

ORIGINAL ARTICLE

Airways Disease

Molecular sensitization patterns and influence of molecular diagnosis in immunotherapy prescription in children sensitized to both grass and olive pollen

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Abstract

Background: The overlapping grass and olive pollen seasons in Spain and the phenomenon of cross-reactivity can make it difficult to determine the true causative agent of seasonal allergic rhinitis when only skin prick tests with whole extracts are used. The aim of the GRAMOLE study was to determine sensitization patterns to the major grass and olive pollen allergens detected using specific recombinant IgE and to explore how this knowledge affected physicians' choice of allergen-specific immunotherapy.

Methods: Epidemiological, observational, multicenter, cross-sectional study. Results from children under 18 years of age diagnosed with seasonal allergic rhinitis by positive skin prick tests to olive and grass pollen were analyzed. Specific IgE to Phl p 1+5, Ole e 1, and Phl p 7+12 was determined. Investigators specified the optimal composition of allergen immunotherapy before and after knowing the results of the molecular diagnosis.

Results: A total of 281 patients with a mean age of 13.4 years were included. Double sensitization to both major allergens was found in vitro in 76% of children for an IgE cutoff point of 0.35 kU/L. When the molecular diagnosis results were known, specialists changed the composition of the prescribed immunotherapy in 52.87% of cases.

Conclusions: Double sensitization to grass and olive pollen is common in Spain and also occurs in the pediatric population. Molecular diagnosis using specific IgE may help improve immunotherapy selection in polysensitized patients.

KEYWORDS

double sensitization, grass, immunotherapy, molecular diagnosis, olive, pediatric population, seasonal allergic rhinitis, specific IgE

1 | INTRODUCTION

Allergic rhinitis (AR) is the most common chronic allergic disease in children, with a prevalence ranging between 8.2%^{1,2} and 38.9%³ in the Spanish pediatric population. Of these, 60% are patients with seasonal allergic rhinitis, mostly caused by sensitization to grass or olive pollen.⁴⁻⁷

The initial examination for the diagnosis of allergic sensitization is a skin prick test (SPT), a simple, inexpensive, and rapid procedure.^{8,9} However, with currently available SPTs it can be difficult to identify the real causative agent in patients sensitized to panallergens (cross-reactivity phenomenon) and in patients who live in areas where plant pollen seasons overlap, as is the case with grass and olive trees in Spain.^{5,10,11}

Molecular diagnosis (MD) can now be used in routine clinical practice to detect sensitization to major allergens and to determine cross-reactivity due to sensitization to secondary allergens.^{12,13} MD, then, can play a crucial role in selecting the right composition of allergen-specific immunotherapy (AIT).^{10,14,15} In children, grass sensitization profiles are highly heterogeneous. Molecularly designed AIT preparations tailored to patients' needs and driven by locally performed population studies can counter this feature.¹⁶

The aim of this study was to determine the sensitization pattern to major grass (Phl p 1+5) and olive (Ole e 1) pollen allergens detected using specific IgE in a Spanish pediatric AR population who presented positive SPTs to both grass and olive pollen. We also evaluated the presence of associated sensitizations (secondary allergens, Phl p 7+12) and whether knowledge of this information might influence the composition of the prescribed AIT.

2 | METHODS

In this paper, we describe an analysis of the pediatric population (younger than 18 years of age) of a larger, recently published series of 1263 patients aged between 5 and 65 years.¹⁷ The study methods are comprehensively described in the general publication and are summarized below.

2.1 | Study design and patient selection

This was an epidemiologic, multicenter, observational, cross-sectional study that included patients with double sensitization to grass and olive pollens. We performed SPTs with a panel containing the following extracts: *Alternaria alternata*, *Artemisia vulgaris*, *Canis familiaris*, *Dermatophagoides pteronyssinus*, *Felis domesticus*, *Juniperus ashei*, *Olea europaea*, *Parietaria officinalis*, *Phleum pratense*, *Plantago lanceolata*, and *Salsola kali* (Stallergenes, Antony, France). Histamine (10 mg/mL) and glycerol-saline solution (Stallergenes, Antony, France) were used as controls. An SPT was considered positive if the wheal size was at least 3 mm larger than the wheal of the negative control.¹⁷ Patients were recruited over a 6-month period in 87 allergy clinics located throughout Spain.

