Cluster Subanalysis of Patients With Severe Asthma Who Responded to Omalizumab

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Asthma is a heterogeneous disease that manifests with variations in signs and symptoms, age of onset, triggers, disease progression, pulmonary function, and airway inflammation [1].

Recently, significant efforts have been made to phenotype asthma, with the objective of identifying patients who are responsive to specific therapies [2]. The different methods used to phenotype asthma have generated bias [3]. In this sense, cluster approaches are one of the most frequently used unbiased techniques [4]. They are generally based on cohorts of patients analyzed using a cluster methodology, which gives rise to various phenotypes [5-7]. Here, we used an innovative contrasting approach, namely, a real-world study in which we selected patients with an excellent response to omalizumab (hyperresponders) and performed a cluster analysis to identify responder phenotypes.

FENOMA was a multicenter, retrospective observational real-world study of patients aged ≥18 years with severe asthma who achieved complete asthma control according to the Spanish Guideline on Asthma Management (GEMA) [8] after 1 year of treatment with omalizumab. The design of this study has been published elsewhere [9]. Asthma control was considered to be complete if the patient had no diurnal asthma symptoms or asthma symptoms ≤2 d/wk, no nocturnal symptoms, no need for rescue medication ≤2 d/wk, normal pulmonary function, no activity limitation, and no severe asthma exacerbations during this period. These patients were considered hyperresponders. Patients had been retrospectively assigned by their physician to a pre-established phenotype [5,6,10] before receiving treatment with omalizumab. However, the definition of severe asthma phenotypes has evolved since the study was designed (2014), with current phenotypes being more concise and less numerous. The older definitions in the FENOMA study meant a large degree of overlap between phenotypes, thus making it difficult for physicians to select the phenotype (as required by the design of the study) [9]. Therefore, in order to obtain an unsupervised description of responders to omalizumab, we performed a post hoc cluster analysis to find phenotypes among patients who had achieved complete control of the disease during the first year of treatment with omalizumab and identify them in the real-world clinical setting. The variables used to determine clusters and Materials and Methods are described in the Table and Supplementary Information, respectively.

Four clusters were identified in 256 patients, namely, C1, C2, C3, and C4, which included 141 (55.1%), 96 (37.5%), 12 (4.7%), and 7 patients (2.7%), respectively. The cluster

Table. Variables Used to Determine Clusters

	Variables
Age	Forced expiratory volume in 1 second
Sex	Blood eosinophil count
Smoking history	Number of nonsevere asthma episodes
Comorbidities[a]	Number of visits to the emergency room due to asthma exacerbation
Time from asthma diagnosis to severe asthma diagnosis	Admissions to ICU due to asthma exacerbation
Duration of severe asthma until therapy	Dose of inhaled corticosteroids
BMI	Oral corticosteroids
Rescue medication (short-acting β_2 agonist)	Total serum IgE
Asthma control (GEMA criteria)	Skin prick tests

Abbreviations: BMI, body mass index; GEMA, Spanish Guideline on the Management of Asthma; ICU, intensive care unit.
[a]Allergic rhinitis, nasal polyps, chronic sinusitis, and atopic dermatitis.

analysis is described in Supplementary Table 1, and cluster demographics and clinical characteristics are presented in Supplementary Table 4. A correlation analysis was carried out to analyze the response to treatment among the main clusters and specific posttreatment parameters. The parameters included were severity, improvement in asthma control, decrease in exacerbations, use of health care resources, and background treatment (rescue medication and inhaled and oral corticosteroids [OCS]). Given the low number of patients, clusters C3 and C4 were not considered for further analysis. Supplementary Tables 5 and 6 show the comparison for C1 and C2 and summarize the results of the multivariate analysis.

We found 2 distinct and predominant severe asthma phenotypes in patients who responded fully to omalizumab, as clusters C1 and C2 accounted for 92% of the patients. C1 reflected a less allergic phenotype, namely, middle-aged patients (median, 55 years) who were overweight (median body mass index [BMI], 29) and mainly female (75.2%), with reduced lung function (forced expiratory volume in 1 second [FEV_1] ≤80%, 86.5%). Patients were highly symptomatic with more clinically significant exacerbations (median, 3.0), although they did not require hospital admission; 74.5% of patients required OCS. The C2 phenotype comprised younger patients (median age, 40.5 years) with a slight female predominance (56.3%), normal weight (median BMI, 23.6), and better pulmonary function (FEV_1 ≤80%, 42.7%). Patients were less symptomatic and experienced clinically significant exacerbations (median, 2.0), with a high percentage of atopy (46.9%) and high total IgE levels (median, 397.5 IU/mL). OCS were necessary in 45.8%.

As a whole, patients' characteristics for both phenotypes, including age, BMI, smoking status, sex, FEV_1, number of comorbidities, IgE levels, and the annual rate of severe asthma exacerbations, were very similar to those reported in previous studies, thus reinforcing the validity of the C1 and C2 clusters in the real-world clinical setting [5,7,11,12]. No differences were found between C1 and C2 for values of biomarkers such as eosinophils or fractional exhaled nitric oxide.

The study patients were selected because they were hyperresponders after treatment with omalizumab, ie, they achieved complete control of their asthma. Recently, there has been a focus on remission of asthma [13,14]. Menzes-Gow et al [14] defined remission as (*1*) sustained absence of significant asthma symptoms based on a validated instrument, (*2*) optimization and stabilization of lung function, and (*3*) no use of systemic corticosteroids to treat exacerbations or control long-term disease. The patients we report fulfilled these criteria after 1 year of treatment with omalizumab, although a longer-term follow-up is needed. Interestingly, the XPORT study population, in which no exacerbations were observed in 47.7% of patients 1 year after discontinuation of omalizumab, comprised mainly obese female asthmatics with poor lung function [15].

In conclusion, after unbiased cluster analyses, we found 2 specific types of responder. One was a middle-aged obese woman with poor lung function, who was highly symptomatic and dependent on corticosteroids. She was not necessarily allergic and had had many exacerbations. The other was an allergic nonobese asthmatic patient with many exacerbations but better lung function and lower dependence on corticosteroids. Prospective studies should be performed to determine whether these phenotypes are particularly responsive to omalizumab.

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Conflicts of Interest

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