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# Costs of treatment affect compliance to specific subcutaneous immunotherapy

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**Summary**

**Background.** *Specific subcutaneous immunotherapy (SCIT) is cost-effective; however its economical burden can lead to non-adherence. We aimed to identify the reported reasons, patient's personal or socio-demographic characteristics and SCIT-related factors associated with non-adherence to SCIT.* **Methods.** *This is a cross-sectional, observational study held in a Portuguese University Hospital. All records from patients starting SCIT in the last 4 years were reviewed in July 2011. Those without registry of SCIT administration in the previous 3 months were included (n = 181). A telephonic survey was performed and 56 were confirmed as non-adherent; reasons for discontinuation were assessed. Univariate and multiple logistic regression models were developed using characteristics previously described as being associated with non-adhesion.* **Results.** *Economical burden of SCIT was the most important factor leading to treatment discontinuation (40%). In the univariate analysis, presence of family history of allergic disease treated with immunotherapy was associated with decreased OR of non-adherence to SCIT (OR [95%CI] = 0.31 [0.11-0.88]). In the multiple logistic regression model, none of the factors was significantly associated with non-adherence.* **Conclusion.** *Adherence is influenced by economic factors. More attention should be given to the impact of economic changes in allergic patient's treatment.*

## Introduction

Specific immunotherapy (IT) is a cost-effective treatment (1). It produces long-lasting clinical benefits even after completion of the treatment course (2, 3). However, subcutaneous IT (SCIT) is costly, implies adherence for 3 to 5 years, administrations at every 4 to 6 weeks and time-spent travelling to a healthcare center for subcutaneous treatment administration, which may have a negative impact on patients' adherence. Adherence, defined as the extent to which patients take the medication prescribed by their physicians (4), requires patients' commitment (2). It can be affected by multiple factors, including psychological and socio-demographic characteristics of the patient; severity and impact of the allergic disease in the patient's quality of life; efficacy, safety and complexity of the treatment; and health system coverage (5). By knowing which are the main factors responsible for treatment

discontinuation, physicians will be able to deal with them more effectively. Few studies addressed this question, as stated in a recent review (2).

The primary aim of this study was to describe reasons that led to SCIT non-adherence in patients with asthma and/or allergic rhinoconjunctivitis. Additionally, we aimed to identify patient's personal or socio-demographic characteristics and SCIT-related factors associated with non-adherence to SCIT.

## Methods

*Study Design and data collection*

This was a cross-sectional, observational study primarily targeting individuals with asthma and/or allergic rhinoconjunctivitis that discontinued SCIT with airborne allergens without me-

dical indication. This study was held in the Allergy Department of a University Hospital in Porto, Portugal, in July 2011. SCIT administration records from patients starting immunotherapy in the previous four years were reviewed (n = 1256). Individuals that started SCIT with airborne allergens during the study period and with no record of SCIT administrations in the 3 months previous to data collection were included. The records specifying that SCIT was stopped due to medical indication or that SCIT was being continued in another health care unit were excluded. The selected individuals were contacted in July/August 2011 and invited to answer a telephonic survey. Calls were performed in working days; each phone number was contacted at least 3 times in different occasions before being abandoned. Individuals that refused to answer and those that could not be reached after 3 attempts were excluded. Individuals that, during the telephonic interview, were found to have ceased treatment with medical indication or to have continued in other healthcare department were used for comparison. Data regarding gender, age, distance from home to the Hospital, type of allergic disease and SCIT-associated characteristics (including type, allergen(s), number of administrations, treatment duration and adverse effects) were collected from the records.

*Survey*

A structured questionnaire was built based on previous studies (6-9). A question to confirm if the patient had discontinued SCIT, specifying whether with or without medical indication, was performed in the beginning of the survey. Individuals that reported to have discontinued without medical indication were asked, in an open question, to appoint reasons for treatment withdrawal. Potentially important factors (including lack of treatment efficacy, difficulty in commuting or reconciling schedule with work/school, costs associated with SCIT and residency/working place changes) were also systematically questioned and registered in a dichotomous scale (Yes/No). The intention to restart SCIT was also asked. Questions regarding the number of years of school education, global improvement with SCIT (self-reported efficacy), personal history of other allergic diseases, family history of IT treatment and questions regarding SCIT efficacy (including changes in symptoms, medication need and emergency visits) were also included in the survey.

