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 improving control of the disease and reducing the frequency of exacerbations. However, a nonnegligible percentage of patients do not respond to these treatments or do so only partially [1-3].

The objectives of this cross-sectional study were to determine the percentage of patients with severe asthma under treatment with biologic drugs who control their disease well and to list the variables that determine poor control. The study sample comprised all patients aged ≥18 years diagnosed with severe asthma who were attended at the specialized severe asthma clinic of a tertiary hospital and who, in February 2021, had been receiving treatment with a biological drug for at least the previous 6 months. The study was approved by the hospital's ethics committee (PR(AG)78/2022). All patients provided their written informed consent prior to participation.

Patients were classified into 2 groups according to whether their asthma was controlled or not, as follows: patients with an Asthma Control Test (ACT) score ≥20 (group 1, controlled) and patients with ACT <20 (group 2, uncontrolled) (Supplementary material). Demographic data, clinical characteristics of the disease, comorbidities, data on lung function, and current treatment were obtained from the medical history (Table 1. Supplementary material). A patient was considered to have a T2-T_H2 phenotype when there was clinically relevant sensitization to respiratory allergens, and a T2-ILC2 phenotype when the blood eosinophil count was >300/mm^3 or the sputum value was >3% in the absence of allergy. A body mass index above 30 indicated obesity. Patients were considered to have experienced an exacerbation when they required oral corticosteroids for at least 5 days at 30 mg/d, regardless of whether they had to attend the emergency department or required hospitalization.

A comparative and multivariate analysis was carried out between the groups to identify the variables that might explain poor asthma control. Normally distributed continuous variables were analyzed using the *t* test. Ordinal variables were assessed using the Mann-Whitney test. Categorical variables were analyzed using the χ^2 test or Fisher exact test.

We studied 113 patients: 62 received omalizumab, 21 mepolizumab, 27 benralizumab, and 3 reslizumab. Ninety-four patients were assigned to group 1 and 19 to group 2. Differences between the groups were found for obesity (15% vs 47%, respectively, *P*=.001), FEV_1 (78% vs 69%, *P*=.05), and exacerbations (17% vs 53%, *P*=.004) (Table). A multivariate analysis confirmed obesity as a risk factor for poor control of asthma with an OR of 5.908 (95%CI, 1.757-19.853; *P*=.004). The OR for exacerbations was 1.612 (95%CI, 1.095-2.371; *P*=.015) in patients with poorly controlled asthma compared to those with controlled asthma. No significant differences were observed according to the biological treatment administered (Table 2, Supplementary material).

Severe asthma is clinically controlled with biologics in most cases. However, up to 17% of patients may present persistent symptoms and exacerbations, possibly owing to obesity and impaired lung function.

There are 3 possible explanations for the impact of obesity on the effectiveness of biological treatment. First, although all the patients studied had a T2 response, this may be attenuated by an increase in the activity of the NLRP3 inflammasome and of ILC3, which produces the cytokines IL-1B and IL-17 (characteristic of obese patients) [4]. In addition, adipose tissue can produce adiponectin, TNF-α, 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]. For example, the increase in oxidative stress at mitochondrial level secondary to the abovementioned changes decreases the bioavailability of nitric oxide at cellular level, thus lowering FeNO and eosinophil values in obese patients compared with normal-weight patients [5,6]. This T2 response, which is 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 prescribed inhaled corticosteroids [7].

Second, 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 body weight, and some obese patients may be undertreated [8]. Third, obesity is a pathology that usually co-occurs with other comorbidities that may interfere with asthma control and 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 they were adjusted according to body weight. Similarly, there were no differences in comorbidity between patients with controlled and poorly controlled disease. In this sense, comorbidities such as nasal polyposis do not seem to influence control of asthma. Moreover, biologics administered in severe asthma have a more marked clinical effect in patients with concomitant nasal polyposis [10].

