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Satisfaction and perceived effectiveness in patients on subcutaneous immunotherapy with a high-dose hypoallergenic pollen extract

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Allergoid; subcutaneous immunotherapy (SCIT); hypoallergenic; high-dose; effectiveness; perceived effectiveness

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Summary
This study was designed to determine the level of satisfaction, tolerance and perceived effectiveness by patients in the first pollen season after starting treatment with Alergovit®. For this purpose, a nationwide, retrospective, multicentre and cross-sectional observational study was carried on 256 patients. Perceived effectiveness by the patients was measured using a visual analogue scale and was clinically significant in 92.4% of the patients. The satisfaction level was evaluated with a specific questionnaire. 32.5% of the patients were totally satisfied with Allergovit® and 48.8% reported a high degree of satisfaction. The treatment was well tolerated by 99.2% of the patients. Our results demonstrate that subcutaneous immunotherapy with Allergovit® is effective and well-tolerated in routine clinical practice.

Introduction

Allergen immunotherapy (AIT) is the only treatment that may affect the natural course of allergic disease and prevent the development of asthma in patients with allergic rhinitis (1). Its efficacy in treating IgE-mediated allergic rhinoconjunctivitis and bronchial asthma has been clearly demonstrated (2,3).
To achieve the greatest possible efficiency, it is recommended to perform AIT for at least 3 years and to start it in an early stage of disease. Moreover, the treatment schedule should be convenient for patients in order to get a good treatment adherence (4).
Matricardi *et al.* (5) recently published a comparative review of various meta-analyses, which included at least 5 double-blind, randomised, placebo-controlled studies, with the aim of assessing the short-term efficacy of both symptomatic medication and subcutaneous immunotherapy (SCIT) for the treatment of seasonal allergic rhinitis. The authors concluded that, based on nasal or total symptom scores, SCIT is at least as effective as symptomatic medication in patients with seasonal allergic rhinitis in the first pollen season after the start of therapy (5).

Short-term efficacy of subcutaneous high-dose hypoallergenic pollen extracts (Allergovit®) as well as its safety using up-dosing cluster schedules, has been widely demonstrated by several previous studies (6-8).

Nevertheless, there is a clear need to supplement the results from clinical trials with "real-life" studies to provide us with specific effectiveness and safety data under routine clinical practice conditions, in addition to information on other subjective aspects such as degree of satisfaction with the treatment, since this will affect adherence to (4,9) and, consequently, the effectiveness of the therapy (10,11).

A German prospective, observational study was recently published which confirms effectiveness and safety of SCIT with Allergovit® under routine clinical practice conditions but provides no data on subjective aspects perceived by the patients (12).

The objective of this study was to determine the level of satisfaction, tolerance and effectiveness as perceived by patients on treatment with Allergovit® after the first pollen season, within the routine clinical practice criteria of the participating investigators.

Materials and Methods

Allergen extract composition

The tested product, Allergovit® (Allergopharma KG, Reinbek, Germany), is a standardised high-dose hypoallergenic aluminium hydroxide-adsorbed depot preparation modified with formaldehyde. This pollen allergen preparation is available in two different concentrations: strength A (1,000 TU/ml), and strength B (10,000 TU/ml). The manufacturer's recommended maintenance dose is 0.6 ml of B strength (6,000 TU). The major allergen contents in strength B are 41.66 μg_{eq}/ml group 5 allergen in *Graminaceae* formulations and 18.33 μg_{eq}/ml Ole e 1 in 100% *Olea europaea* formulations.

Study design

This was a nationwide, retrospective, multicentre, cross-sectional observational study with the participation of 29 investigators distributed across 7 Autonomous Regions in Spain. It was approved by the ethics committees of the participating hospitals and notified to the Spanish Agency of Medicines and Medical Devices (AEMPS). It had several objectives, the primary one being to determine the level of satisfaction, adherence, tolerability and perceived efficacy of patients on Allergovit® treatment. The secondary objective was to examine demographic and clinical variables that could be related to patient satisfaction with Allergovit® treatment.

Patients should have a previous diagnosis of pollen-induced IgE-mediated rhinitis and/or bronchial asthma before being included in the study. The diagnosis of allergic rhinitis was based upon the concordance between the typical symptoms of allergic rhinitis (rhinorrhea, sneezing, nasal obstruction and pruritus) and diagnostic tests (demonstration of allergen-specific IgE in the skin (immediate-hypersensitivity skin tests) or the blood (specific IgE).

