compliance with SLIT, but at least this shortcoming does not reduce the credibility and relevance of the results. In addition, our study sample was large enough to minimize the selection bias and, therefore, avoided overestimating the compliance rates.

The assessment of compliance depending on age was also performed. The groups of children and adolescents were not large, but sufficient to allow the detection of statistically significant differences between the groups. In particular, children under 15 years of age were the group with the highest rate of compliance (86.1%), only slightly lower than that obtained by Bernaola et al. (91.4%) [34]. This pattern is repeated for other chronic conditions, as parents often take close care of their children to ensure the correct administration of the medication. In contrast, adolescents were the group with the highest noncompliance and treatment discontinuation. This is a common situation, particularly when accompanied by the following factors: older adolescent, mental health issues with the caregiver, family

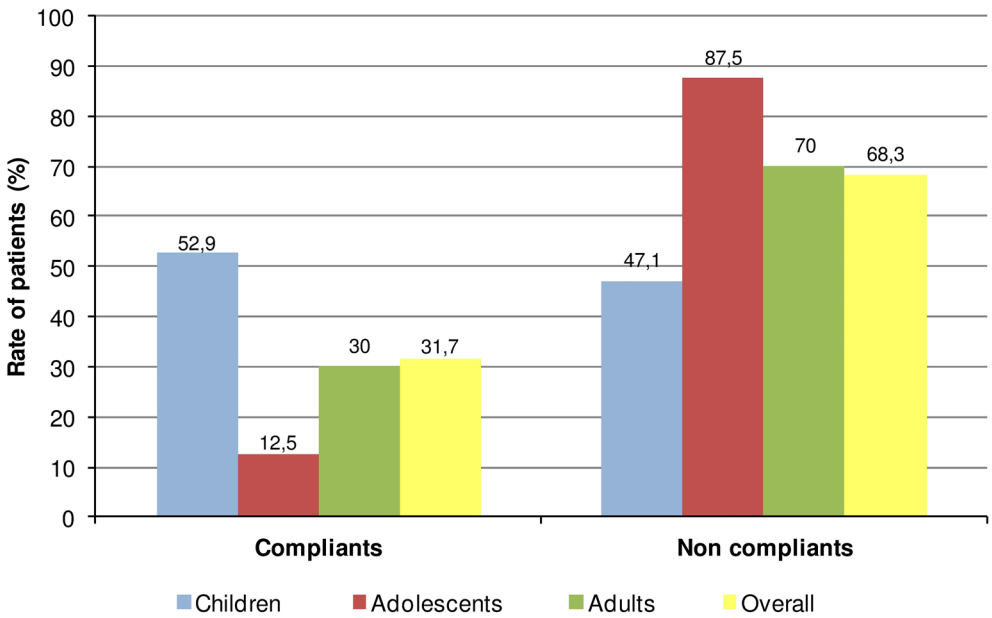

Fig. 3 Rate of discontinuation of the sublingual immunotherapy. The investigator interviewed the patients who permanently discontinued sublingual immunotherapy (SLIT) treatment, regardless of the degree of compliance; they were considered "treatment discontinuation" cases. Participants were stratified by age groups: children (<15 years), adolescents (15–18 years), and adults (>18 years). *Chi-square test, $P < 0.0001$ for children and adolescents in comparison with the overall rate