Patients of both sexes with a diagnosis of AR, with or without asthma, who had symptoms of at least 2 years of duration, clearly related with grass and olive pollination season, irrespective of other sensitizations, were selected. Patients were required to have resided continuously for at least 2 years in provinces of Spain in which a minimum of 1000 hectares were dedicated to olive cultivation; these provinces were then stratified into 5 geographic areas, according to the surface area of cultivation (Table 2). Although this limit is arbitrary, it was chosen to select areas where sensitization to olive was more relevant, as described by Barber et al^{10,18}

Patients were excluded from the study if there was potential interference with SPT interpretation (ie, a condition that might affect wheal size),¹⁹ or if they had previously received AIT. The study was approved by the Ethics Committee of Hospital Nuestra Señora del Prado, Talavera de la Reina (Toledo), and reported to the Spanish

Agency of Medicinal Products and Healthcare Devices. It was conducted in accordance with the Declaration of Helsinki and international regulations set down in the International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences-CIOMS-Geneva, 1991).²⁰

All patients gave their consent to participate in the study. A specific informed consent form for pediatric patients was used that was signed by a legal representative.

2.2 | Study variables

The primary endpoint was to determine the in vitro sensitization pattern to the principal grass (Phl p 1+5) and olive (Ole e 1) pollen allergens, detected using specific IgE with a cutoff point of 0.35 kU/L. Serum samples were analyzed centrally in the Applications Laboratory of the Vitoria Pharmacy Faculty, University of the Basque Country, Spain, using the ImmunoCAP system (ThermoFisher Diagnostics).

Secondary parameters included the presence of other sensitizations (secondary allergens, Phl p 7+12) associated with sensitization to the principal allergens and potential changes in AIT composition introduced after the principal allergens were identified.

2.3 | Statistical analysis

All analyses were conducted on evaluable pediatric patients aged 5-18 years from the main study cohort.

A descriptive analysis of the sociodemographic and clinical characteristics of the study population was performed. Mean and standard deviation were used to describe continuous variables, and the number and percentage of patients per response category were used to describe categorical variables.

To compare qualitative variables, a chi-squared test of independence, Fisher's exact test, or McNemar-Bowker chi-squared test for symmetry was conducted, as applicable. For significant associations, multiple comparisons were assessed, adjusting significance values according to the Bonferroni method. A level of significance of .05 was used for all statistical tests. Results were analyzed globally and stratified by geographic area.

Data analysis was performed using the SPSS statistical package, version 17.0 (SPSS, Chicago, IL, US).

3 | RESULTS

3.1 | Clinical and sociodemographic characteristics

A total of 281 patients with a mean age of 13.4 years were included (standard deviation=3.3 years), of whom 71.9% were aged between 5 and 15 years. In total, 56.2% were male, and most patients had seasonal persistent AR, according to the ARIA classification (32.4% mild and 42.7% moderate/severe). All patients had concomitant sensitization to other pollens, the most common being *Salsola/Chenopodium*, observed in 43.6% of the population. Allergic conjunctivitis (89.7%) and intermittent asthma (45.5%) were the most common

comorbidities. The clinical and sociodemographic characteristics of all study patients are shown in Table 1.