Table. 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* Value
Median (range) age, y	56 (19-81)	56 (19-81)	49 (27-72)	.413
Female sex, No. (%)	70 (62)	57 (61)	13 (68)	.524
Smoking habit, No. (%)				.215
Smoker	6 (5)	4 (4)	2 (10)	
Nonsmoker	83 (74)	72 (77)	11 (58)	
Ex-smoker	24 (21)	18 (19)	6 (32)	
Median (range) BMI	26 (19-52)	26 (19-38)	29 (21-52)	.001[d]
Asthma phenotype, No. (%)				.203
T2-T_H2	75 (66)	60 (64)	15 (79)	
T2-ILC2	38 (34)	34 (36)	4 (21)	
Median (range) eosinophils, × 10^9	0.4 (0-29)	0.4 (0-29)	0.3 (0-1.10)	.147
Median (range) total IgE, kU/L	276 (4-3178)	248 (4-3178)	342 (28-1498)	.249
FeNO[a]	43 (6-187)	43 (6-186)	43 (12-187)	.465
Polyps, No. (%)	56 (50)	48 (51)	8 (42)	.476
Rhinitis, No. (%)	78 (69)	65 (69)	13 (68)	.950
Sinusitis, No. (%)	50 (44)	44 (47)	6 (31)	.223
Dermatitis, No. (%)	26 (23)	23 (24)	3 (16)	.412
Comorbidities, No. (%)[b]	84 (74)	68 (72)	16 (84)	.280
Rheumatic disease, No. (%)	18 (16)	18 (19)[b]	0 (0)	.037[d]
Obesity, No. (%)	23 (20)	14 (15)	9 (47)	.001[d]
NSAID intolerance, No. (%)	34 (30)	29 (31)	5 (26)	.694
Bronchiectasis	25 (22)	22 (23)	3 (16)	.133
Severe exacerbations, No. (%)[c]	26 (23)	16 (17)	10 (53)	.004
Hospital admissions last 18 months, No. (%)	3 (3)	3 (3)	0 (0)	.732
Pulmonary function, % predicted				
FVC	84 (43-122)	87 (43-122)	78 (54-107)	.163
FEV_1	76 (30-121)	78 (30-121)	69 (41-91)	.055
FEV_1/FVC ratio	70 (42-100)	71 (42-100)	66 (55-80)	.288
Pulmonary function, z score				
FVC	–0.71 (–3.97 to 2.60)	–0.58 (–3.97 to 2.60)	–0.77 (–2.71 to 1.04)	.463
FEV_1	–1.39 (–4.41 to 2.14)	–1.24 (–4.41 to 2.14)	–1.73 (–3.43 to 0.29)	.657
FEV_1/FVC ratio	–1.41 (–4.32 to 1.74)	–1.35 (–4.32 to 1.74)	–1.93 (–3.46 to –0.08)	.246
Median (range) follow-up, mo	20.5 (6-156)	21.5 (6-156)	15.5 (6-95)	.374
Median (range) duration of treatment,[d]	707 (0-4791)	656 (0-4791)	497 (73-2915)	.999
Treatment adherence, yes, No. (%)	107 (95)	89 (95)	18 (95)	.992

Abbreviations: ACT, Asthma Control Test; BMI, body mass index; FeNO, fractional exhaled nitric oxide; NSAID, nonsteroidal anti-inflammatory drug.
[a]FeNO: Quantified in 60 patients (47 in ACT ≥20 and 13 in ACT <20).
[b]Vasculitis 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 1 patient, treated with methotrexate. The remaining patients had osteoporosis and did not receive treatment with oral corticosteroids.
[c]Number of exacerbations in patients with a follow-up of <12 months: 2 in ACT ≥20 and 2 in ACT <20.
[d]Significant values. Nonsignificant comorbidities are shown in Table 3 of the supplementary material.

Although the difference was at the limit of significance, patients with poorly controlled asthma had worse lung function despite treatment with biological drugs. A decreased FEV_1 has been associated with persistence of symptoms, impaired quality of life, and, above all, more frequent exacerbations [11]. The remodeling phenomena involved in this decrease in FEV_1, which is sometimes nonreversible, may also condition the response to biological drugs. While some of these drugs have been found to improve FEV_1 by up to 300 mL [12], there is no clear evidence to date that they can also act on airway remodeling.

The present study is not without limitations. First, it is a single-center, real-life, retrospective, noncontrolled study that only evaluated clinical control of asthma; other essential therapeutic objectives such as exacerbations, lung function itself, and dependence on oral corticosteroids were not assessed. In this sense, response to biologic drugs must be assessed globally, considering all 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. Second, poor symptom control and a greater number of exacerbations led to the overuse of oral corticosteroids.

We conclude that obesity and impairment of lung function could be relevant obstacles to control of severe asthma in patients treated with biologic drugs. Therefore, when attempting to improve the efficacy of biological treatments in asthma patients with obesity, we should make every effort to adopt strategies to improve lung function and, above all, to reduce weight.

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Conflicts of Interest

Dr. Munoz reports personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva, Mundifarma, Chiesi, and Faes, outside the submitted work. The remaining authors declare that they have no conflicts of interest.

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