Impact of obesity and lung function on the efficacy of biological treatment in patients with asthma

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Severe, uncontrolled asthma represents a major therapeutic challenge. Biological drugs have changed the prognosis of asthma patients by achieving better control of the disease and reducing exacerbations. However, a non-negligible percentage of patients do not respond to these treatments or do so only partially [1-3]Haga clic o pulse aquí para escribir texto..

The objective of this cross-sectional study was to determine the percentage of patients with severe asthma under treatment with biologic drugs who have good control of their disease, and to list the variables that determine poor control. The study sample comprised all patients, over the age of 18, diagnosed with severe asthma who were attended at a specialized severe asthma clinic at a tertiary hospital and who were receiving treatment with a biological drug in February 2021 for at least during de last 6 months. The study was approved by the hospital's Ethics Committee (PR(AG)78/2022). All patients provided written informed consent prior to participation.

Patients were classified into two groups according to whether their asthma was controlled: patients with ACT≥20 (group 1, controlled) and patients with ACT<20 (group 2, uncontrolled) (Supplementary material). In all patients, demographic data, clinical characteristics of the disease, comorbidities, data on lung function and the treatment they were undergoing (Table 1. Supplementary material) were obtained from the medical history. A patient was considered to have a T2-Th2 phenotype when there was clinically relevant sensitization to respiratory allergens, and a T2-ILC2 phenotype when there was eosinophilia in blood (>300 cells/mm^3) or sputum (>3%) without the presence of allergy. A BMI above 30 indicated obesity. Patients were considered to have suffered an exacerbation when they required at least 30 mg/day for 5 days of oral

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corticosteroids, regardless of whether they had to go to the emergency room or required hospitalization.

A comparative and multivariate analysis was carried out between the groups to identify the variables that might explain the poor asthma control. Continuous variables with normal distribution were analyzed using the Student t test, and variables that followed an ordinal scale using the Mann-Whitney test; Categorical variables were analyzed using the Chi-square test or Fisher's exact test.

One hundred and thirteen patients were studied; 62 received omalizumab, 21 mepolizumab, 27 benralizumab, and three reslizumab. Ninety-four patients were assigned to group 1 and 19 to group 2. Differences between the groups were found in the rate of obese patients (15% vs 47% respectively p=0.001), in FEV1 (78% vs 69% p=0 .05) and in the rate of exacerbations (17% vs 53% p = 0.004) (Table 1). A multivariate analysis confirmed obesity as a risk factor for non-control of asthma with an OR of 5.908 (95% CI 1.757-19.853; p=0.004). The OR of presenting exacerbations was 1.612 (95% CI 1.095-2.371; p=0.015) in patients with uncontrolled asthma compared to those with controlled asthma. No significant differences were observed according to the biological treatment (Table 2. Supplementary material).

The majority of patients with severe asthma treated with biologics have good clinical control of the disease. However, up to 17% may present persistent symptoms and exacerbations. Obesity and impaired lung function seem to be associated with this poor control.

There are three possible explanations for the impact of obesity on the effectiveness of biological treatment. Firstly, although there was a T2 response in all the patients studied, it may be attenuated by an increase in the activity of the NLRP3 inflammasome and of the ILC3 which produce the cytokines IL-1B and IL-17 characteristic of patients with obesity [4]. In addition, adipose tissue can produce adiponectin, TNF alpha, leptin, and IL-6, increasing the proinflammatory state and leading to metabolic dysfunction. These events have been related to the activation of monocytes and macrophages and to disruptions in eosinophil recruitment and survival [5]Haga clic o pulse aquí para escribir texto.. For example, the increase in oxidative stress

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at mitochondrial level secondary to these changes decreases the bioavailability of nitric oxide at cellular level, which lowers FENO and eosinophil values in obese patients compared with patients of normal weight [5,6]Haga clic o pulse aquí para escribir texto.. This T2 response, either attenuated and/or replaced by the inflammatory response associated with obesity, may explain the lack of efficacy of biological treatments, as in the case of obese patients administered inhaled corticosteroids [7]Haga clic o pulse aquí para escribir texto..

Secondly, the possibility that the dose of the biological treatment may be insufficient should also be considered. Indeed, not all biological drugs can be adjusted based on the patient's weight, and some obese patients may be under-treated [8]. Finally, obesity is a pathology that usually coexists with other comorbidities which may interfere with asthma control and may therefore condition the response to treatment with biological drugs [9]. However, we stress that in this study there were no differences between drugs depending on whether or not they were adjusted according to the patient's weight, nor any differences in terms of comorbidities between controlled and uncontrolled patients. In this sense, comorbidities such as nasal polyposis do not seem to influence asthma control and even it is shown that, biologics administered in severe asthma, have a more marked clinical effect in patients with concomitant nasal polyposis [10].

Although at the limit of significance, patients with uncontrolled asthma had worse lung function despite treatment with biological drugs. A decreased FEV1 has been associated with persistence of symptoms, impaired quality of life and, above all, a higher frequency of exacerbations [11]. The remodeling phenomena involved in this decrease in FEV1, which is sometimes non-reversible, may also condition the response to biological drugs. Although some of these drugs have been found to improve FEV1 by up to 300 mL [12], to date there is no clear evidence that they can also act on airway remodeling.

