

## Seasonal administration of omalizumab in patients with uncontrolled asthma and sensitization to olive pollen

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Sensitization to olive pollen leads to the development of asthma. Particularly, in areas with high pollen counts, such as the south Mediterranean, sensitization to Ole e 7 involves a greater severity of asthma [1-3].

In Cordoba, olive and grasses are important sources of pollen causing rhinoconjunctivitis and asthma during the spring season. Only olive pollen reaches extreme counts (>20.000 grains/m<sup>3</sup>/year).

Allergen immunotherapy (AIT) is indicated when sensitization is clinically relevant and pharmacologic asthma control is not satisfactory. When sensitization to Ole e 7 is single or predominant AIT is associated with a higher incidence of adverse reactions [4]. Moreover, the lack of control of minor allergens in the vast majority of extracts represents an additional difficulty[5]. Therefore, for patients predominantly sensitized to Ole e 7, AIT could be unappropriated.

Omalizumab has been widely used to treat perennial allergic severe asthma [6], however, we do not know about severe asthma due to pollen sensitization. The aim of this study was to analyze the results of a pilot seasonal treatment with omalizumab, in

daily practice conditions, in patients with uncontrolled seasonal asthma, strong sensitization to minor olive allergens and exposed to high pollen counts.

Retrospective data from 33 patients (84.4% women; mean age:31.4; SD:12.35) were selected based on: 1) high exposure to olive pollen; 2) moderate-severe persistent asthma [7]; 3) poor control of symptoms in two previous springs according to GEMA guide [7]; 4) relevant sensitization to minor olive allergens (mean values and SD of sIgE were Ole e 1 24.5(26.5); Ole e 7 67.5 (70.8); Ole e 9 19.5(28.6). More data in Supplementary Fig 1); 5) having been treated off-label with omalizumab for 16 weeks (March-June 2013 including olive pollination season) under standardized clinical practice (according to the manufacturer's product data sheet) [8].

The single exclusion criterion was to be sensitized to other pollens.

Interestingly, 66% of included patients had received olive immunotherapy with poor clinical response and unacceptable rate of adverse reactions.

Clinical variables were collected from medical records: 1) daytime symptoms (dyspnea, cough, wheezing, chest tightness), activity limitation, night symptoms/awake, need for relief medication (SABA), exacerbations, maintenance medication (inhaled corticosteroids with or without LABA, antileukotriene, others); 2) severity qualitative parameters (oral corticosteroids-emergency visits).

An asthma control synthetic index (ACSI) was established based on GEMA guide [7]:

ACSI value 2 (well controlled asthma): absence of night symptoms, activity limitations, exacerbations, daytime symptoms  $\leq 2$  days/week, need for SABA  $\leq 2$  times/week, FEV1  $\geq 80\%$  of theoretical value.

ACSI value 1 (partially controlled asthma): At least 4 out of 6 conditions from ACSI 2.

ACSI value 0 (badly controlled asthma): Less than 4 out of 6 conditions from ACSI 2.

ACSI was monthly obtained from March to June 2013 in all patients matching with omalizumab administration visits. The worst ACSI obtained for each patient was selected to perform statistical analysis. Global spring ACSI of 2011 was obtained from medical records.

We performed a descriptive analysis of variables. Comparison were made between 2013 and 2011 (before and after omalizumab). The season of 2012 was not considered in order to avoid a possible bias due to lower pollen counts (Supplementary Fig 2). McNemar's test was used to measure the consistency in changes of ACSI and severity parameters (oral corticosteroids-emergency visits). A bivariate independence analysis ( $\chi^2$ ) was performed between the dependent variable (ACSI) and the independent variables, gender and age. Significance was set at  $\alpha=0.05$ .

The study protocol was approved by local Ethics Committee and informed consent was obtained from each patient, or their legal representative.

Omalizumab doses ranged from 150mg/4weeks to 600mg/2weeks. Most frequently dose was 450mg/2weeks (27.2% of patients). Both ACSI and severity parameters were significantly improved ( $P<0.001$ ) after treatment with omalizumab (Table 1). Detailed data can be seen in Supplementary Fig 3. Patients from GEMA-step 6 obtained the best results (Supplementary Table 1).  $\chi^2$  test showed no significant differences between ACSI and independent variables (gender:  $P = 1.000$ ; age:  $P = 0.688$ ).

This study showed that seasonal treatment with omalizumab in patients with uncontrolled asthma due to olive pollen allergy improves the disease control. Our patient cohort had poorly controlled asthma during olive pollination but remained mostly asymptomatic for the rest of the year. Despite this reality, guidelines do not classify seasonal asthma as perennial, depending on severity.

Asthma control is a complex health problem from the perspective of its indicators. In the present study, omalizumab had an impact on all patients with a reduced need of oral corticosteroids and fewer emergency visits. Patients suffered fewer symptoms using fewer drugs and medical interventions. Whether omalizumab further than providing a better control of asthma, has a possible preventive role in future worsening, as well as potential cost savings [9] are questions unsolved yet.

Seasonal treatment with omalizumab in pollinic patients with rhinitis was previously investigated, resulting in improvement of symptoms and quality of life, and reduced use of rescue medication [10,11].