3.2 | In vitro sensitization patterns

Four in vitro sensitization patterns were observed: 214 patients (76.2%) had a positive result to both Phl p 1+5 and Ole e 1; 36 patients

TABLE 1 Clinical and sociodemographic characteristics of patients

Sociodemographic data	
Age (years), Mean (SD)	13.4 (3.3)
Age (years), n(%)	
5-15	202 (71.9)
16-18	79 (28.1)
Sex, n(%)	
Male	158 (56.2)
Area of residence, n(%)	
Urban	200 (71.2)
Race ^a , n(%)	
Caucasian	280 (99.6)
Years of residence in the area, Mean (SD)	12.3 (3.7)
Clinical characteristics	
ARIA rhinitis classification, n(%)	
Intermittent mild	54 (19.2)
Intermittent moderate/severe	16 (5.7)
Persistent mild	91 (32.4)
Persistent moderate/severe	120 (42.7)
Years since onset of symptoms, Mean (SD)	4.5 (2.5)
Sensitizations, n(%)	
Pollens	281 (100)
Platanus	79 (28.1)
Cypress	57 (20.3)
Artemisia/Sunflower	32 (11.4)
Plantain	64 (22.8)
Salsola/Chenopodium	108 (38.4)
Parietaria	21 (7.5)
Dermatophagoides	49 (17.4)
Alternaria	60 (21.4)
Dog	66 (23.5)
Cat	85 (30.2)
Concomitant diseases, n(%)	
Asthma	176 (62.6)
Intermittent	80 (45.5)
Mild persistent	52 (29.5)
Moderate persistent	43 (24.4)
Severe persistent	1 (0.6)
Allergic conjunctivitis	252 (89.7)
Allergy to plant-based foodstuffs	22 (7.8)

^a1 missing.

(12.8%) to Ole e 1 exclusively; and 26 patients (9.3%) to Phl p 1+5 exclusively. Five more patients (1.8%) showed a negative result to both Phl p 1+5 and Ole e 1 (Figure 1).

Results stratified according to the 5 selected geographic areas are shown in Table 2.

More than 60% of patients showed a pattern of positivity to both principal allergens in all areas, with Area 3 revealing the highest percentage of double sensitization (90%). The area with the greatest number of patients sensitized exclusively to Ole e 1 was Area 2 (24.4%), followed by Area 5 (16.9%), the region with the largest area of olive cultivation. The highest percentages of patients with Phl p 1+5 sensitization only were found in Area 1 (16.7%) and Area 5 (14.5%). Significant differences between areas are shown in Table 2.

With respect to other sensitizations (Table 3), 62 patients (22.1%) were sensitized to panallergens Phl p 7+12. Most of these patients (83.9%) were also sensitized to Phl p 1+5 and Ole e 1, while the rest (16.1%) were sensitized to only one or the other. No patients were exclusively sensitized to panallergens Phl p 7+12. Area 2 was the area with the greatest percentage of patients sensitized to panallergens (28.9%).

3.3 | Specific immunotherapy prescription

On the basis of clinical history and SPT results alone, 72.8% of patients would have received AIT with an extract of grass and olive pollen, whereas 15% would have received AIT with a grass extract and 12% would have received AIT with an olive extract. When MD results were known, these percentages were 39.1%, 25.6%, and 19.9%, respectively. Results stratified according to the major molecular patterns (Ole e1, Phl p1+5, Ole e1+Phl p1+5, and negative) are shown in Figure 2. In all cases, except for the negative pattern, differences before and after receiving the MD results were significant. When investigators received the information on in vitro sensitization patterns, 73.44% stated that they would change the prescribed AIT. Overall, treatment would have been modified in 52.87% of patients. It is also interesting to note that once the in vitro information was known, 15.3% of patients would not have received any AIT.