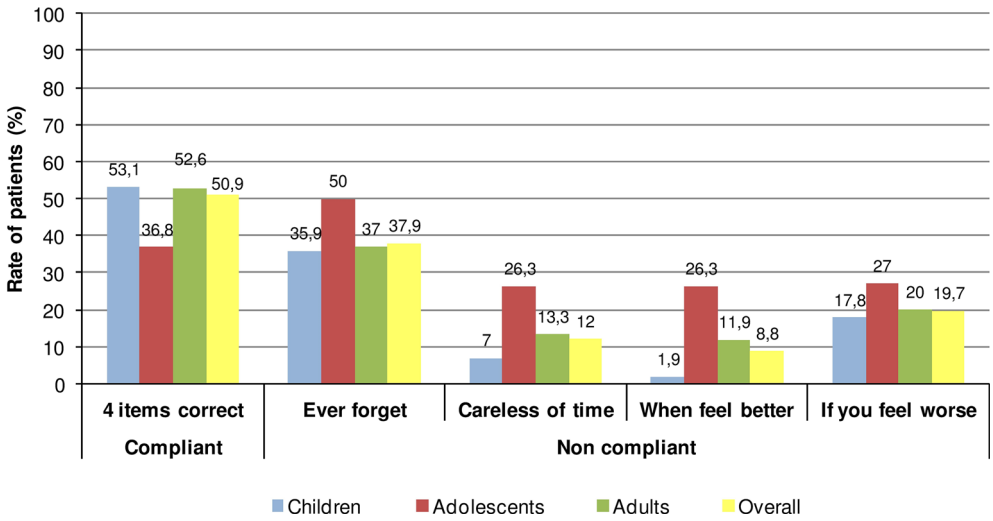

Fig. 4 Rate of patients compliant with the sublingual immunotherapy based on the results of the Morisky–Green test $N = 334$. A compliant subject was expected to give appropriate answers to the four questions of the Morisky–Green test. Noncompliant subjects are represented according to the item failed in the Morisky–Green test (Do you ever forget to take your medicine? Are you careless at times about taking your medicine? When you feel better, do you sometimes stop taking your medicine? If you feel worse when you take your medicine, do you stop taking it?). Participants were stratified by age groups: children (<15 years), adolescents (15–18 years), and adults (>18 years). *Chi-square test, $P < 0.0001$ for adolescents in comparison with the overall rate

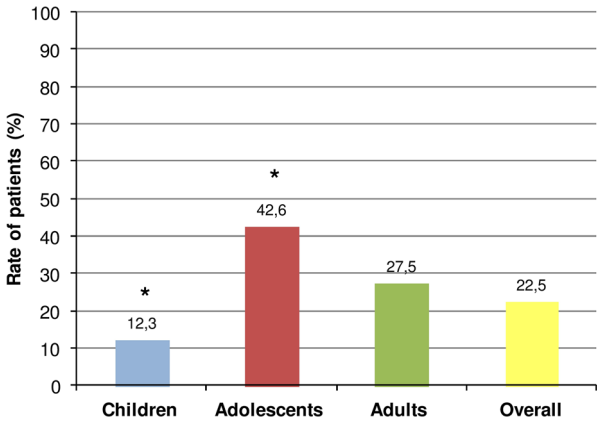

Fig. 5 Information on compliance with sublingual immunotherapy based on the results of the noncompliant patient report form $N = 63$. Participants identified as noncompliants by the investigators were asked to fill a patient report form. Subjects and/or their caregivers were requested to answer the questions regarding their compliance and continuation of the sublingual immunotherapy (SLIT) doses. The answers supplied socioeconomic information, including sex, age, educational level, marital status, and employment status, and data on SLIT treatment ("did you take all the doses?", "had you terminated the treatment before your doctor instructed?", and "reasons why you did not fulfill the treatment"). Participants were stratified by age groups: children (<15 years), adolescents (15–18 years), and adults (>18 years). *Chi-square test, $P < 0.0001$ for children and adolescents in comparison with the overall rate

conflicts, complex therapy, medication with side effects, and denial of illness [35].

Regarding the treatment dropouts, the mean duration up to discontinuation of SLIT was approximately 6 months. Our results (22.5%) are broadly in accord with the previously published reports, which show discontinuation rates ranging from 8% to 50% [14, 16]. The latter value has been derived from the sales figures of two large manufacturers in Italy [14], using the methods significantly different from the methodology of the present study. Interestingly, Vita et al. have assessed the discontinuation rate in three groups of patients classified according to the type of PAR care program (control visits scheduled four times, twice, or once a year). The patients attending the allergist four times a year showed the lowest rate of discontinuation (8.1%), followed by the twice-a-year group (14.7%) and the once-a-year group (29.3%). In our study, the patients attended an average of 2.4 appointments per year; the compliance was similar to that in the last two groups of Vita et al. We designed a follow-up of 12 months, a long-term evaluation in comparison with the data for these types of studies available in 2009. Since then, several studies have tried to collect information throughout the entire 3-year course of SLIT. However, the reported range of withdrawals remains inconclusive, between 7% and 40% [13, 14, 16, 17, 21].