*Participants*

Overall, 181 individuals were selected, 67% (n = 122) completed the questionnaire and 46% (n = 56) were confirmed as non-adherent to SCIT (**figure 1**). Individuals that, at the time of the survey, were still under SCIT and those who stopped due to medical indication were considered as adherents. The characteristics of the participants are presented in **table 1**. Most patients (88%)

began SCIT using a rush protocol. More than half (56%) were performing treatment with a mixtures of allergens, most (75%) with house dust mites combinations (*Dermatophagoides pteronyssinus, farinae* and *Lepidoglyphus destructor*). Mixtures of grasses were the more frequently used pollens (82% of pollens SCIT); weeds (*Parietariae Officinalis* [n = 23] or *Plantago lanceolata* [n = 6]) and tree-pollens (olive tree or birch), isolated or in combination, were also used. The SCIT characteristics were similar to those previously published in the same population(10). Moreover, no statistically significant differences were found between the interviewed and non-interviewed individuals in what refers to demographic data and SCIT-associated characteristics.

*Statistical Analysis*

Data analyses were performed using SPSS® version 20.0 for Windows (IBM SPSS, Chicago, IL, USA). When necessary, variables were re-coded for statistical analysis: school education in three categories (accounting for the Portuguese school system) and self-reported professional activity in four categories - unemployed, student, undifferentiated profession and differentiated profession. Analyses regarding school education were restricted to individuals aged 18 years or older. Categorical variables were described using absolute frequencies and proportions and compared using Chi-square tests. Continuous variables were described by medians with interquartile range (IQR) and compared using the Mann-Whitney test (non-normal distribution). A p-value of $< 0.05$ was considered as statistically significant. Univariate and multiple logistic regression models were developed using independent variables as risk factors for non-adhesion in adults; results were presented as odds ratio (OR) with 95% confidence interval (CI). Variables used in the model included gender, age, scholarship, profession, family history of allergic disease, home distance from hospital, asthma diagnosis, SCIT period (pre-seasonal *vs.* perennial), allergen, adverse reactions to SCIT and self-reported SCIT efficacy. The model was progressively adjusted considering its goodness-of-fit (Hosmer-Lemeshow test) and predictive power (ROC curve analysis).

**Results**

The main reasons for discontinuing SCIT without medical indication are presented in **figure 2**. Forty percent of the participants considered the cost of SCIT as the most important factor for treatment discontinuation and 19% also reported other costs associated with SCIT (including price of administrations and commuting for treatment). Almost 27% of the participants referred that the lack of improvement with SCIT was a reason to discontinue treatment and 20% reported adverse events. Systemic reactions occurred in three patients from each group; all were mild except for an asthma exacerbation in a patient from the non-adherent group. The number of large local reactions,

either with immediate or late onset, was similar between groups (33 [59%] in the non-adherent group *vs.* 33 [50%] in those adherent to SCIT). One patient stopped treatment due to pregnancy and two others because they were diagnosed with another medical condition and considered, without medical advice, not to be possible to perform SCIT at the same time. At least 7% of the patients frequently forgot to attend to SCIT administration and 5% assumed not to understand SCIT benefits or were unaware of the need to continue treatment after completion of the first batch of vials. Seventy three percent (n = 41) of the non-adherents reported improvement during SCIT and 77% (n = 43) considered to resume treatment.

