Basal clinical characteristics and phenoendotypes of patients with severe asthma in Alergodata: The Spanish Allergy Society Registry

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Palabras clave: Asma grave. Rinosinusitis crónica con pólipos nasales. Evidencia basada en la práctica clínica. Registro.

Asthma is a heterogeneous chronic condition, which includes several phenotypes that share similar clinical manifestations [1]. 5% to 10% of asthmatics suffer from severe asthma (SA) [2], and despite appropriate therapy, approximately 50% of them remain with uncontrolled symptoms [3].

Chronic rhinosinusitis (CRS) is a group of disorders that also includes several phenotypes, the most debilitating of which is CRS with nasal polyps (CRSwNP), which affects 2.1% to 4.4% people in Europe [4]. CRSwNP lacks highly efficacious treatment approaches and can influence lower airway disease (AD) status in adults [4].

Severe Asthma and CRSwNP are often associated as comorbidities [4].Asthma is estimated to affect 40% to 70% of patients with CRSwNP, and CRSwNP ranges from 57% to 62% in SA, both situation being associated with worse outcomes [4].

Recent studies evidenced that similar pathophysiological mechanisms underlie CRSwNP and asthma, the type 2 (T2) endotype being the most frequent in western latitudes [5]. Advances in the understanding of the T2 inflammation mechanisms [4] has led to the development of new classes of biological drugs [6] and to the emergence of the "united airways diseases" (UAD) concept, establishing the need for an integrated approach to the diagnosis and treatment of airway diseases [7, 8].

However, upper and lower AD are still considered separate entities in routine clinical practice, so further studies and real-world data are needed to address the lack of evidence in the management of UAD [8], as well as to determine the most appropriate biologics and how they fare in the long run to help with treatment decision-making. [8]

In this context, and as part of an action plan to provide *real-word evidence* on health outcomes in major allergic diseases, the Spanish Society of Allergology and Clinical Immunology (SEAIC) implemented the Alergodata Registry, whose primary objective was to describe patients' characteristics and the use of biological drugs in SA and/or CRSwNP.

In the present manuscript, we present and discuss the SA and CRSwNP data collected during the baseline visits in the first year (from November 19, 2021, to December 1, 2022) of the Alergodata study.

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Patients with a diagnosis of SA and/or CRSwNP (EPOS2020), on treatment with biologic drugs and/or with other non-biologics therapies, attended in allergy units, were included, after signing the informed consent (see inclusion/exclusion criteria in Table 1, Supplemental Files), for a follow-up of 5 years with at least one annual visit. Each principal investigator recorded the patient's information in an electronic case report form (eCRF) designed specifically for the study, the data of which was stored in a database and periodically reviewed to detect possible inconsistencies and/or missing data. This database includes ranges and internal consistency rules to ensure correct data completion and thus ensure optimal quality. The protocol was evaluated by the autonomous community health agencies and Research Ethics Committees (RECs) of the 61 Spanish hospitals participating in the study, and the favourable opinion of the REC of the Hospital Clinic de Barcelona was obtained on March 4, 2021. The most relevant collected variables are presented in Table 2, Supplemental Files. The precise methodology was published previously [9].

Two hundred and seventy-nine patients with SA were included, of whom 170 received biological treatment (60.9%), with 79.5% of patients with uncontrolled asthma. Of these 170 patients, 75 had comorbid CRSwNP (44.2%), which is consistent with the results of other series [10] even if lower than the usual prevalence data [4]. Regarding the biologic treatments at the time of inclusion, Dupilumab was much more prescribed than all other treatments in case of SA with comorbid CRSwNP. Also, it is worth noting that even if Benralizumab is not indicated for the treatment of CRSwNP, it was prescribed in 4.2% of cases for asthma with comorbid CRSwNP which is consistent with the good results obtained in the phase 3 OSTRO Study [11]. In the table 1 we gathered the main characteristics, comparing patients with SA with patients with both SA and CRSwNP.

The Alergodata registry provides valuable data, that can be compared to other series as, for example, the ENEAS series [12] or the Spanish MEGA Cohort [13]. Particularly, we found that more than 50% of the patients presented allergic asthma whereas in the ENEAS series, the majority (58.1%) presented an eosinophilic endotype. But it must be considered that these phenoendotypes may change and even overlap during the patient's lifetime[14]. As a matter of fact, one of the main reported triggers of asthma exacerbations (AE) was allergens (see Table 2, Supplemental Files), even if we must be cautious with these results given that AE is usually triggered by various factors. Also, it was reported a clinically relevant allergic sensitization in 65.7% of the cases and, for the first time in a registry, the cumulative annual dose of corticoids. These last three data highlight the originality of the Alergodata registry, given that they are not usually reported in series of that kind.

The study also presents limitations. One of them is that the registry is still young to extract meaningful and comparative data. But we must keep in mind that it is a project that will remain open for five years, allowing us to compare initial, intermediate, and final results, and to measure the impact of biological treatment on the disease's progression. Another limitation comes from the registry itself and the analytical methodology. On one hand, the analysed data come from the clinical practice, so the sample size will depend on the fluctuation of patients in consultation, which could generate missing data. On the other hand, statistical analysis was done according to protocol, so subanalysis would be required to extract the full value of the data.

