

Diagnosis and treatment of grass pollen-induced allergic rhinitis in specialized current clinical practice in Spain

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ABSTRACT

Allergic rhinitis (AR) is the leading cause of consultation at the allergy specialist's office, but detailed, reliable, and validated clinical data on this condition are limited. This study was designed to define the clinical features, diagnostic methods, and therapeutic approaches of patients with AR induced by grass pollen in Spain. Two hundred twelve specialists participated in a multicenter, observational, epidemiologic, questionnaire-based study. Each investigator had to recruit at least two patients consulting for the first time and with a diagnosis of AR induced by grass pollen. Five hundred twenty-four patients (52% men; mean age, 29.3 years) with grass pollen-induced rhinitis (mean disease duration, 8.7 years) were recruited. Just 18.4% of patients reported that their symptom status had improved since the beginning of the condition, 89.4% had moderate-severe rhinitis (Allergic Rhinitis and Its Impact on Asthma classification) and 35.1% had concomitant bronchial asthma. For 52.1% of patients, control of symptoms with previous drug treatment was poor. Most of the patients were polysensitized to other pollens (sensitization to olive tree pollen, 57.1%). Oral antihistamines (97.3%) and nasal corticosteroids (82.3%) were the most frequently prescribed drugs and 43.1% of patients received specific immunotherapy. The clinical profile for the majority of Spanish patients consulting an allergy specialist for AR induced by grass pollen corresponds to a young adult with a lengthy moderate-severe rhinitis, often accompanied by bronchial asthma. Their symptoms progressively worsen and rhinitis is poorly controlled by symptomatic treatment. Oral antihistamines and nasal corticosteroids are the most frequently used therapeutic approaches and less than one-half receive specific immunotherapy.

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The prevalence of allergic rhinitis (AR) is increasing worldwide, and particularly in the western countries.^{1–3} According to data from different studies, the prevalence of AR in Spain is 15.5% in children⁴ and 21.5% in adults.⁵ In two Spanish surveys (Alergológica 1992 and Alergológica 2005),^{6,7} among patients attending an allergy service in Spain in 1992 and 2005, the prevalence of diagnosed allergic rhinitis was 52.0 and 55.0%, respectively. *Dermatophagoides pteronyssinus* and grass pollen were the single allergens with greatest prevalence in the study by Navarro *et al.*,⁷ with a prevalence of 39 and 35%, respectively.

In addition to its high prevalence, AR is a major health problem with an important impact on quality of life^{8–11} and socioeconomic burden.^{9,12} Furthermore, AR has been identified as a risk factor for asthma.^{13–15}

Besides patient education and environmental control measures, there are two main therapeutic strategies for AR: a symptomatic approach, including many drugs that improve and relieve symptoms but do not prevent their recurrence after discontinuation, and an allergen-specific immunotherapy (SIT) approach, which acts on the immune system to modify the response to the allergen responsible for the illness, relieving symptoms, reducing drug intake, and preventing evolution toward worse stages of the disease, such as polysensitization and/or allergic asthma.¹

Despite the high prevalence of AR and its well-known pathophysiology,¹⁶ few studies have investigated the diagnostic procedures used by specialists^{6,7,9} or the real rates of application of the different treatment strategies in routine clinical practice. The Proyecto Epidemiológico relacionado con el Tratamiento de la Rinitis Alérgica (PETRA) Study (Epidemiologic Survey of Therapeutical Approaches to Allergic Rhinitis) was conceived to assess patients with AR induced by *Dermatophagoides* spp. and grass pollen, the most common sources of allergy all over the world, and to evaluate the strategies used for diagnosis and treatment in Spain. The analysis of the results for the overall population has already been reported.¹⁷ In this article, we show the results for AR induced by grass pollen.

MATERIALS AND METHODS

Investigators and Patients

Investigators (mainly allergists and pediatricians specialized in allergy) from all over Spain participated

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in the study. They were randomly selected from public and private clinics from all regions of Spain, based on quotas reflecting the population of each province and in accordance with the prevalence of sensitization to grass pollen in the different regions of Spain. The study was conducted between November 2007 and May 2008 at allergy outpatient clinics, under standard medical practice conditions and as part of the clinical practice of each investigator.