**Table 1 -** *Baseline characteristics of the participants and comparison between non-adherent and adherent patients*

| | Total | Groups | | |
| --- | --- | --- | --- | --- |
| | | **Non Adherent** | **Adherent** | *p-value* |
| | **(n = 122)** | **(n = 56)** | **(n = 66)** | |
| **Gender, *n (%)*** | | | | 0.390 |
| Male | 43 (35.2) | 22 (39.3) | 21 (31.8) | |
| **Age, years, *median [IQR]*** | 24 [20;32] | 26 [21;32] | 24 [18;33] | 0.579 |
| **Scholarship (≥ 18 years), *n (%)*** | | | | 0.283 |
| < 9 years | 13 (13.1) | 4 (8.5) | 9 (17.3) | |
| 9-12 years | 58 (58.6) | 31 (66.0) | 27 (51.9) | |
| > 12 years | 28 (28.3) | 12 (25.5) | 16 (30.8) | |
| **Profession, *n (%)*** | | | | 0.119 |
| Unemployed | 14 (11.6) | 5 (8.9) | 9 (13.8) | |
| Student | 26 (21.5) | 8 (14.3) | 18 (27.7) | |
| Undifferentiated profession | 58 (47.9) | 33 (58.9) | 25 (38.5) | |
| Differentiated profession | 23 (19.0) | 10 (17.9) | 13 (20.0) | |
| **Family history of Allergic Disease *n (%)*** | | | | 0.068 |
| Absent | 46 (39.0) | 25 (45.5) | 21 (33.3) | |
| Yes, no immunotherapy | 46 (39.0) | 23 (41.8) | 23 (36.5) | |
| Yes, treated with immunotherapy | 26 (19.0) | 7 (12.7) | 19 (30.2) | |
| **Distance to Hospital, Km, median *[IQR]*** | 11.5 [6.1;20.7][1] | 10.1 [5.9;16.4] | 12.6 [7.4;21.1][1] | 0.201 |
| **Pathology, *n (%)*** | | | | |
| Rhinitis | 117 (95.9) | 55 (98.2) | 64 (97.0) | 0.235 |
| Asthma | 49 (40.2) | 24 (42.9) | 25 (37.9) | 0.576 |
| Conjunctivitis | 41 (33.6) | 17 (30.4) | 24 (36.4) | 0.484 |
| **SCIT period, *n (%)*** | | | | 0.589 |
| Perennial | 89 (84.0) | 43 (86.0) | 46 (82.2) | |
| Pre-seasonal | 17 (16.0) | 7 (14.0) | 10 (17.9) | |
| **SCIT type, *n (%)*** | | | | 0.945 |
| Polimerized | 104 (86.0) | 48 (85.7) | 56 (86.2) | |
| Depot | 17 (14.0) | 8 (14.3) | 9 (13.8) | |
| **Allergen, *n (%)*** | | | | 0.801 |
| Mites | 72 (59.5) | 34 (60.7) | 38 (58.5) | |
| Pollens | 49 (40.5) | 22 (39.3) | 27 (41.5) | |
| **Administrations, number, median *[IQR]*** | 10 [6;19][1] | 11 [7;20] | 7 [5.5;15.0][1] | 0.092 |
| **Duration of treatment, months, median *[IQR]*** | 7 [2;16][1] | 8 [3;18] | 5 [2;14][1] | 0.216 |
| **Immediate reactions, number, median *[IQR]*** | 0[0-2] | 0 [0;3] | 0[0;2] | 0.756 |
| **Late reactions, number, median *[IQR]*** | 0[0-2] | 0[0;2] | 0[0;2] | 0.795 |

[1] Participants that continued SCIT at other Health-Care Units were excluded

When comparing the patients that discontinued SCIT without medical indication with those from the adherent group, no differences were found (**table 1**). Improvement with the treatment was not statistically different between the non-adherent and the adherent groups (73% [n = 41] *vs.* 82% [n = 54], respectively; p = 0.373); both reported a decrease in symptoms of the allergic disease (77% [n = 31] in non-adherent *vs.* 94% [n = 51] in the adherent), medication need (63% [n = 26] *vs.* 61% [n = 33], respectively) and emergency department visits (12% [n = 5] *vs.* 26% [n = 14], respectively).

