Cluster sub-analysis of patients with severe asthma who responded to omalizumab

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Asthma is a heterogeneous disease manifested by a diversity in signs and symptoms, age of onset, triggers, disease progression, pulmonary function, and airway inflammation [1]. Recently, significant efforts have been made for phenotyping asthma, with the final objective of finding which patients are responsive to specific therapies [2]. Phenotyping has been biased by methods for phenotyping asthma [3]. In this sense, clustering approaches have been one of the unbiased techniques most frequently used [4]. Usually, these techniques use cohorts of patients analyzed using a clustering methodology, giving rise to different phenotypes [5-7]. Here, we have performed a cluster analysis using an opposite and innovative approach: in a real-life setting, we selected patients with an excellent response to omalizumab (“hyper responders”) and performed a cluster analysis to identify responder phenotypes.

FENOMA was a multicenter, retrospective observational real-life study, which included patients ≥18 years with severe asthma who achieved complete asthma control according to the Spanish Guideline of asthma management, GEMA [8] after one year of treatment with omalizumab. Design of this study has been published elsewhere [9]. Complete asthma control was considered if the patient had no diurnal asthma symptoms or asthma symptoms ≤2 days/week, no nocturnal symptoms, no need for rescue medication or ≤2 days/week, normal pulmonary function, no activity limitation, and non-severe asthma exacerbation during this period. These patients can be considered hyper responders. Each patient had been
retrospectively assigned by their physician within 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), being the phenotypes nowadays more concise and less numerous. The use of older definitions in the FENOMA study led to difficulties in selecting phenotype by the physician, as required by the design of the study, due to phenotype overlapping [9]. Thus, in order to find an unsupervised manner description of responders to omalizumab, we performed a post hoc cluster analysis of this population with intending to find phenotypes among these patients who had achieved complete control of the disease during the first year of treatment with omalizumab and provide their identification in the real-life clinical setting. Variables used to determine clusters and Materials and Methods are described in Table 1 and Supplementary Information, respectively.

Four clusters were identified in 256 patients: C1, C2, C3, and C4, which included 141 (55.1%), 96 (37.5%), 12 (4.7%), and 7 patients (2.7%), respectively. The cluster analyses is described in Supplementary Table 1 and cluster demographics and clinical characteristics are presented in Supplementary Table 4. Correlation analysis was carried out to analyze response to treatment among the main clusters and specific post-treatment parameters. The included parameters were severity criteria, improved asthma control, exacerbation decrease, use of health care resources, and background treatment (rescue medication, inhaled and oral corticosteroids (OCS). Due to the low number of patients, C3 and C4 clusters were not considered for further analysis. Supplementary Tables 5 and 6 show the comparison of C1 and C2 and the summary of multivariate analysis results.

We found two distinct and predominant phenotypes of severe asthma in patients showing full response to omalizumab, as C1 and C2 clusters accounted for 92% of the patients. C1 cluster reflected a less allergic phenotype with middle-aged (median: 55 years), overweight (median
BMI: 29), female predominance (75.2%) patients, who had reduced lung function (forced expiratory volume in one second (FEV\textsubscript{1}) \(\leq\)80%; 86.5%). Patients were highly symptomatic with more number of clinical significant exacerbations (median, 3.0) but, did not require hospital admission; 74.5% patients required OCS. The C2 phenotype had younger patients (median age: 40.5 year) with discrete female predominance (56.3%), normal weight (median BMI: 23.6), better pulmonary function (FEV\textsubscript{1} \(\leq\) 80%; 42.7%). Patients were less symptomatic and clinically significant exacerbations (median, 2.0) with a high percentage of atopy (46.9%) and high total IgE levels (median: 397.5 IU/mL), with 45.8% patients requiring OCS.

As a whole, patients’ characteristics of both phenotypes, including age, BMI, smoking status, gender, FEV\textsubscript{1}, number of comorbidities, IgE levels, and the annual rate of severe asthma exacerbations were very similar to previous studies, reinforcing the validity of C1 and C2 clusters in the real-life clinical setting [5, 7, 11, 12]. Regarding the values of biomarkers as eosinophils or fractional exhaled nitric oxide (FeNO), there were no differences between C1 and C2.

Our study patients were selected because they were hyper responders after treatment with omalizumab, i.e., they achieved complete control of asthma. Recently, there has been a focus on remission of asthma [13, 14]. Menzes-Gow et al. [14] considered remission if (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 corticosteroid therapy for exacerbation treatment or long-term disease control. Our patients fulfilled these criteria after one year of treatment with omalizumab, although confirming longer term follow-up is logically needed.

Interestingly, the XPORT study population, in which no exacerbations were observed in 47.7% of patients one year after discontinuation of omalizumab, were mainly of obese female asthmatics with low lung function [15].
In conclusion, after unbiased cluster analyses, we found two particular responder groups of patients. One was middle-aged obese women, highly symptomatic, corticodependent, low lung function, not necessarily allergic, and having many exacerbations. The other one was allergic non-obese asthmatic patients with many exacerbations but better lung function and lower corticodependency. Whether these phenotypes are particularly response prone to omalizumab should be confirmed by prospective studies.

Conflict of interests:
Dr. Dávila reports non-financial support from Novartis, during the conduct of the study; personal fees from Novartis, Sanofi, GSK, ASTRA-ZENECA, LETI; ALK, STALLEGENSES, DIATER, CHIESI, INMUNOTEK; grants and personal fees from THERMOFISHER, outside the submitted work.
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Data sharing statement

Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.
References

## Table

### Table 1. Variables used to determine clusters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Forced Expiratory volume in one second (FEV&lt;sub&gt;1&lt;/sub&gt;)</td>
</tr>
<tr>
<td>Sex</td>
<td>Blood eosinophil count</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Number of non-severe asthma episodes</td>
</tr>
<tr>
<td>Comorbidities&lt;sup&gt;§&lt;/sup&gt;</td>
<td>Number of visits to the emergency room due to asthma exacerbation</td>
</tr>
<tr>
<td>Time from asthma diagnosis to severe asthma diagnosis</td>
<td>Admissions to ICU due to asthma exacerbation</td>
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<tr>
<td>Duration of severe asthma until therapy</td>
<td>Dose of inhaled corticosteroids</td>
</tr>
<tr>
<td>BMI</td>
<td>Oral corticosteroids</td>
</tr>
<tr>
<td>Rescue medication (short-acting β&lt;sub&gt;2&lt;/sub&gt; agonist)</td>
<td>Total serum IgE</td>
</tr>
<tr>
<td>Asthma control (GEMA criteria)</td>
<td>Skin prick tests</td>
</tr>
</tbody>
</table>

<sup.§</sup> Allergic rhinitis, nasal polyps, chronic sinusitis, and atopic dermatitis

BMI, body mass index; GEMA, Spanish Guideline on the Management of Asthma; ICU, intensive care unit; IgE, immunoglobulin E