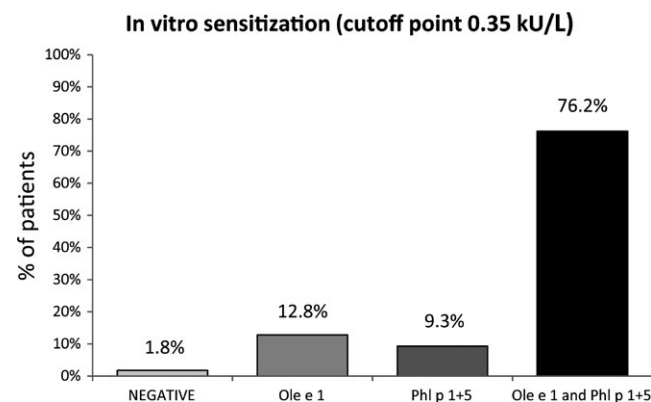


FIGURE 1 In vitro sensitization pattern to Ole e 1 and Phl p 1+5

TABLE 2 In vitro sensitization patterns by geographic area

	Area 1 n = 42 %	Area 2 n = 45 %	Area 3 n = 50 %	Area 4 n = 61 %	Area 5 n = 83 %	P-value*
>0.35 kU/L						
Positive to Ole e 1 only	4.8	24.4 ^a	4.0	11.5	16.9	.013
Positive to Phl p 1 + 5 only	16.7	2.2	6.0	4.9	14.5	.041
Positive to Ole e 1 and Phl p 1 + 5	76.2	66.7	90.0 ^b	82.0	68.7	.024
Negative	2.4	6.7	0.0	1.6	0.0	.044

Area 1: provinces with <1% of surface area dedicated to olive cultivation (minimum 1000 Ha); Area 2: provinces with 1%-5% of surface area dedicated to olive cultivation; Area 3: provinces with 6%-10% of surface area dedicated to olive cultivation; Area 4: provinces with 11%-20% of surface area dedicated to olive cultivation; Area 5: provinces with >20% of surface area dedicated to olive cultivation. Multiple comparisons: (Bonferroni correction).

^aSignificantly greater percentage than in Area 3.

^bSignificantly greater percentage than in Area 5.

*Fisher's exact test or chi-squared test were used according to the data.

TABLE 3 Other sensitizations by geographic area

	Total n = 281 % of total	Area 1 n = 42 % of total	Area 2 n = 45 % of total	Area 3 n = 50 % of total	Area 4 n = 61 % of total	Area 5 n = 83 % of total
Other sensitizations						
Positive to Phl p 7+12	22.1	19.0	28.9	22.0	23.0	19.3
Positive to Phl p 7 + 12 associated with:						
Positive to Ole e 1 only	6.5	0	0	0	28.6	0
Positive to Phl p 1+5 only	9.7	25.0	0	0	7.1	18.8
Positive to Ole e 1 and Phl p 1+5	83.9	75.0	100	100	64.3	81.3

See Table 2 for information on geographic areas.

4 | DISCUSSION

This analysis reveals a high percentage (76.2%) of pediatric patients with double sensitization. Polysensitization is common in the general population, and figures as high as 20%-40% have been reported, depending on the population type and geographic area.^{21,22}

This prevalence increases considerably when patients who attend allergy clinics are studied, and figures of over 70%, similar to those found in our study, have been reported in certain series.¹⁵ Moral et al²³ also reported a significant rate of polysensitization (74% of all atopic patients), even in the pediatric population.

Some authors report that polysensitization increases with age.^{21,24} In our study, an insignificant trend towards higher rates of double sensitization to olive and grass pollen was observed among the pediatric population compared with the adult population from the GRAMOLE series (76.2% vs 69.8%).¹⁷ Moreover, sensitization to grass pollen (Phl p 1+5) was significantly lower in children (9.3% vs 15.40%; $P = .027$). The proportion of individuals positive to Ole e 1 only was similar

between the 2 groups. The percentage of positive SPTs to the different extracts was consistently higher among the adult population, with a significant difference compared to the pediatric population for profilins, *Artemisia*, and *Parietaria*.¹⁷ Barber et al¹⁰ also found age-related differences in sensitization patterns and reported a greater percentage of sensitization exclusively to olive pollen in the pediatric population.

In general, no differences were found between geographic areas for sensitization to Phl p 1+5 and Ole e 1. A high percentage of patients (90%) with sensitization to both allergens were observed in Area 3 only, a finding that can be attributed to the fact that Area 3 is an area with high exposure to grasses. In line with other authors,¹⁰ we found a high percentage of patients monosensitized to Ole e 1 in Area 2, an area with a lower level of olive cultivation, although the differences were not statistically significant when compared with high-exposure areas 4 and 5.