In the univariate analysis, the presence of family history of allergic disease treated with immunotherapy was associated with a decreased OR of non-adherence to SCIT (OR [95%CI] = 0.31 [0.11-0.88]). In the multiple logistic regression model, none of the tested factors were significantly associated with non-adherence (**table 2**); the model had good calibration (p = 0.269) and predictive power (area under the curve = 0.757).

**Table 2 -** *Odds ratio (OR [95% confidence interval, CI]) of being non-adherent to SCIT (age ≥ 18 years; n = 149). Statistically significant factors are presented in bold*

|  | Unadjusted | | Adjusted§ | |
|---|---|---|---|---|
|  | OR | [95%CI] | OR | [95%CI] |
| **Gender** (male) | 1.39 | [0.66-2.92] | 0.78 | [0.20-3.06] |
| **Age** (≥ 30 years) | 0.91 | [0.44-1.91] | 0.37 | [0.08-1.73] |
| **Scholarship** | 0.266* | | 0.724* | |
|   < 9 years | 1 | | 1 | |
|   9 to 12 years | 2.58 | [0.71-9.35] | 0.97 | [0.13-7.04] |
|   > 12 years | 1.59 | [0.40-6.38] | 2.25 | [0.13-39.62] |
| **Profession** | 0.127* | | 0.417* | |
|   Unemployed | 1 | | 1 | |
|   Student | 0.80 | [0.20-3.16] | 0.79 | [0.05-12.65] |
|   Undifferentiated profession | 2.38 | [0.71-7.97] | 3.31 | [0.44-24.72] |
|   Differentiated profession | 1.39 | [0.35-5.45] | 2.00 | [0.13-31.78] |
| **Family history of allergic disease** | 0.078* | | 0.331* | |
|   Absent | 1 | | 1 | |
|   Yes, no immunotherapy | 0.84 | [0.37-1.91] | 1.24 | [0.30-5.12] |
|   Yes, treated with immunotherapy | **0.31** | **[0.11-0.88]** | 0.38 | [0.08-1.90] |
| **Distance to Hospital**† (> 20 km) | 0.63 | [0.25-1.57] | 0.46 | [0.11-1.87] |
| **Asthma** | 1.23 | [0.60-2.54] | 0.76 | [0.21-2.75] |
| **Rhinitis** | 3.55 | [0.39-32.71] | NI | |
| **Conjunctivitis** | 0.76 | [0.36-1.63] | 0.29 | [0.08-1.02] |
| **Atopic dermatitis** | 0.87 | [0.30-2.52] | 1.97 | [0.36-10.78] |
| **Food allergy** | 2.39 | [0.42-13.54] | NI | |
| **Drug Allergy** | 0.55 | [0.13-2.30] | 0.14 | [0.02-1.19] |
| **SCIT period** (Pre-seasonal *vs.* perennial) | 0.75 | [0.26-2.14] | 0.58 | [0.14-2.49] |
| **Allergen** (Mites *vs.* pollens) | 1.10 | [0.53-2.28] | NI | |
| **Adverse reactions to SCIT** | 1.35 | [0.66-2.77] | 0.97 | [0.25-3.76] |
| **Absence of self-reported SCIT efficacy** | 1.65 | [0.70-3.89] | 0.79 | [0.18-3.53] |

