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

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.18176/jiaci.0731

Key words: IgE, Asthma, Allergens and Epitopes, Eosinophils.

Palabras clave: IgE, Asma, Alérgenos y Epítopos, Eosinófilos.

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

doi: 10.18176/jiaci.0731

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), overweighed (median

doi: 10.18176/jiaci.0731

BMI: 29), female predominance (75.2%) patients, who had reduced lung function (forced expiratory volume in one second (FEV_1) ≤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 ($FEV_1 \leq 80\%$: 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_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].

doi: 10.18176/jiaci.0731

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, STALLERGENES, DIATER, CHIESI, INMUNOTEK; grants and personal fees from THERMOFISHER, outside the submitted work.

Dr. CAMPO reports personal fees from NOVARTIS, during the conduct of the study.

Dr. Cimbollek reports non-financial support from Novartis Farmacéutica, during the conduct of the study; personal fees from AstraZeneca, GSK, Chiesi, Novartis, Sanofi, TEVA, LETI, Diater, Termofisher Diagnostics, ALK, outside the submitted work.

Dr. Almonacid has participated in grants, speaking activities, advisory committees and consultancies during the period 2017-2020 sponsored by: AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, ALK Mundipharma, Novartis, Pfizer, SEPAR and NEUMOMADRID. Dr. Almonacid declares not receiving ever, directly or indirectly, funding from the tobacco industry or its affiliates.

Dr. Quirce reports personal fees and non-financial support from GSK, AstraZeneca, Sanofi, Novartis, Mundipharma, Teva, Allergy Therapeutics, outside the submitted work.

Dr. Moreira reports personal fees from Novartis Farmacéutica, S.A, outside the submitted work.

Andreina Ramirez reports personal fees from Novartis Farmacéutica, S.A, outside the submitted work.

Dr. Soto-Campos reports non-financial support from Novartis, during the conduct of the study; personal fees from Astrazeneca, Boehringer, Novartis, GSK, Chiesi, Bial, Menarini, outside the submitted work.

doi: 10.18176/jiaci.0731

Acknowledgements

This study was sponsored by Novartis Farmacéutica SA, Spain, in accordance with principles of ICH for Good Clinical Practices (GCP). We would like to thank the following contributors to this work: Ada Luz Andreu Rodríguez, Adalberto Pacheco Galván, Adolfo Baloira Villar, Aizea Mardones Charroalde, Alberto Levy Nahon, Alicia Padilla Galo, Ana Gómez-Bastero Fernández, Ana Montoro de Francisco, Ángel Blasco Sarramian, Ángel Ferrer Torres, Antonio León Jiménez, Antonio Moreno Fernández, Antonio Pablo Arenas Vacas, Astrid Crespo Lessmann, Beatriz Huertas Barbudo, Beatriz Rodríguez Jiménez, Carlos Martínez Rivera, Carlos Sanjuas Benito, Celia Pinedo Sierra, Consuelo Fernández Rodríguez, Enrique Macias Fernández, Eva Martínez Moragón, Fernando Ruiz Mori, Francisco Javier Guerra, Gemma Jorro Martínez, Gerardo Pérez Chica, Héctor Manuel González Expósito, Irene de Lorenzo García, Isabel María Flores Martín, Isabel Molero Sancho, Jacinto Ramos González, Joan Serra Batlles, Joaquín Quiralte Enríquez, José Angel Carretero, José Antonio Gullón Blanco, José Carlos Orta Cuevas, José Fernando Florido López, Juan Guallar Ballester, Lucía Gimeno Casanova, Luis Carazo Fernández, Luis Mateos Caballero, María José Torres Jaén, Marina Blanco Aparicio, Manuel Agustín Sojo González, Manuel García Marron, Mar Mosteiro Añón, María Ángeles Peña, María Jesús Rodríguez Nieto, Maria Purificación Jiménez, Marta Reche Frutos, Mercedes Cimarra Alvarez, Miguel Angel Díaz Palacios, Miguel Angel Tejedor Alonso, Patricia Mata Calderón, Pedro Cabrera-Navarro, Pilar Cebollero Rivas, Pilar Serrano Delgado, Rafael Llatser Oliva, Ramón Rodríguez Pacheco, Rosa Irigay Canals, Ruperto González Pérez, Sandra Dorado Arenas, Sheila Cabrejos Perotti, Teodoro Montemayor Rubio,Vanesa Vicens Zygmunt, and Anna Lladonosa Montull.
The authors were provided assistance in the preparation of the manuscript by Ernesto Estefanía (Pivotal), Aakash Katdare and Rabi Panigrahy (Novartis) and was funded by Novartis

doi: 10.18176/jiaci.0731

Farmaceutica S.A., in accordance with Good Publication Practice (GPP3) guidelines (http ://www.ismpp.org/gpp3).

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.

doi: 10.18176/jiaci.0731

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doi: 10.18176/jiaci.0731

Table

Table 1. Variables used to determine clusters

Variables	
Age	Forced Expiratory volume in one second (FEV_1)
Sex	Blood eosinophil count
Smoking history	Number of non-severe asthma episodes
Comorbidities[§]	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

[§]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