In our study, the main reason for not complying with SLIT was "forgetting some doses." Nevertheless, the results differed depending on age, although the statistical power was insufficient to apply a hypothetical test allowing the corroboration of the mentioned differences. The "adverse effects" were reported as the second main cause of noncompliance in the group of children, which was consistent with the results of other studies [19]. Adult patients reported both the "complexity and prolonged duration of treatment," as well as "difficulty in taking the medication according to the timetable or schedule." Interestingly, in the adolescent group, not only the "complexity and prolonged duration of treatment," but also the "perception of illness improvement" was recorded. The five dimensions affecting compliance with long-term or chronic treatments, suggested by the WHO, were represented to a larger or smaller extent by the noncompliant patients in our study [4]. Therefore, compliance as a multi-causal condition may vary in magnitude according to the patient characteristics, which fit in with the

Table 3 Reported causes of noncompliance with the sublingual immunotherapy in different age groups and according to the World Health Organization (WHO) 5-dimension model

WHO 5 dimensions	Factors[a]	Children (n = 29)	Adolescents (n = 25)	Adults (n = 47)
Patient-related	Forgetting some doses	9 (31.0)	12 (48.0)	25 (53.2)
	Logistic reasons regarding treatment	0	3 (12.0)	4 (8.5)
Therapy-related	Complexity and prolonged duration of treatment	6 (20.7)	7 (28.0)	16 (34)
	Intolerance or adverse effects	8 (27.6)	4 (16.0)	5 (10.6)
	Difficulty in taking the medication according to timetable or schedule	3 (10.3)	1 (4.0)	13 (27.7)
	Treatment ineffectiveness	2 (6.9)	2 (8.0)	4 (8.5)
Socioeconomic-related	High cost of treatment	3 (10.3)	3 (12.0)	10 (21.3)
Health care system-related	Lack of information regarding the illness or its treatment	5 (17.2)	0	3 (6.4)
Condition-related	Perception of illness improvement	0	4 (16.0)	3 (6.4)

This is a self-registered questionnaire, including five dimensions suggested by the WHO: socioeconomic, health-care system-, condition-, therapy-, and patient-related factors [29]
The primary reason given by patients/parents is highlighted in red, the second reason in orange, the third in yellow, and the fourth in green
Data are shown as *N* (%)
[a] Patients could indicate more than one reason. Data are shown only for those factors that have accumulated >5% of responses

model defined for adherence to long-term or chronic treatments [4]. All these factors should be taken into account when designing individual solutions and defining strategies to improve compliance with allergen immunotherapy. The information given to each subject before and during SLIT should clearly describe the schedule of administration and the duration of the treatment. The collaboration of patients is essential to

Table 4 Factors affecting patient compliance with sublingual immunotherapy

Characteristics		Compliants (*N* = 254)	Noncompliants (*N* = 101)	Bivariate analysis[a] *P* value	Multivariate analysis[b]		
					OR	(IC 95 %)	*P* value
Sociodemographic	Age, *N* (%)						
	Children	135 (82.3)	29 (17.7)		NA	NA	0.001
	Adolescents	23 (47.9)	25 (52.1)	0.001	5.0	(2.1–12.1)	<0.001
	Adults	95 (66.9)	47 (33.1)		2.5	(1.3–4.7)	0.007
Clinical management/ health-care system use	Time with each patient, *N* (%)						
	<15 min	119 (66.5)	60 (33.5)	0.022	NA	NA	NA
	>15 min	135 (76.7)	41 (23.3)				
	Number of visits/year, mean (SD)	2.6 (1.4)	1.9 (1.1)	<0.001	0.7	(0.5–0.9)	0.006
	Educational approach, *N* (%)						
	Oral explanation	116 (78.4)	32 (21.6)	0.01	NA	NA	NA
	No oral explanation	138 (66.7)	69 (48.3)				
	Treatment prior to SLIT, *N* (%)						
	Corticoids	152 (67.6)	73 (32.4)	0.015	NA	NA	NA
	No corticoids	92 (79.3)	24 (20.7)				
Self perceived assessment	Change in PAR type after 12 months, *N* (%)[c]						
	PAR improvement	128 (81.5)	29 (18.5)	0.004	NA	NA	NA
	PAR stable or worsening	101 (67.8)	48 (32.2)				
	Change in PAR severity after 12 months, *N* (%)[d]						
	Patients improving at least one level	104 (83.2)	21 (16.8)	0.001	NA	NA	NA
	Patients stable or worsening	97 (66.4)	49 (33.6)				
	Change in PAR treatment after 12 months, *N* (%)						
	Stable or increased	30 (44.8)	37 (55.2)	<0.001	5.3	(2.8–9.9)	<0.001
	Diminished	206 (82.7)	43 (17.3)		NA	NA	NA