An important aspect of this study was that patients were treated with omalizumab only for 16 weeks. Whether we had overlooked the seasonal nature of asthma and treated patients based on their severity and control criteria, we would have spent 6.708 pre-filled syringes of 150mg (2.931.328,92 €). In contrast, we only consumed 516 (225.486,84 €).

In summary, the drug administration reduction and the better control of severe pollen asthma obtained by seasonal treatment with omalizumab results appropriate cost-benefit balance regarding a perennial schedule. Healthcare systems should not ignore this protocol.

The main limitations of the study were its retrospective design and the small simple size, nevertheless, we consider the results a call for attention on asthma classification and the allocation of therapeutic resources.

Our results indicate that this schedule of omalizumab in severe asthmatic patients with a complex profile of sensitization to olive pollen may lead to better control of asthma and therefore, could represent a successful alternative therapy for these patients. However, more studies to validate this proof of concept are needed.

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**REFERENCES**

1. Barber D, De La Torre F, Feo F, Florido F, Guardia P, Moreno C, et al. Understanding patient sensitization profiles in complex pollen areas: A molecular epidemiological study. *Allergy Eur J Allergy Clin Immunol*. 2008;63(11):1550–8.
2. M Alcántara, B Sáenz de San Pedro, C Cañada, M A Muñoz, L Jimeno, M Villalba F de la T. Steps towards clarifying the clinical relevance of minor olive allergen in areas. *J Investig Allergol Clin Immunol*. 2017;27(2):138–40.
3. S Porcel Carreño, E Gómez Nieves, E Fernández-Caldas, E Abel Fernández, B Cases, J I Tudela, et al. Immunochemical and physical quantitation of grass and olive pollen allergens and correlation with asthma admissions in Cáceres, Spain. *J Investig Allergol Clin Immunol*. 2019;Jul 8.
4. Peñuelas E, Serrano P, Barasona MJ, Saiz V, Fernandez L, Moreno C. Sensitization to minor allergens has a direct influence on the outcome of subcutaneous immunotherapy in olive-allergic patients. *J Investig Allergol Clin Immunol*. 2016;26(3):202-4.
5. Duffort O, Palomares O, Lombardero M, Villalba M, Barber D, Rodríguez R, et al. Variability of ole e 9 allergen in olive pollen extracts: Relevance of minor allergens in immunotherapy treatments. *Int Arch Allergy Immunol*. 2006;140(2):131–8.
6. Normansell R, Walker S, Milan SJ, Walters EH NP. Omalizumab for asthma in adults and children. *Cochrane Database Syst Rev*. 2014;1(1):2014;1(1):CD003559.

7. SEPAR. GEMA. Guia Española para el Manejo del Asma [Internet]. 2009. 2009.  
Available from: [www.gemasma.com](http://www.gemasma.com)
8. <http://www.ema.europa.eu/> [Internet]. Available from:  
[http://www.ema.europa.eu/docs/es\\_ES/document\\_library/EPAR\\_-\\_Product\\_Information/human/000606/WC500057298.pdf](http://www.ema.europa.eu/docs/es_ES/document_library/EPAR_-_Product_Information/human/000606/WC500057298.pdf)
9. Entrenas Costa LM, Casas-Maldonado F, Soto Campos JG, Padilla-Galo A, Levy A, Álvarez Gutiérrez FJ, et al. Economic Impact and Clinical Outcomes of Omalizumab Add-On Therapy for Patients with Severe Persistent Asthma: A Real-World Study. *Pharmacoecon Open*. 2019;3(3):333–42.
10. Nagakura T, Ogino S, Okubo K, Sato N, Takahashi M IT. Omalizumab is more effective than suplatast tosilate in the treatment of Japanese cedar pollen-induced seasonal allergic rhinitis. *Clin Exp Allergy*. 2008;38(2):329–37.
11. Okubo K, Ogino S, Nagakura T, Ishikawa T. Omalizumab is Effective and Safe in the Treatment of Japanese Cedar Pollen-induced Seasonal Allergic Rhinitis. *Allergol Int* [Internet]. 2006;55(4):379–86. Available from:  
<http://linkinghub.elsevier.com/retrieve/pii/S132389301530993X>

**TABLE**

Table. Asthma control synthetic index (ACSI) based on the GEMA gradation and severity variables before and after receiving omalizumab pre-intraseasonally.

	ACSI	n (%)	McNemar	OCS n (%)	McNemar	Emergency n (%)	McNemar
<b>Before omalizumab (2011)</b>	2	0		10 (30.3%)		12 (36.3%)	
	1	11 (33.3%)					
	0	22 (66.7%)					
<b>After omalizumab (2013)</b>	2	12 (36.4%)	<b>21</b> <b>(p&lt;0.001)</b>	5 (15.1%)	<b>16.2</b> <b>(p&lt;0.001)</b>	2 (6%)	<b>17.2</b> <b>(p&lt;0.001)</b>
	1	14 (42.4%)	2.777 (p=0.095)				
	0	7 (21.2%)	0.88 (p=0.345)				

n, number of patients; OCS, oral corticosteroids