A diagnosis of asthma was made following a clinical assessment of symptoms (dyspnea, cough, intermittent and variable wheeze, chest tightness, and shortness of breath) and demonstration of variable airflow obstruction, which was assessed by performing pre-bronchodilator and post-bronchodilator spirometry. An improvement of forced expiratory volume in 1 second (FEV1) and/or forced vital capacity (FVC) of greater than 12% or 200 mL was considered a significant BD response, consistent with asthma.

Moreover, since the focus of this study was to determine summary statistics characterizing the study population, no calculation to determine sample size was performed. It was considered appropriate to include 250 patients who were representative of the Spanish population. To do so, each investigator who participated in the study had to consecutively include roughly 10 patients satisfying the inclusion / exclusion described above; it was estimated that it would be appropriate to involve a minimum of 25 investigators.

During the observational period, the investigators gathered data from those patients who met the inclusion criteria for the study (age 5-65 years, pollen-induced IgE-mediated rhinitis and/or bronchial asthma) and who, as part of routine practice, had been treated with Allergovit®, and had a follow-up visit in the first 6 months of treatment, for those on a perennial administration protocol; or who had completed at least one therapeutic cycle, if the administration was preseasonal.

For the evaluation of perceived effectiveness, patients assessed their conditions on a visual analogue scale from 1 (worst condition) to 100 (best condition). A clinically relevant improvement was defined as improvement by at least 20 points between the self-assessments made before they started the treatment and at the time of the evaluation (7).

In addition, effectiveness was also measured as a continuous variable resulting from the difference between state of health at the time of the study and before starting the treatment, based on the data collected on the patient chart review.

Patients' satisfaction with SCIT with Allergovit® was evaluated based on a specific questionnaire (included in the appendix section). A paper Case Report Form (CRF) including several sociodemographic variables (patient's date of birth, educational level, occupational status, nationality and marital status) and clinical variables (previous treatments, family history, severity and Allergovit® treatment) was prepared, also including treatment adherence.

The variables included in the questionnaire were: the need for treatment to be administered subcutaneously and for this to be done by a healthcare professional, the impact having to go to the health centre had on subjects' daily routine, the level of improvement in symptoms with treatment and overall satisfaction with treatment. A Likert scale was used to objectively evaluate the questionnaire's variables, with 0 representing strongly unsatisfied and 5 totally satisfied.

Data analysis and statistical techniques

A descriptive analysis was performed on the whole sample, calculating the mean and standard deviation (SD) as descriptive statistics for the quantitative variables with normal distribution, and median and interquartile range if the distribution was not normal. Proportion was used for categorical variables.
The data collected in the CRFs were entered into a database using simple data entry for statistical analysis. The database was validated to ensure its quality prior to the start of the analysis, first by using a frequency analysis to detect extreme or impossible values and then by analyzing any intra-CRF inconsistencies. Bivariate association techniques were used to study the relationship between the main dependent variables (satisfaction, tolerability and effectiveness) and the explanatory variables such as patient age, diagnosis and the allergy specialist's workplace. The Pearson correlation coefficients were calculated for dependent variables with sufficient sample size (designing multivariate models to determine the associated factors).
The level of significance considered in the statistics calculated was $p < 0.05$.

Results

Between September and November of 2012, data were collected from patients diagnosed with pollen-induced IgE-mediated rhinitis and/or bronchial asthma who had started treatment with Allergovit® and met the inclusion and exclusion criteria stated in the protocol.
A total of 256 patients were included. In terms of diagnosis, 246 of the patients (96.5%) had rhinitis and 163 patients (63.9%) had bronchial asthma. 81.6% of the SCIT preparations contained grasses, 36.6% olive and 7% other allergens (trees and weeds) (table 1).

Perceived effectiveness by the patients

Patients assessed their condition on the visual analogue scale as improved by mean 33.5 points (40 to 73.5 points; $p < 0.001$), improving by between 30 and 50 points in 51.6% of the total population (132 patients) and being clinically significant (improving by over 20 points) in 92.4% (234 patients) (**figure 1**).

***Table 1** - Demographic characteristics of patients and quality of life questionnaire results for the treatment given (scale from 0 to 5).*