The present study is not without limitations. Basically, it is a single-center, real-life, retrospective, not controlled study in which only the clinical control component of asthma is evaluated; other essential therapeutic objectives such as exacerbations, lung function itself or dependence on oral corticosteroids were not assessed. In this sense, response to biologic drugs must be assessed

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globally, considering all the clinically meaningful therapeutic goals [3]. However, as this study has also shown, it is the lack of clinical control that is most closely related to the risk of presenting exacerbations. Likewise, a poor symptom control and a greater number of exacerbations lead to the overuse of oral corticosteroids. We conclude that obesity and impairment of lung function could be relevant factors involved in the non-control of severe asthma patients receiving treatment with biological drugs. Therefore, it seems essential to adopt strategies to improve lung function and, above all, to reduce weight, if the aim is to improve the efficacy of biological treatments in asthmatic patients with obesity.

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Conflict of interest

Dr. Munoz reports personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva, Mundifarma, Chiesi, Faes, outside the submitted work. The other authors have no competing interests to declare.

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Table 1: Demographic characteristics of patients with ACT ≥ 20 (group 1, controlled) and patients with ACT < 20 (group 2, uncontrolled).

		n = 113	ACT ≥ 20 n = 94	ACT < 20 n = 19	p
Age, median (range)		56 (19 - 81)	56 (19 – 81)	49 (27 – 72)	0.413
Gender, female, n (%)		70 (62)	57 (61)	13 (68)	0.524
Smoking habit, n (%)					0.215
Smoker		6 (5)	4 (4)	2 (10)	
Non-smoker		83 (74)	72 (77)	11 (58)	
Ex-smoker		24 (21)	18 (19)	6 (32)	
BMI, median (range)		26 (19 – 52)	26 (19 – 38)	29 (21 – 52)	**0.001**
Asthma phenotype, n (%)					0.203
T2-TH2		75 (66)	60 (64)	15 (79)	
T2-ILC2		38 (34)	34 (36)	4 (21)	
Eosinophils, x 10^9; median (range)		0.4 (0 – 29)	0.4 (0 – 29)	0.3 (0 – 1.10)	0.147
Total IgE, KU/L; median (range)		276 (4 - 3178)	248 (4 – 3178)	342 (28 – 1498)	0.249
FeNO*		43 (6 – 187)	43 (6 – 186)	43 (12 – 187)	0.465
Polyps, n (%)		56 (50)	48 (51)	8 (42)	0.476
Rhinitis, n (%)		78 (69)	65 (69)	13 (68)	0.950
Sinusitis, n (%)		50 (44)	44 (47)	6 (31)	0.223
Dermatitis, n (%)		26 (23)	23 (24)	3 (16)	0.412
Comorbidities, n (%)**		84 (74)	68 (72)	16 (84)	0.280
Rheumatic disease, n (%)		18 (16)	18 (19)**	0 (0)	**0.037**
Obesity, n (%)		23 (20)	14 (15)	9 (47)	**0.001**
NSAID intolerance, n (%)		34 (30)	29 (31)	5 (26)	0.694
Bronchiectasis		25 (22)	22 (23)	3 (16)	0.133
Severe exacerbations, n (%)***		26 (23)	16 (17)	10 (53)	0.004
Hospital admissions last 18 months, n (%)		3 (3)	3 (3)	0 (0)	0.732
	FVC,	84 (43 – 122)	87 (43 – 122)	78 (54 – 107)	0.163
	FEV1,	76 (30 – 121)	78 (30 – 121)	69 (41 – 91)	0.055

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Pulmonary function, (%predicted)	**FEV1/FVC Ratio**	70 (42 – 100)	71 (42 – 100)	66 (55 – 80)	0.288
Pulmonary function, z score	**FVC**	-0.71 (-3.97 – 2.60)	-0.58 (-3.97 – 2.60)	-0.77 (-2.71 – 1.04)	0.463
	FEV1	-1.39 (-4.41 – 2.14)	-1.24 (-4.41 – 2.14)	-1.73 (-3.43 – 0.29)	0.657
	FEV1/FVC Ratio	-1.41 (-4.32 – 1.74)	-1.35 (-4.32 – 1.74)	-1.93 (-3.46 - - 0.08)	0.246
Follow-up, month; median (range)		20.5 (6 – 156)	21.5 (6 – 156)	15.5 (6 – 95)	0.374
Days of treatment; median (range)		707 (0 – 4791)	656 (0 – 4791)	497 (73 - 2915)	0.999
Treatment adherence, Yes, n (%)		107 (95)	89 (95)	18 (95)	0.992

BMI – Body mass index; NSAID - Non-steroidal anti-inflammatory drugs. * FeNO: Quantified in 60 patients (47 in ACT > 20 and 13 in ACT < 20 Groups); ** Vasculiits in 11 patients (10 eosinophilic granulomatosis with polyangiitis and 1 granulomatosis with polyangiitis), treated with oral corticosteroids (daily prednisone equivalent dose; median (range) = 5 (2.5 – 20). Psoriasis/dermatitis in one patient, treated with (methotexate). The rest of the patients presented osteoporosis and did not receive treatment with oral corticosteroids. *** Number of exacerbations in patients with a follow-up of less than 12 months: ACT ≥ 20 = 2 and ACT < 20 = 2. Non-significant comorbidities are shown in Table 3 of the supplementary material.

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