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Patients with UAD, in particular SA and CRSwNP, are more refractory to treatments, due to increased airway obstruction and higher number of exacerbations [15], and such a registry will help provide insight for clinicians regarding the real benefit of biological drugs, both in terms of efficacy and safety, as well as their impact in reducing the use of other non-biological treatments.

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Conflict of interests

In the last three years, Javier Domínguez-Ortega has received fees for advisory from GSK, SANOFI, and AstraZeneca and has received speaker's honoraria from Sanofi, TEVA GSK, AstraZeneca, Bial, Novartis, Chiesi, and LETI Pharma.

In the last three years, Carlos Colás has received honoraria for consultancy and conferences from Novartis, GSK, Sanofi, Viatris, Chiesi, MSD, Takeda, Roxall, and ThemoFisher.

In the last three years, Julio Delgado Romero has received fees for advisory boards from Bial, has received speaker's honoraria from AstraZeneca, Bial, Chiesi, GlaxoSmithKline Novartis, and Sanofi, and received Grant/Research Support from AstraZeneca and Orion. He also received help assistance with meeting travel from Sanofi and Menarini.

In the last three years, Alicia Habernau Mena has received payment or honoraria for consultancy and conferences from ALK-Abelló, Leti, GSK, Sanofi, Chiesi, GlaxoSmithKline, Bioproject, AstraZéneca, MSD and FaesPharma

In the last three years Ana Montoro has received honoraria for consultancy and conferences from GSK, Astra Zeneca, Chiesi and Letipharma and received research/training support from Faes Farma, Allergy therapeutics, ALK and DIATER. She also received assistance with meeting travel from Roxall and Takeda.

In the last three years, Pilar Barranco has received speaker's honoraria from GlaxoSmithKline

In the last three years, Patricia Prieto Montaño declares payment or honoraria for presentations, speakers or educational events by Leti, Allergy Therapeutics, Diater, Astra Zeneca, GSK and Sanofi and payment for expert testimony by Astra Zeneca , Sanofi and GSK.

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In the last three years, Juan Fraj Lázaro has received consulting fees from AstraZeneca and Sanofi, and has received speaker fees from Gebro, AstraZeneca, GSK, Sanofi, Novartis and Chiesi.

In the last three years, Pedro Galindo, has received honoraria for conferences from Novartis, GSK, Sanofi, Chiesi and Astra-Zeneca.

In the last three years Maria Gil Melcón has received honoraria for consultancy and conferences from AstraZeneca, Novartis, Sanofi y GSK

In the last three years, María Magdalena Lluch Bernal, has received speaker's fees from GSK, and manuscript writing and help to congress assistance by Menarini.

In the last three years, Ruperto González-Pérez, has received fees related to advisory boards from GSK, AstraZeneca, Leo Pharma and Sanofi; speaker's honoraria from GSK, AstraZeneca, Sanofi, Inmunotek, Diater, and Leti, and research grants from SEAIC and FUNCANIS.

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In the last three years, Javier Montoro Lacomba has received speaker's honoraria from GSK, Sanofi, Diater, Chiesi, Abbvie, and Faes.

In the last three years, Antonio Valero was an advisor for Sanofi, Uriach, AstraZeneca, ALK, and Allergy Therapeutics; received speaker's fees in meetings sponsored by AstraZeneca, Chiesi, Bial, and GSK; and received research project grants by Novartis and Uriach.

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Table 1. Main clinical and socio-demographic variables of the patients included in the Alergodata Registry

Clinical and socio-demographic variables	Severe Asthma	Severe Asthma [a] with CRSwNP
Age	**N=170**	**N=30**
Adults, Mean ± SD (n)	50.6 ± 14.4 (n=158)	51.4 ± 12.4
Children, Mean ± SD (n)	13.8 ± 3.8 (n=12)	N/A
Sex	**N=170**	**N=30**
Woman (%)	64.1%	50.0%
Comorbidities (%)	**N=170**	**N=30**
CRSwNP [a]	44.1%	N/A
CRS without nasal polyps	7.1%	N/A
Atopic Dermatitis [a]	10.0%	10.0%
Rhinitis	68.0%	65.5%
Gastroesophageal reflux	17.1%	10.0%
Psychiatric disturbance	11.8%	6.67%
Respiratory disease exacerbated by NSAIDs	18.2%	50.0%
Bronchiectasis	7.7%	10.0%
Obstructive sleep apnea	7.1%	6.9%
Exacerbations, Mean ± SD	1.9 ± 2.3 (N=143)	N/A
Level of uncontrolled asthma, %	79.5% (N=132)	N/A
Phenotypes of asthma (%)	**N=146**	**N=22**
Eosinophilic (T2)	47.9%	77.3%
Allergic (T2)	50.7%	22.7%
Non-eosinophilic	1.4%	0.0%
Prescribed biologic treatment, % (N)		
Omalizumab	28.6% (N=168)	12.5% (N=24)
Dupilumab	27.9% (N=165)	69.6% (N=23)
Mepolizumab	23.4% (N=167)	20.8% (N=24)
Benralizumab	20.4% (N=157)	4.2% (N=24)
Reslizumab	3.8% (N=158)	4.0% (N=25)

[a] (with or without associated biologic treatment)

N/A, Not applicable; CRSwNP, chronic rhinosinusitis with nasal polyps; CRS, chronic rhinosinusitis; NSAIDs, Non-steroidal anti-inflammatory drugs.