§ Sixty nine individuals were included;
* p-value for trend; † Participants that continued SCIT at other Health-Care Units were excluded; NI - not included
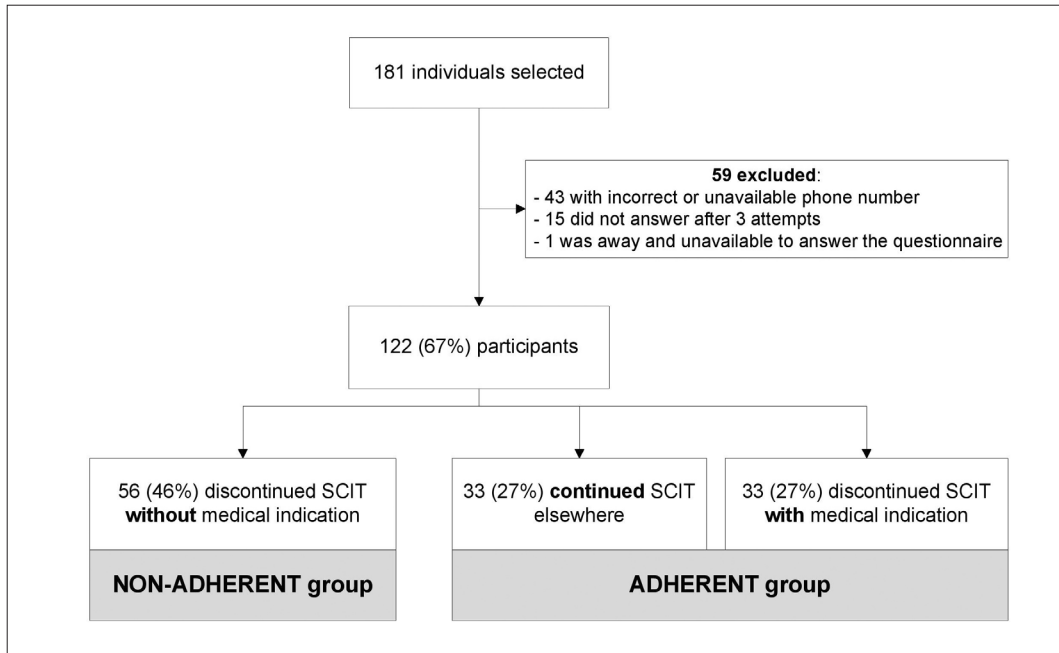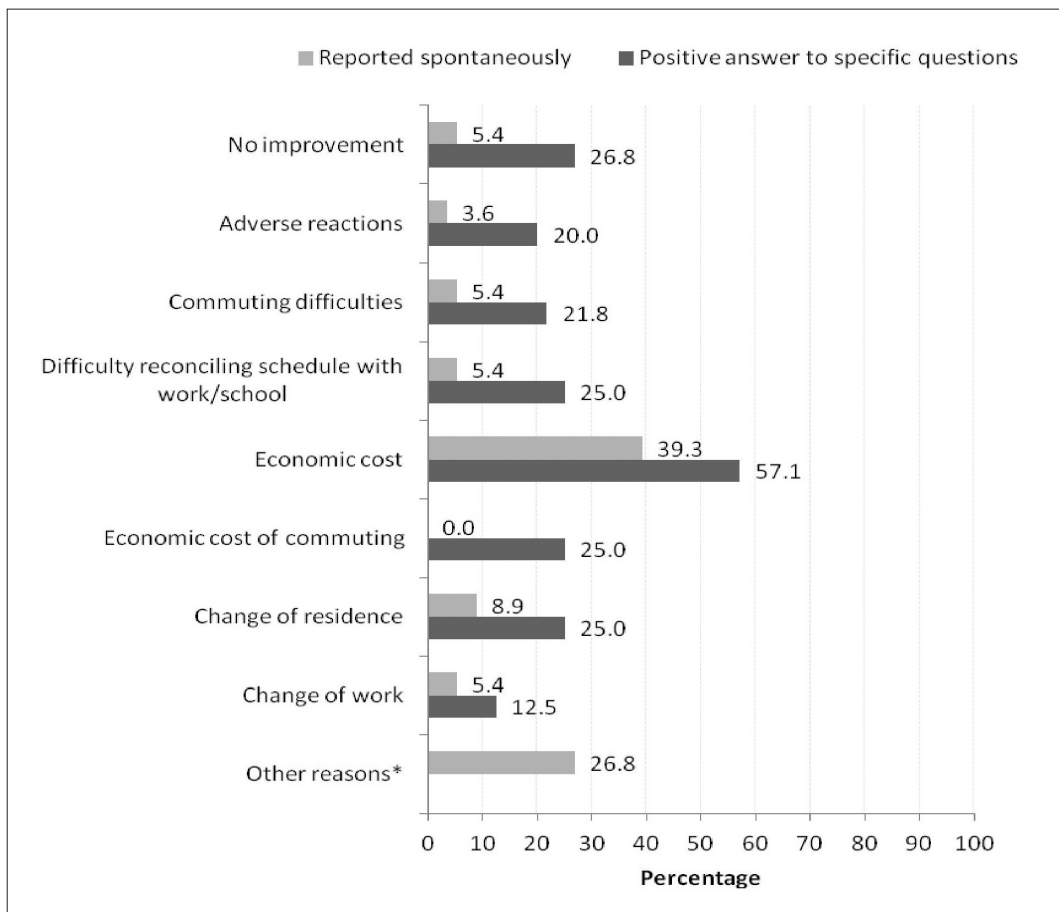
*Figure 1 - Patient selection diagram*