The investigators who agreed to participate in the study had to recruit at least two consecutive patients of both sexes, aged ≥ 5 years, consulting the specialist for the first time, with a diagnosis of AR (with or without asthma) induced by grass pollen. Sensitization to grass pollen was determined by positive skin-prick test (SPT) and/or specific immunoglobulin E (IgE) >0.70 kU/L (CAP System, Phadia, Sweden). Patients participating in other studies or clinical trials at the time of the study were excluded. Patients who met all of the selection criteria were included, regardless of whether they were receiving treatment for AR or not. The methodology of the PETRA study has already been described.¹⁷

The study fulfilled the principles of the Declaration of Helsinki regarding medical research in humans (World Medical Association, 2004), and confidentiality of patients was strictly maintained according to the Spanish legal requirements. An accredited Clinical Research Ethics Committee (Hospital Clinic, Barcelona, Spain) approved the study protocol. Written informed consent was obtained before participation in all cases.

Study Design

An epidemiologic, observational, cross-sectional, multicenter study was performed in allergy outpatient clinics in Spain. Sample size was established according to the guidelines of the International Conference on Harmonization¹⁸ in relation to the study objectives. According to Navarro's study⁷ and Agrupación de Investigación y Marketing Farmacéutico SIT data, $\sim 10\%$ of patients with AR received sublingual immunotherapy (SLIT) at specialized outpatient health care centers. Administration of SLIT was chosen to estimate the sample size. Accordingly, and positing an infinite population size, a sample size of 865 individuals per treatment was estimated to provide $\pm 2\%$ accuracy in estimating the proportion of patients being treated with SLIT, with a 95% confidence interval. The final sample size of 524 evaluable patients provided $\pm 3.5\%$ accuracy for estimating the proportion of patients being treated with SLIT (found to be 18.3%), with a 95% confidence interval.

Variables

To describe the profile of patients with AR, sociodemographic and general clinical data were collected on the questionnaire-based case report form. Data on

characteristics of AR were also recorded, including severity (normal/alterd sleep, normal/alterd daily activities/sport/leisure, normal/alterd work/school activities, and absence/presence of troublesome symptoms) and frequency of symptoms (intermittent, symptoms <4 days/week or <4 weeks; persistent, symptoms ≥ 4 days/week and ≥ 4 weeks) according to the Allergic Rhinitis and Its Impact on Asthma classification,^{1,19} illness evolution (much better, better, equal, worse or much worse) and sensitization to other allergens (if present). The impact of the rhinitis on overall health status was assessed using a 100-mm visual analog scale (0 = no impact and 100 = maximum impact). In addition, presence of other comorbid illnesses was recorded, in particular, diagnosis of asthma severity (intermittent, mild persistent, moderate persistent, and severe persistent) and control (controlled, partly controlled, and uncontrolled) according to the Global Initiative for Asthma classification.²⁰ In addition to recording the patients' sociodemographic and clinical data, investigators answered questions regarding the strategies used for diagnosis and treatment, the use of environmental control measures, pharmacotherapy, allergen SIT, and/or patient education and their reasons for using or not using them.

Statistical Analysis

A single set of evaluable patients was used for all of the analyses. All data were analyzed using descriptive statistics. The mean, SD, and range were calculated for quantitative variables. Categorical variables were described using absolute and relative frequency tables. The SAS Statistical Package Version 9.1 (SAS Institute, Inc., Cary, NC) was used.

RESULTS

Evaluable Patients

Data were recorded for 579 patients with AR to grass pollen recruited by the 212 specialists participating in the study from 149 centers from all the regions of Spain. Of those, 55 patients (9.5%) who failed to meet the study's criteria were excluded. The main reason for exclusion was lack of confirmation of allergic sensitization by positive SPTs and/or specific IgE >0.70 kU/L to grass pollen (37 patients, 6.4%). Other reasons for exclusion were patients not consulting the specialist for the first time ($n = 2$), patients without a diagnosis of AR to grass pollen ($n = 12$), and patients participating in another study ($n = 6$).