Characteristics		
Patients, n (%)	256 (100%)	
Sex, n (%)		
Women	133 (51.8%)	
Men	123 (48.2%)	
Age, years, mean (SD)	27 (13.8)	
Diagnosis of allergic rhinitis, n (%)	246 (96.5%)	
Rhinitis classification		
Mild intermittent	31 (13.7)	
Moderate / severe intermittent	127 (56.2)	
Persistent	29 (12.8)	
Moderate / severe persistent	39 (17.3)	
Diagnosis of allergic bronchial asthma, n (%)	163 (63.9%)	
Bronchial asthma classification (total n: 148)		
Episodic / intermittent	128 (86.5)	
Persistent	20 (13.5)	
SCIT Composition, n (%)		
Grasses	144 (56.5%)	
Grasses + Olea	65 (25.5%)	
Olea	29 (11.4%)	
Others	17 (6.8%)	
Patients' satisfaction with the treatment based on asthma and rhinitis diagnosis	Moderate / Not satisfied (%)	Satisfied (%)
Rhinitis	33.3	35.5
Asthma	66.7	64.5
Total	100	100
Patients' satisfaction with the treatment given (scale 0-5)	General Population[1] Mean (SD)	
The healthcare professional who administers	4.3 (0.7)	
Improvement of symptoms	4.1 (0.7)	
The frequency (number of visits to be treated)	3.3 (1.1)	
Displacement (impact on daily life)	3.6 (1.2)	
Administration by puncture	3.2 (1.1)	
Physical discomfort following jab	3.1 (1.2)	
Overall satisfaction with treatment	4.1 (0.8)	

SD: standard deviation.
[1]Results of the questionnaire of patient satisfaction with the treatment given by satisfaction scale of 0 (very unsatisfied) to 5 (very satisfied).

***Figure 1** - Change in perceived effectiveness by patients between pre-treatment and post-treatment pollen season. Bars represent the individual improvement for each patient and the two vertical lines reflect the values in the pre-treatment and post-treatment pollen season, (p < 0.001). SD: Standard deviation.*

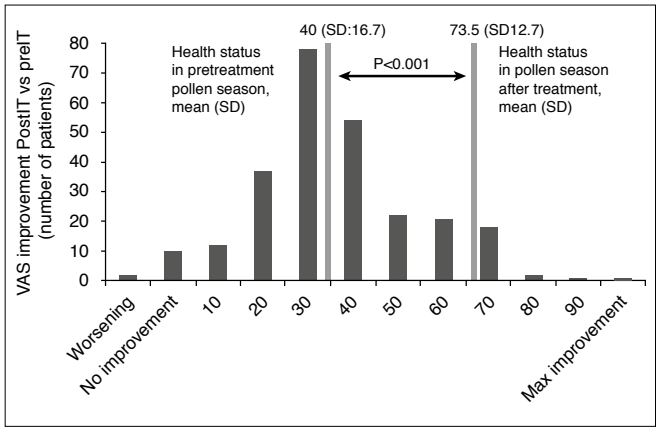
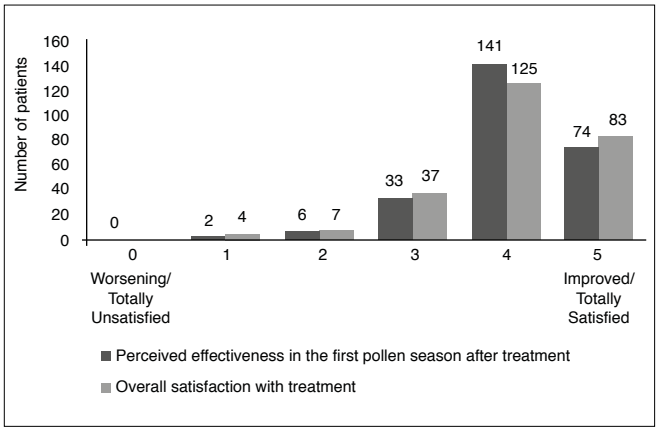


***Figure 2** - Perceived effectiveness in the first pollen season after treatment, and overall satisfaction with treatment.*
84% (215 patients) reported satisfaction or totally satisfied with improvement of symptoms. Pearson test 0.49; p < 0.001.



Satisfaction questionnaire

Overall patients' satisfaction with Allergovit® was close to very satisfied (mean 4.1; SD 0.8); 32.5% (83 patients) were totally satisfied (score 5) with Allergovit® and 48.8% (125 patients) reported a high degree of satisfaction (score 4) (**figure 2**).
In terms of degree of satisfaction, the most highly-rated aspect was the administration of the treatment by a healthcare professional, with 252 patients (98.4%) rating this positively, followed by the perceived clinical improvement of symptoms after having the treatment compared to before (mean 4.1; SD 0.7) (**table 1**).
According to **figure 2**, clear clinical improvement was reported by 84% of the patients (215 patients), with a positive correlation found between this variable and "Improvement of my allergy symptoms with this treatment" scale, using Likert scale to evaluate the correlation, taking into account the difference between the health status before and after treatment with Allergovit® (Pearson's Correlation: 0.49; p < 0.001).
There was also a positive correlation of satisfaction with the treatment's degree of effectiveness (coefficient of correlation: 0.34, p < 0.001).
The most critical aspects for the patients were those relating to discomfort following subcutaneous administration (mean 3.2; SD 1.1) and the associated to local adverse reactions (mean 3.1; SD 1.2).
However, in terms of the repercussions on daily activities of having to make the trip, 158 patients (61.7%) stated that it was no trouble at all (Score 4 and 5) and 61 patients (23.85%) said that it was not an issue (Score 3).