*Figure 2 - Reasons for discontinuing immunotherapy without medical indication obtained by telephonic survey in 56 patients (%). In the survey it was initially asked to state the main reason for discontinuing subcutaneous immunotherapy, labeled as "Reported spontaneously", and latter questioned specific factors that had influenced the decision, labeled as "Positive answer to specific questions"*

*\*Other reasons included: forgetfulness of treatment (7.2%), onset of a new disease (3.6%), difficulty in understanding the treatment (3.6%), thinking that treatment continuation was not necessary (1.8%) and pregnancy (1.8%)*

## Discussion

The main reason for SCIT discontinuation without medical indication was the cost associated with the treatment, which was reported by 59% of the respondents. The high proportion of patients that discontinued SCIT in spite of improvement supports the potential impact of the economical obstacle. Family history of allergic disease treated with immunotherapy was associated with lower risk of non-compliance to SCIT (univariate analysis), however in the multiple logistic regression model none of the evaluated factors/characteristics were significantly associated with non-adhesion.

### Strengths and limitations

This study, to our knowledge, was the first reporting reasons for non-adherence to SCIT in Portugal and one of the few studying personal and SCIT-related characteristics possibly associated with adhesion to treatment (9, 11). Considering that this study was performed at a time of major economic disturbances in Europe, it adds a recent new social reality to the published literature on this topic.

The study design limits the generalization, as it was only performed in one center and with a small sample. Across different countries, immunotherapy cost, funding, organization and real-life practices vary (1), which prevents a straightforward comparison. Moreover, the use of different definitions of non-adherence adds further difficulties. In fact, non-adherence can be defined according to the time when immunotherapy was stopped (usually 3 (8) or 6 months (9, 12) before the study) or considering the number of injections received (usually using < 50% of the target number to define non-adherence). In this study, a time cut-off of 3 months was considered. Recall bias could have been introduced as this was a retrospective telephonic survey and some reasons could have been forgotten at the time of the interview. Only SCIT with airborne allergens was evaluated, as it is the most frequently performed treatment; however, SCIT with other allergens, namely hymenoptera venom, may have different reasons for non-adherence and results cannot be extrapolated to these populations. The inclusion of patients under sublingual immunotherapy (SLIT) could also lead to other findings, as previously reported (13); nevertheless, the difficulties regarding SLIT administration monitoring and the specific characteristics of treatment adhesion restricted their inclusion. Data on economical income of the participants was not obtained, which limits our ability to accurately compare the specific impact of economic factors; however, questioning income in a telephonic survey performed by doctors from the department where the patients are followed could be uncomfortable for the participants.

### Comparison with literature

Specific subcutaneous immunotherapy with airborne allergens is the most widely used immunotherapy in Portugal; at least three years of treatment are required to obtain a favorable clinical and immunological response (4). Non-adherence jeopardizes the benefits of this treatment and its cost-effectiveness (1).