Patients' Characteristics

Patients' most important clinical and demographic features are shown in Table 1. Male patients accounted for 51.8% of subjects, with a mean age of 29.3 years (range, 5–71 years). Most patients were recruited in public health care centers (64.4%) and were referred to

Table 1 Patients' demographic and clinical characteristics

	Mean (SD) [range]/n (%)
Age (yr) (n = 519)	29.3 (12.8) [5–71]
Gender (n = 512)	
Male	265 (51.8)
Female	247 (48.2)
Home area (n = 520)	
Rural	144 (27.7)
Urban	376 (72.3)
Pets (n = 522)	
No	360 (69.0)
Yes	162 (31.0)
Disease duration (yr; n = 470)	8.7 (7.9) [0–46]
Health status (VAS)* (n = 523)	59.4 (21.7) [0–100]
ARIA classification# (n = 511)	
Intermittent–mild	26 (5.1)
Persistent–mild	28 (5.5)
Intermittent–moderate	90 (17.6)
Persistent–moderate	292 (57.1)
Intermittent–severe	2 (0.4)
Persistent–severe	73 (14.3)
Other allergic diseases§ (n = 524)	
Conjunctivitis	338 (64.5)
Bronchial asthma	184 (35.1)
Asthma GINA classification (n = 184)	
Intermittent	112 (60.9)
Mild–persistent	40 (21.7)
Moderate–persistent	32 (17.4)
Severe–persistent	0 (0.0)

*VAS graded from 0 to 100 mm, 0 indicating the best health status and 100 indicating the worst health status.

#ARIA classification modified according Valero et al.¹⁵

§Frequency of >5%.

ARIA = Allergic Rhinitis and Its Impact on Asthma; GINA = Global Initiative for Asthma; VAS = visual analog scale.

the specialist by their primary care physician (58.2%). The mean duration of the AR disorder was 8.7 years (SD, 7.9 years); illness duration was 2 years or more in 94.3% of patients. Moderate–severe rhinitis was diagnosed in 89.4% of patients, being persistent in most cases (71.4%).

Only 18.4% of patients perceived that their symptoms had improved (much better or better) since the beginning of AR. For the rest of patients, severity of

symptoms was equal (27.9%), worse (47.1%), or much worse (6.6%) than at the onset of illness.

Comorbidity of Asthma and Other Diseases

At least one additional allergic disease other than AR was recorded in 413 patients (78.8%). The most frequent other allergic disease was conjunctivitis, found in 338 patients (64.5%). Bronchial asthma was present in 184 patients (35.1%). According to the Global Initiative for Asthma classification, bronchial asthma was intermittent in the majority of patients (112, 60.9%), although it was mild–persistent in 40 (21.7%) and moderate–persistent in 32 (17.4%) patients. In addition, bronchial asthma was not sufficiently controlled in 44 of the 140 patients evaluated (31.4%): it was partially controlled in 31 (22.1%) and uncontrolled in 13 (9.3%). Forty-one patients (7.8%) had some other additional nonallergic diseases.

Symptoms

The symptoms with the highest mean intensity on a scale from 0 to 10 during the pollen season were nasal obstruction (mean, 7.1, SD, 2.2) and nasal drip (mean, 7.0; SD, 2.1). The symptoms appeared most frequently in April, May, and June and reached their highest intensity at this time. For 52.1% of patients, control of symptoms with pharmacologic treatment was poor (fair, bad, or very bad).