The treatment was well tolerated by most of the patients included in the study (254 patients, 99.2% of population). Only 2 patients reported to suffer "adverse events problems / intolerance", and that was the reason of treatment discontinuation. Due to this number of patients (n = 2), no specific exploratory analysis was developed.

5. Discussion

There are some randomised clinical trials (RCT) confirming the effectiveness and safety of SCIT with Allergovit® (6,7,18,20). In particular, it is worth mentioning the published studies that demonstrate the sustained long-term effectiveness of Allergovit® grass pollen in children, even for up to 12 years after having stopped the treatment (21,22).
Our study is the first Spanish study that tried to assess, under routine clinical practice conditions, the effectiveness, satisfaction and tolerability perceived by the patients, while also tried to confirm the effectiveness and safety data previously obtained in clinical trials conducted with this same high-dose hypoallergenic extract of pollen allergens.
Despite the limitations inherent to retrospective observational studies, they produce data on effectiveness and different variables in the context of routine clinical practice, providing useful and important information to supplement the RCT. With this in mind, The Brussels Declaration on Asthma recently announced the need for pragmatic studies that collect evidence from routine clinical practice (23).
One limitation of this study is in relation to the bias of memory the influence of other disorders which might affect all of the

questions, particularly those about general health before and after the treatment. In an attempt to minimise the influence of this limitation, the analysis of effectiveness focused on the responses to the question on improvement or worsening of the allergic symptoms after the treatment.

In this project, the short-term effectiveness observed after SCIT with Allergovit® in various clinical trials (6,7,8,17) could be aligned with what was observed from the perspective of the patients, since there was an improvement of 33.5 points on the visual analogue scale (from 0 to 100 points). We could therefore hypothesize that the effectiveness of the treatment was perceived after administration of Allergovit®, since the health of the patients improved significantly ($p < 0.001$). In terms of improvement as perceived effectiveness by the patient (at least a 4 on the 0 to 5 scale), the treatment was effective in 4 out of every 5 patients. Therefore, it should be emphasised that a high proportion of patients (over 96%) in the trial on hand reported to be very satisfied with the treatment, which could be related to increasing the adherence to SCIT, which in turn is a precondition for the aforementioned effects during and after SCIT.

More specifically, the aspect which, for the patient, represented greater satisfaction with the treatment was the fact that the subcutaneous injection was administered by a healthcare professional. The fact that patients have to attend their medical centre periodically to have Allergovit® administered, far from being an inconvenience, could mean that they are better monitored and have better control and follow-up of their condition by a specialist, and this in turn could encourage adherence to treatment. A recently published study demonstrated that adherence to treatment is significantly higher, and in line with patients treated with conventional immunotherapy, when the patient is monitored quarterly and not annually as in usual routine practice with patients who are prescribed AIT (4).

In this study, the effectiveness and tolerance results expected by patients could be confirmed. Moreover, patients treated with Allergovit® reported to be satisfied with the treatment, while the route of administration could not represent any inconvenience in terms of the desired adherence to treatment. The general level of patient satisfaction was positively associated with the improvement in their health after receiving SCIT with Allergovit®, and this was even greater when it was administered by specialist healthcare personnel.

VAS improvement could be comparable to that found in the post-marketing surveillance study by Hoheisel *et al.* (17).

In conclusion, the results obtained in this study show that subcutaneous immunotherapy with high-dose hypoallergenic pollen preparations could be effective and well-tolerated in "real-life" practice. The patients' conditions improved noticeably, with an effect in the first pollen season after starting treatment.

Appendix

Questionnaire to collect the patient satisfaction

Each of the following questions was answered by a Likert scale, with 0 representing strongly unsatisfied and 5 totally satisfied.

1. Which is your current satisfaction if the drug administration is done by a health professional?
2. Which is your current satisfaction if the drug administration is done by an injection?
3. Which is your current satisfaction with the treatment administration frequency (number of medical visit needed for the injection)?
4. My allergic symptoms have been improved or are worst with this treatment.
5. Which is your current satisfaction with the physical discomfort after the injection?
6. Choose from 0 (a lot) to 5 (nothing) the impact on your daily activities (quality of life, the need to travel, to receive the treatment, etc.)

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Conflict of interest

The authors declare that there are no conflicts of interest.

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