In this study, reasons perceived by the patients for discontinuing SCIT without medical indication were mainly driven by social and economic factors, namely SCIT acquisition and administration expenses, inconvenience associated with commuting to the hospital and difficulty in reconciling their daily life with SCIT administrations. These results differ from most previously published studies where the main reason for immunotherapy drop-out was inconvenience (7, 8, 12, 13), with proportions ranging from 35 to 65% in different settings (7, 8, 13, 14). To our knowledge, few studies reported economic expenses as the most important reason for SCIT discontinuation (15).

In 20% of our patients, adverse events influenced the decision to discontinue SCIT; however it was the primary reason for discontinuation in only 4%. This is in agreement with the previously published impact of adverse events on treatment discontinuation, which was reported as the responsible for 5% to 16% of SCIT withdrawals (8, 13, 15, 16).

Most of the patients that discontinued SCIT in this study (73%) referred an improvement and more than three-quarters would like to restart treatment. This is concordant with the main reason for discontinuing SCIT found in this study (costs related to the treatment) and supports the need of adequate cost-effectiveness and cost-utility studies of SCIT. Immunotherapy, being a long-term and expensive treatment (with a cost ranging from 200€ to 400€/year in Portugal and currently without reimbursement), may reduce other costs related to the treatment of allergic diseases. Hankin et al. demonstrated short-term cost offsets in patients with allergic rhinitis who received immunotherapy (6), however Donahue et al. found that individuals who completed immunotherapy had higher non-immunotherapy related costs (17). A recent systematic review pointed out that cost-effectiveness depends on the long-term clinical benefit and also on the break-even point of cumulative costs between immunotherapy and pharmacotherapy (1). From a clinical point of view, these results highlight the importance of informing patients, before starting immunotherapy, not only about SCIT efficacy, but also SCIT-associated costs and potential inconvenience related with the treatment. In order to reduce treatment drop-outs, the individual and social environments have to be taken into account when starting and following-up a patient under immunotherapy (18). Moreover, it seems that providing some form of funding/reimbursement or lowering the costs of immunotherapy could be essential to promote adherence to the treatment.

Non-adherence risk factors have been studied in case-control (6, 9) and cross-sectional studies (19), using multivariate logistic regression to infer which characteristics are associated with immunotherapy discontinuation. These factors vary according to different countries and settings (6). In a retrospective case-control study in India, having no family history of allergic diseases, missing doses repeatedly, maintaining similar medicine requirements, negative perception of immunotherapy or having allergic conjunctivitis were associated with non-adherence (9). With a similar study design and using a Cox proportional hazard, in the USA, Hankin et al. found variations based on race (Hispanic patients were 1.5 times more likely to discontinue immunotherapy); More et al. reported that non-compliant patients were younger and usually from the active population (8). In a large cross-sectional study in Germany, the strongest predictor for non-compliance in women was the presence of sensitization to food allergens (19). The inconsistency between studies can be due to the divergent population characteristics, study designs or the use of different methods for statistical analysis. In this study, family history of allergic disease treated with immunotherapy was the only factor significantly associated with SCIT adherence in the univariate analysis. As suggested by Mahesh et al. (9), this could be explained by patients' better knowledge of allergic diseases and the need for a long-term treatment to achieve clinical results. In our multiple logistic regression model, this association lost statistical significance, which may be related to the loss of statistical power due to a small sample size.

*Unmet needs*

More evidence is needed from multicenter studies with larger sample and a prospective design, where more detailed information, focusing in all dimensions of adherence (social and economical, health system and treatment-related factors), is collected and assessed together (5). Moreover, future research should investigate the long-term economical impact of SCIT and direct and indirect costs related to the treatment (20). High quality studies exploring cost-effectiveness of treating allergic patients with immunotherapy are lacking (1, 3).

## Conclusion

In this study, economic burden associated with specific subcutaneous immunotherapy was the most relevant factor leading to treatment discontinuation without medical indication. As economical changes are occurring throughout Europe, more attention should be given to their impact in the allergic patient's treatment.

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