Diagnostic Strategies

SPT was performed for all patients. Total immunoglobulin IgE was measured in 34.4% of patients, specific IgE in 35.3%, and specific IgG in 2.7%. Component-resolved diagnosis detecting specific IgE to rPhl p1, rPhl p5, and/or nOle e1 was performed in 5% of patients. Monosensitization to grass pollen, detected by SPT, was present in 14.9% of patients and the rest (85.1%) showed polysensitization to other allergens—76% to other pollens, above all to olive tree pollen (57.1%), and 43% to mites, molds, or dander—(Table 2). Additionally, clinical examination, respiratory auscultation, rhinoscopy, and spirometry procedures were performed in 84.8, 70.9, 58.5, and 37% of patients, respectively.

Therapeutic Strategies

Table 3 shows the distribution of treatment strategies used. Environmental control measures and patient education were recommended for most patients (91.4 and 87.6% of patients, respectively). Drug symptomatic treatment was prescribed for all patients (100.0%), oral antihistamines (510 patients, 97.3%), and topical intranasal corticosteroids (431 patients, 82.3%) being the most frequent.

Table 2 Allergen sensitization detected by SPT in patients with allergic rhinitis induced by grass pollen

Allergen	n (%)
Grasses	524 (100)
Olive tree	299 (57.1)
<i>Plantago</i>	140 (26.7)
Cypress	136 (26.0)
Plane tree	134 (25.6)
<i>Salsola</i>	86 (16.4)
<i>Artemisia</i>	79 (15.1)
<i>Parietaria</i>	58 (11.1)
Birch	13 (2.5)
Mites	122 (23.3)
Dog	110 (21.0)
Cat	98 (18.7)
<i>Alternaria</i>	29 (5.5)
Cockroach	9 (1.7)

Table 3 Strategies of treatment for allergic rhinitis induced by grass pollen

	n (%)
Environmental control measures	479 (91.4)
Patient education	459 (87.6)
Drug symptomatic treatment	524 (100)
Oral antihistamines	510 (97.3)
Nasal corticosteroids	431 (82.3)
Montelukast	86 (16.4)
Nasal antihistamines	68 (13.0)
Nasal vasoconstrictors	36 (6.9)
Chromones	17 (3.2)
Parenteral corticosteroids	12 (2.3)
Oral corticosteroids	3 (0.6)
Nasal anticholinergic	1 (0.2)
Other	1 (0.2)
Specific immunotherapy	226 (43.1)*
Subcutaneous (native)	82 (15.6)
Subcutaneous (allergoids)	49 (9.4)
Sublingual	96 (18.3)

*Two types of immunotherapy were specified for one patient simultaneously.

Oral antihistamines included principally desloratadine (26.9%), ebastine (24.8%), rupatadine (18.7%), and levocetirizine (17.9%); topical intranasal corticosteroids were mainly mometasone (43.4%), fluticasone (25.6%), and budesonide (23.7%); and the most frequent topical nasal antihistamines used were azelastine (60.3%) followed by levocabastine (38.1%). Allergen SIT was prescribed in 226 patients (43.1%), by subcutaneous route in 57.7% (native extracts,

36.1%; allergoids, 21.6%) and by sublingual route in 42.3% (Table 3).

The administration schedule varied according to the route of administration; it was perennial in most patients (85.9%) using native depot extracts by subcutaneous route, but was mostly seasonal (71.3%) in the case of the sublingual route. When scheduled as seasonal, the mean treatment duration was ~5 months. Vaccines were composed by grass pollen alone in 56% of patients, by grass pollen and olive tree pollen in 32.5%, by grass pollen combined with other allergens in 6.8%, and by other allergens in 4.7% of patients.

DISCUSSION

The PETRA study is the most exhaustive study ever conducted of the diagnostic and therapeutic procedures applied by specialists (mainly allergists) in the management of patients with AR due to grass pollen in Spain. Two previous surveys have been performed in this country—Alergológica 1992⁶ and Alergológica 2005⁷—but the PETRA study is the first to focus on AR due to grass pollen with patients in the specialist setting and also the first to provide full information on all diagnostic and treatment strategies used. The results of this observational study in 524 patients with AR to grass pollen in Spain confirm the importance of this increasing health problem: most patients are classified as having persistent moderate–severe rhinitis, with an illness average duration of 9 years; they express dissatisfaction with their current symptomatic treatment because of the lack of efficacy; and around one-third (35%) present bronchial asthma not always well controlled. These findings corroborate those of the study by Navarro *et al.*⁷ in which time of duration of illness was >10 years in 30% of patients and 37% presented asthma.