Molecular diagnosis is a useful tool in polysensitized patients as it distinguishes between real sensitizations and cross-reactions, and helps to define the correct AIT composition expected to improve

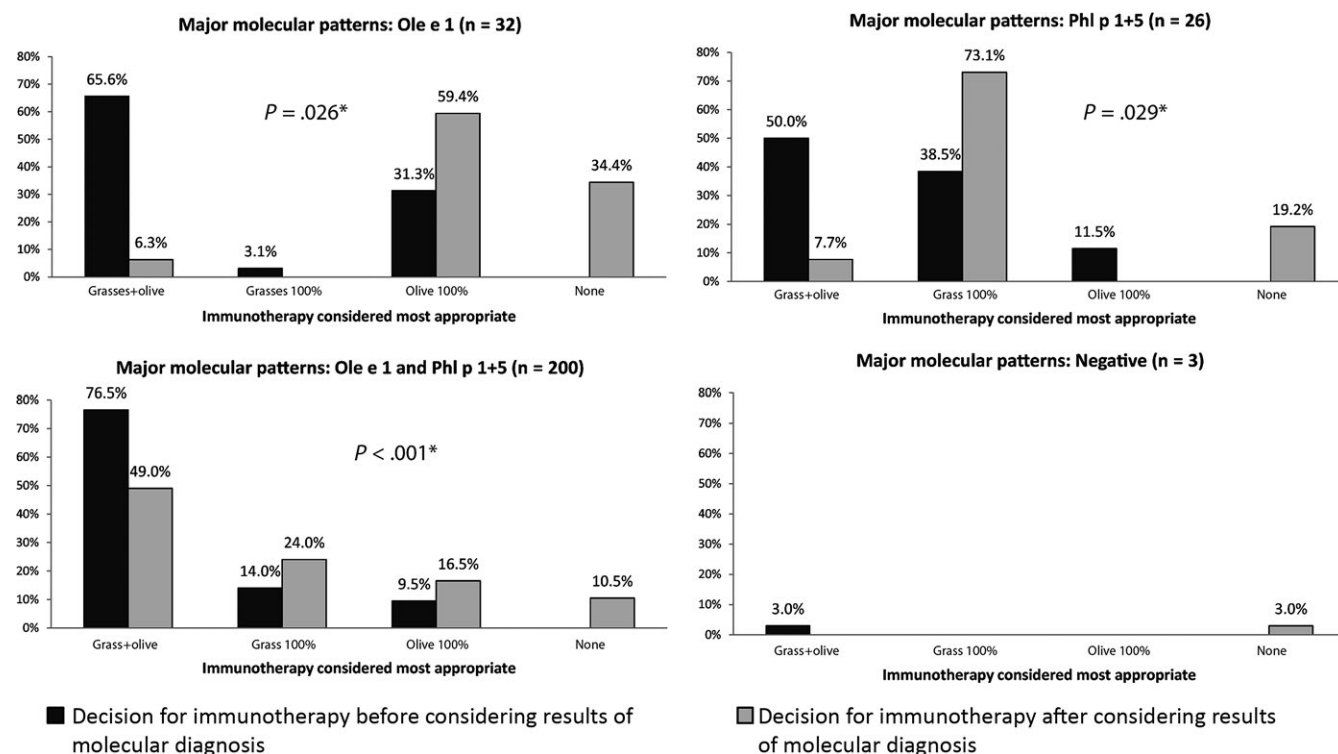


FIGURE 2 Percentage of patients who, in the investigators' opinion, were treated with the appropriate immunotherapy components before and after receiving molecular diagnosis results. Results stratified according to major molecular patterns. *McNemar-Bowker chi-squared test for symmetry (in cases with some immunotherapy treatment after the investigator received the molecular diagnosis results)

outcomes.¹⁵ The appropriate selection of patients and allergenic extracts is highly recommended, although the evidence to support this claim is scant.¹⁴ Further studies on the influence of MD in the efficacy of AIT are clearly needed. Experts agree on several different factors associated with AIT in polysensitized patients: There is a direct relationship between prompt prescription of AIT and efficacy; it should be used only in cases in which the quality of the extracts can be guaranteed; its use is justified even when pollination periods overlap; and it should not be automatically contraindicated in patients sensitized to more than 2 clinically significant pollens.¹⁵ Some authors have found subcutaneous AIT to be useful, even in the short-term symptomatic treatment of patients with seasonal allergic rhinitis.²⁵

