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**Pollen-Induced Allergic Asthma and Rhinoconjunctivitis: Differences in Outcome Between Seasonal and Nonseasonal Exposure to Allergens Under Real-Life Conditions (The LANDSCAPE Study)**

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The clinical manifestations of asthma and rhinitis vary with phenotypes and endotypes [1,2]. Sensitization to a specific allergen may involve clinical profiles with significant differences in symptoms, quality of life, and even choice of therapy by specialists [3,4]. However, classifications of asthma

and rhinitis are based mainly on severity and/or control, with no reference to the role of current or absence of exposure to allergens in the development of symptoms. Furthermore, exclusively pollen-allergic patients are not appropriately represented in clinical practice guidelines for asthma and rhinitis.

We performed a multicenter, epidemiological, prospective, observational study to compare clinical and pathophysiological features during and outside the pollen season in adults diagnosed with allergic asthma and rhinitis who manifested exclusively seasonal symptoms caused by grasses and/or olive tree pollens at inclusion.

We defined patients as being allergic to grass and/or olive pollens based on skin prick testing and/or specific IgE (ImmunoCAP, Thermo Fisher Scientific). Patients had to have presented symptoms on exposure to these pollens exclusively during the pollen season and in their geographical area. We excluded pregnant women, patients sensitized to occupational and other perennial or seasonal allergens to which they were exposed during the same period, patients who had previously received immunotherapy, and patients with other associated nasal or bronchial diseases or any other condition recorded during the pollen season. Patients sensitized to allergens other than those studied here were included if their sensitization was not clinically relevant, that is, with no symptoms induced by the allergen in question.

We assessed symptoms and lung function (FEV<sub>1</sub>, FVC, FEV<sub>1</sub>/FVC) and recorded the Asthma Control Test (ACT) score, the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) score, fractional inhaled nitric oxide (FeNO), the visual analog scale (VAS) score for rhinitis and conjunctivitis, and the ESRINT questionnaire score. Sociodemographic data and clinical variables were assessed during and outside the pollen season (autumn and winter), ie, at visit 1 (V1) and visit 2 (V2).

Patients were included at V1 at least 2 weeks after being subject to pollen levels that induced a clinical response (>50 grains/mm<sup>3</sup> for grasses, >200 grains/mm<sup>3</sup> for olive) [5]. Each investigator consecutively included patients with a confirmed diagnosis of seasonal allergic asthma and rhinitis caused by grass/olive-tree pollens, with or without allergic conjunctivitis, according to published diagnostic criteria for asthma [6] and rhinitis [7].

Participation in the study by investigators and patients was voluntary, and patients had to sign an informed consent document. The Ethics Committee of Hospital Universitario La Paz approved the study (SEA-ASM-2014-01).

The study population comprised 101 patients (mean [SD] age, 35.79 [10.97] years). Patients were already taking treatment on enrolment, or treatment was prescribed at V1 in 81.3% of patients with rhinitis and 79.6% of patients with asthma. At V2, only 2.4% were receiving treatment for rhinitis and 11.3% for asthma. Nevertheless, a significant difference was observed between the visits with respect to markers of severity for rhinitis and asthma. At V1, 25% of patients had intermittent asthma, 28.6% mild-persistent asthma, 41.8% moderate-persistent asthma, and 4.1% severe asthma. At V2, 67% of patients had no asthma symptoms, 22.4% had intermittent asthma, 4.1% had mild-persistent asthma, 6.1% had moderate-persistent asthma, and 0% had severe

Table. Clinical Characteristics at Visits 1 and 2

	Visit 1, Mean (SD [range])	Visit 2, Mean (SD [range])	<i>P</i> Value
ACT score	16.59 (5.14 [6-25])	23.36 (2.54 [14-25])	.0001
AQLQ score	4.60 (1.29 [1.47-7])	6.28 (0.81 [3.60-7])	.0001
FeNO, ppb	57.2 (37.4 [10-186])	21.9 (10.6 [2-61])	.0001
FVC, L	3.91 (0.83 [1.7-6.1])	3.94 (0.85 [1.8-6.1])	.33
FEV <sub>1</sub> , L	3.15 (0.70 [1.7-5.1])	3.25 (0.67 [1.4- 4.8])	.01
FEV <sub>1</sub> , %	94.45 (15.01 [52-131])	98.06 (14.40 [58-127])	.001
FEV <sub>1</sub> /FVC	0.80 (0.09 [0.5-1])	0.84 (0.08 [0.7-1])	.001
ESPRINT 15 score	2.46 (1.51 [0-5])	0.28 (0.61 [0-3])	.0001
VAS (rhinitis)	47.68 (27.54)	14.51 (22.48)	.0001
VAS (conjunctivitis)	47.3 (29.33)	8.4 (17.12)	.0001
Symptom score (conjunctivitis)	7.34 (4.15 [0-16])	0.81 (1.74 [0-10])	.0001

Abbreviations: ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; FeNO, fractional exhaled nitric oxide; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; VAS, visual analog scale.

asthma. At V1, 22.4% of patients had mild rhinitis, 62.2% had persistent rhinitis, and 14.3% had severe rhinitis. At V2, 58.2% of patients had no rhinitis symptoms, 32.6% had mild rhinitis, 8.2% had moderate rhinitis, and only 1% had severe rhinitis.

Significant differences were observed between the visits with respect to severity for both diseases and for ACT, FeNO, MiniAQLQ, FEV<sub>1</sub> (%), FEV<sub>1</sub>/FVC ratio, VAS for rhinitis and conjunctivitis, and the ESRINT score, but not for FVC values (Table).

The results of our study confirm exposure to the allergen as the determining factor for the symptoms of allergic asthma and rhinoconjunctivitis. Furthermore, exposure to allergens can affect diagnostic yield in asthma by modifying the results for FeNO and lung function.

However, our findings also show that clinical features do not disappear completely outside the exposure period, as almost one-third of asthmatic patients and 41.8% of those with rhinitis continued to present symptoms, albeit with clearly lower severity than at V1. Therefore, it seems clear that clinical manifestations in the respiratory tract depend on the allergic response, even during periods when the patient is not directly exposed to the allergen responsible for his/her symptoms.

Contact with the allergen may cause pathophysiological abnormalities that lead to clinical manifestations [8]. This possibility could prove to be important in circumstances that trigger respiratory symptoms, such as infections or contact with irritants [9].

Furthermore, consistent with the results of similar studies [10], measurement of FeNO as an indicator of the presence of type 2 inflammation [11], also revealed a significant increase during the exposure period, thus indicating that FeNO could be a sensitive parameter for determining exposure to the allergen. The FeNO value decreased significantly outside the pollen season. In addition, the values of some lung function parameters, such as FEV<sub>1</sub>, were associated with exposure to the allergen, whereas values such as FVC did not vary significantly, indicating that the presence of clinical manifestations could be more sensitive to limited allergen exposure over time than lung function abnormalities, especially in patients who receive antiasthma treatment.

A potential limitation of the present study is its small sample size. However, the population was very homogeneous, and patient selection was very strict, since patients in whom other possible sensitizations could have had a clinical effect were excluded. While sensitization to multiple allergens is common in Spain [12,13], most patients were sensitized only to pollens whose pollination period was markedly seasonal, such as grasses and olive.

In conclusion, most patients diagnosed with allergic rhinoconjunctivitis and asthma due to sensitization to grass/olive pollens experience clinical manifestations, lung function abnormalities, and airway-inflammation exclusively during the pollen season. However, a few continue to experience abnormalities outside the exposure period.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

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