Comparing our study (performed by specialists) with another one conducted in a primary care setting,⁹ we can see differences in duration (5.8 years versus 8.7 years) and severity (moderate–severe, 67% versus 89.4%) of the rhinitis in these two environments. Taking into account that the patients of the PETRA study consulted the specialist for the first time, these paradoxical findings (a lengthy and more severe rhinitis attended by the specialist) may be explained, in part, by an excessively long time since onset of symptoms until referral to a specialist for an earlier specific diagnosis and treatment.

This study also provides valuable information about the current strategies used to diagnose patients with AR in routine clinical practice. Some studies^{21,22} have suggested that component-resolved diagnosis (CRD) detecting specific IgE against recombinant allergens can help to provide an accurate diagnosis of reactivity to individual allergens and thus help in the design of

more efficacious allergen-based immunotherapy strategies. Nonetheless, our study shows that CRD was only used in 5% of patients. Considering that 57.1% of them were found to be sensitized simultaneously to grass and olive tree pollen and the difficulty of ascertaining the etiology of the AR in these cases, the potential usefulness of CRD should probably be taken into account. Finally, Allergic Rhinitis and Its Impact on Asthma guidelines also recommend checking for asthma, especially in patients with severe and/or persistent rhinitis, but we found that the methods that most enhance diagnostic confidence for asthma—i.e., spirometry and peak expiratory flow²⁰—were performed in only 37% and 2.9% of patients, respectively.

Our study also offers exhaustive, updated information on the use of the options available to treat patients with AR due to grass pollen in Spain. Although nasal corticosteroids are considered the most effective treatment for AR,²³ antihistamines were the drugs most frequently prescribed (97.7%). In 80% of cases both drugs (antihistamines and nasal corticosteroids) were used concomitantly, although there is no evidence, at least in seasonal AR, of any extra benefit of adding an antihistamine to a nasal corticoid.^{24,25} The combination was probably used because, in accordance with the treatment guidelines that recommend the addition of an antihistamine only when nasal corticosteroids do not produce the desired effect,^{1,26} 9 of 10 patients had moderate-severe AR and 1 of 2 did not have a good response to pharmacologic treatment used before the patient visited the specialist.

The use of allergen SIT in the present study in 226 patients (43.1%) is higher than that observed in the Spanish study mentioned previously⁷ (31% of patients). However, although in the present study most patients had moderate-severe AR, and despite the evidence of the preventive efficacy of SIT against asthma,^{27,28} around 60% of patients were not yet receiving SIT treatment. With regard to seasonality, subcutaneous immunotherapy administration was mainly perennial, and SLIT administration was mainly pre-seasonal or pre-seasonal. Perennial administration of SLIT in a seasonal disease, such as AR due to grass pollen, might negatively affect compliance with treatment, and probably for this reason its administration is more often seasonal. In any case, the overall review of the literature on SLIT suggests that a pre-seasonal regimen, starting at least 8 weeks before the pollen season, is the best choice for pollen SLIT.²⁹

In conclusion, this study reveals that the clinical profile for the majority of Spanish patients consulting a specialist for AR induced by grass pollen corresponds to a young adult with lengthy moderate-severe rhinitis. Although their symptoms worsen progressively and rhinitis is poorly controlled by previous drug treatment, oral antihistamines and nasal corticoste-

roids are the most frequently used therapeutic approaches, with less than one-half of patients receiving allergen SIT. Furthermore, the results from this extensive study evidence the need to educate physicians and the public about the need for treatment of AR. The education of the public about AR would be helpful to enable them to recognize AR symptoms and their consequences and to encourage those with AR to seek medical attention and follow their management program.

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