Other variables were also tested but were not significantly associated with compliance with the SLIT, neither in the bivariate analysis nor in the multivariate analysis. These were age and sex of the allergist, public or private health center, patient sex, suffering from asthma, type of PAR, severity of PAR [26], using only corticosteroids versus other drugs, and response to treatment

Compliant patients took ≥80% of the prescribed SLIT doses, while noncompliants took <25%, 25–50%, and 50–80%

IC confidence interval, *NA* not available, *OR* odds ratio, *PAR* perennial allergic rhinitis, *SD* standard deviation, *SLIT* sublingual immunotherapy

[a] The Mann–Whitney *U* test was used for continuous variables and the Pearson's Chi-square test for categorical variables

[b] *P* values for retained variables within the equation are reported. The model gives a predictive value of 35.5% for noncompliant patients and 94.7% for compliant patients

[c] According to the ARIA classification [22]

[d] According to the Valero et al. work [23]

integrate the SLIT treatment into their daily routines. Adequate information on managing the most common local reactions in the mouth or gastrointestinal tract [10, 36] might also be of value.

Two interesting findings are worth emphasizing. First, the cost of treatment only took the fourth place in the ranking by noncompliant adult patients. This result did not support the previous findings indicating that the cost is not relevant in Spain [11]. In many countries, the SLIT treatment is not reimbursed [11]. Second, our exhaustive assessment showed that several additional factors independently affected the compliance with SLIT. These factors were the age of the patient (less than 15 years), an increase in treatment efficacy by the reduction of symptomatic drug consumption after 12 months, since the initiation of SLIT, and a close patient-physician relationship (increased frequency of control visits). These factors have also been mentioned by other authors [11, 16]. Other variables associated with the compliance with SLIT have been widely discussed (e.g., teaching the patient to control the illness severity [33]). In the present study, similar aspects (educational measures at the initiation of SLIT and change in the frequency and severity of allergic rhinitis) and other not previously reported variables (e.g., medical consultation length or use of corticosteroids as a treatment before the SLIT) were associated with compliance with SLIT in the bivariate analysis. However, this was not the case in the subsequent multivariate logistic regression analysis (data not shown). The change in the PAR type after 12 months, change in PAR severity, and change in PAR treatment are some of the dimensions in the multivariate analysis that could also be a consequence of the poor compliance rather than an influence factors. However, except for the last factor (change in PAR treatment), none of these was associated with a lack of compliance.

Improvement in the compliance with allergen immunotherapy, therefore, requires multidisciplinary and integral solutions, including patient education, strict follow-up, and regular contacts before and during treatment [33, 37]. A consensual agreement between the patient and the specialist to tailor the schedule [38] and establishing a mechanism to remind the patients to take their medication [39, 40] should also improve the compliance outcomes.

CONCLUSION

This observational study supplied some real-life data on compliance with SLIT in patients with house dust mite-PAR and showed variations caused by different methods of compliance measurement. Our results showed that two out of three patients with house dust mite-induced allergic rhinitis adhered properly to the SLIT treatment. In addition, a comprehensive assessment of age groups demonstrated once again that adolescents between 15 and 18 years of age were the population with the significantly worst compliance and the highest discontinuation rates. Therefore, the allergists in a multidisciplinary team should promote good standards of self-medication and persistence. They should employ educational material and activities and develop a close relationship with the patient. The team should pay special attention to adolescent patients.