Although other approaches have been used for selecting immunotherapy (eg, nasal provocation tests and others), these procedures are not usually performed in routine clinical practice, because they are complex and time-consuming, and lack standardization. The characteristics of MD make it especially useful in patients with double sensitization to olive and grass pollens.²⁶ However, Ciprandi et al²⁷ report a worryingly low use of AIT in sensitized patients, with less than 50% of patients with grass pollen sensitization receiving AIT. This situation is of particular concern in the case of *Parietaria* and olive pollen sensitization, for which only one-third of patients received AIT.

Our analysis reveals continuing discrepancies in the composition of AIT prescribed to the pediatric population before and after performing MD: Two-thirds of participating physicians would have changed the AIT components and would have done so in over 50% of patients. Moreover, they would have withdrawn AIT in 15% of cases. No significant differences were found compared to the adult population.¹⁷

These results are similar to those of Sastre et al¹⁴ who reported differences in AIT composition before and after MD in 54% of a population of Spanish patients (mean age 31 years) with grass pollen sensitization.

Although the study endpoint did not include the analysis of perennial allergens, the low percentage of house dust mite sensitization in our cohort is remarkable. In Spain, according to SPT results, the overall percentage of sensitization to *D. pteronyssinus* among patients with AR is 52%,⁵ but this percentage falls to 22% in the central region of Spain, which is more arid. It should be noted that most of the provinces included in the study were located in the center of Spain. Furthermore, patients were selected based on a previous positive SPT to both grass and olive pollens, and not from a global population, which could be another factor supporting this low prevalence.

This study is a post hoc analysis of a subgroup population of the GRAMOLE Study,¹⁷ and some limitations must be mentioned:

1. Ole e 7 and Ole e 9 were not analyzed.¹⁷ These are major allergens in areas of high exposure and directly related with the severity of the allergic clinical profile,¹⁰ although we do not believe that this fact could have significantly modified the results.
2. Pollen counts were not studied, although it has been shown that provinces with more intensive olive cultivation produce higher olive pollen counts.²⁸ Nevertheless, possible differences in allergenic pollen levels in the different areas that might influence sensitization patterns to the principal allergens could not be detected.
3. Although exposure to grass pollens is known to be high in some areas, no information was provided on the surface area of pastures within the selected areas.

The GRAMOLE is a large-scale epidemiological study in which olive and grass pollen allergies were diagnosed for the first time using a molecular approach in real-world clinical practice. In conclusion, double sensitization to olive and grass pollen is common in the Spanish pediatric population, with similar percentages to the adult population. Children who are prescribed AIT solely on the basis of SPT results may be receiving extracts to which they are not allergic. MD can help determine a correct etiologic diagnosis, leading to the prescription of a better selection of AIT. To confirm these findings, further studies evaluating improvements in clinical response of pediatric patients with olive and grass polysensitization treated with AIT selected on the basis of MD are warranted.

CONFLICT OF INTEREST

Ignacio Dávila declares having received honoraria for lectureship from ALK and Stallergenes Greer, and for participation in advisory boards from Alk-Abelló and Stallergenes Greer. He has also received research support from Merck Foundation and ThermoFisher Diagnostics. Ana Martínez-Cañavate, Javier Torres-Borrego, Ana Belén Molina Terán, José Luis Corzo, Blanca Esther García, Ramón Rodríguez Pacheco and Carmen Moreno Aguilar have no conflict of interest to declare.

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