ACKNOWLEDGMENTS

Sponsorship and article processing charges for this study were funded by Stallergenes Greer

Spain. All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Editorial assistance in the preparation of this manuscript was provided by Irantzu Izco-Basurko. Support for this assistance was funded by Stallergenes Iberica.

Disclosures. Alfonso Malet, Angel Azpeitia, Diego Gutiérrez, Francisco Moreno, María del Mar San Miguel Moncín, José Angel Cumplido, Magdalena Lluch, Eva Baró, and Albert Roger have nothing to disclose.

Compliance with Ethics Guidelines. All procedures were in accordance with the ethical standards of the responsible committees on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients included in the study.

REFERENCES

1. Radulovic S, Calderón MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010;12:CD002893. doi:10.1002/14651858.CD002893.pub2.

2. Sikora JM, Tankersley MS, ACAAI Immunotherapy and Diagnostics Committee. Perception and practice of sublingual immunotherapy among practicing allergists in the United States: a follow-up survey. Ann Allergy Asthma Immunol. 2013;110(3):194–7.

3. Erny-Albrecht K, Valentine WJ, Christensen J, Roze S, Cobden D, Palmer AJ. Sublingual immunotherapy in allergic rhinitis and asthma: a review of recent clinical evidence. J Appl Res. 2007;7(1):17–31.

4. World Health Organization Position Paper. Allergen immunotherapy: therapeutical vaccines for allergic diseases. In: Bousquet J, Lockey R, Malling HJ, editors. Allergy 1998; 53(suppl.):1–33, 43.

5. Bousquet J, Khaltaev N, Cruz AA, Papadopoulos NG, Bousquet PJ, Burney PG. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). Allergy. 2008;63(Suppl 86):S8–160.

6. Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2013 update. Allergy. 2009;64(Suppl. 91):1–59.

7. Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Allergen immunotherapy: a practice parameter second update. J Allergy Clin Immunol. 2007;120(Suppl. 3):S25–85.

8. Christensen AJ. Patient adherence to medical treatment regimens: bridging the gap between behavioral science and biomedicine. Current perspectives in psychology series. New Haven: Yale University Press; 2004.

9. Sabaté E, editor. Adherence to long-term therapies: evidence for action. Geneva, Switzerland: World Health Organization. 2003. http://whqlibdoc.who.int/publications/2003/9241545992.pdf. Accessed 10 May 2016.

10. Köberlein J, Kothe A, Schaffert C. Determinants of patient compliance in allergic rhinoconjunctivitis. Curr Opin Allergy Clin Immunol. 2011;11(3): 192–9.

11. Passalacqua G, Baiardini I, Senna G, Canonica GW. Adherence to pharmacological treatment and specific immunotherapy in allergic rhinitis. Clin Exp Allergy. 2013;43(1):22–8.

12. Aboshady OA, Elghanam KM. Sublingual immunotherapy in allergic rhinitis: efficacy, safety, adherence and guidelines. Clin Exp Otorhinolaryngol. 2014;7(4):241–9.

13. Kiel MA, Röder E, Gerth van Wijk R, Al MJ, Hop WC. Rutten-van Mölken MP. Real-life compliance and persistence among users of subcutaneous and sublingual allergen immunotherapy. Allergy. Clin Immunol. 2013;132(2):353–60.

14. Senna G, Lombardi C, Canonica GW, Passalacqua G. How adherent to sublingual immunotherapy prescriptions are patients? The manufacturers' viewpoint. J Allergy Clin Immunol. 2010;126(3): 668–9.

15. Chang H, Han DH, Mo J, Kim JW, Kim DY, Lee CH, et al. Early compliance and efficacy of sublingual immunotherapy in patients with allergic rhinitis for house dust mites. Clin Exp Otorhinolaryngol. 2009;2(3):136–40.

16. Vita D, Caminiti L, Ruggeri P, Pajno GB. Sublingual immunotherapy: adherence based on timing and monitoring control visits. Allergy. 2010;65(5): 668–9.

17. Marogna M, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, et al. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. Ann Allergy Asthma Immunol. 2008;101(2):206–11.

18. Passalacqua G, Musarra A, Pecora S, Amoroso S, Antonicelli L, Cadario G, et al. Quantitative assessment of the compliance with once-daily sublingual immunotherapy in children (EASY project: evaluation of a novel SLIT formulation during a year). Pediatr Allergy Immunol. 2007;18(1):58–62.

19. Passalacqua G, Musarra A, Pecora S, Amoroso S, Antonicelli L, Cadario G, et al. Quantitative assessment of the compliance with a once-daily sublingual immunotherapy regimen in real life (EASY Project: Evaluation of A novel SLIT formulation during a Year). J Allergy Clin Immunol. 2006;117(4):946–8.

20. Lombardi C, Gani F, Landi M, Falagiani P, Bruno M, Canonica GW, et al. Quantitative assessment of the adherence to sublingual immunotherapy. J Allergy Clin Immunol. 2004;113(6):1219–20.

21. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. Allergy. 2004;59(11):1205–10.

22. Köberlein J, Kothe AC, Sieber J, Mösges R. Determining factors of patient compliance to treatment in allergic rhinitis. Asian Pac J Allergy Immunol. 2013;31(2):148–56.

23. Pajno GB, Vita D, Caminiti L, et al. Children's compliance with allergen immunotherapy according to administration routes. J Allergy Clin Immunol. 2005;116(6):1380–1.

24. The global Initiative for Asthma (GINA). Pocket guide for asthma management and prevention. 2016. http://ginasthma.org/2016-pocket-guide-for-asthma-management-and-prevention/. Accessed 10 May 2016.

25. Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126(3): 466–76.

26. Valero A, Ferrer M, Baro E, Sastre J, Navarro AM, Martí-Guadaño E, et al. Discrimination between moderate and severe disease may be used in patients with either treated or untreated allergic rhinitis. Allergy. 2010;65(12):1609–13.

27. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24(1):67–74.

28. Val Jiménez A, Amorós Ballestero G, Martínez Visa P, Fernández Ferré ML, León Sanromà M. Estudio descriptivo del cumplimiento del tratamiento farmacológico antihipertensivo y validación del test Morisky y Green. Aten Primaria. 1992;10(5):767–70.

29. WHO. Adherence to long-term therapies: evidence for action. WHO/MNC/03.01.

30. SPSS. Statistical Package for the Social Sciences. Version 13.

31. Lee S, Nolte H, Benninger MS. Clinical considerations in the use of sublingual immunotherapy for allergic rhinitis. Am J Rhinol Allergy. 2015;29(2):106–14.

32. Fitzgerald D. Non-compliance in adolescents with chronic lung disease: causative factors and practical approach. Paediatr Respir Rev. 2001;2(3):260–7.

33. Incorvaia C, Rapetti A, Scurati S, Puccinelli P, Capecce M, Frati F. Importance of patient's education in favoring compliance with sublingual immunotherapy. Allergy. 2010;65(10):1341–2.

34. Bernaola G, Corzo JL, Domínguez-Ortega J, Lucas C, Ojeda I, Torres-Borrego J, et al. Sublingual immunotherapy: factors influencing adherence. J Investig Allergol Clin Immunol. 2012;22(6):458–9.

35. Taddeo D, Eggedy M, Frappier JY. Adherence to treatment in adolescents. Paediatr Child Health. 2008;13(1):19–24.

36. Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. Clin Exp Allergy. 2005;35(5):565–71.

37. Gold DT, McClung B. Approaches to patient education: emphasizing the long-term value of compliance and persistence. Am J Med. 2006;119(4 Suppl 1):S32–7.

38. Wilson SR, Strub P, Buist AS, Knowles SB, Lavori PW, Lapidus J, et al. Shared treatment decision

making improves adherence and outcomes in poorly controlled asthma. Am J Respir Crit Care Med. 2010;181(6):566–77.

39. Strandbygaard U, Thomsen SF, Backer V. A daily SMS reminder increases adherence to asthma treatment: a three-month follow-up study. Respir Med. 2010;104(2):166–71.

40. Bender BG. Motivating patient adherence to allergic rhinitis treatments. Curr Allergy Asthma Rep. 2015;15(3):10.