A real life asthma biologic treatment comparison

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Abstract

Introduction: Biologic drugs have proven to be highly effective in managing severe asthma, improving quality of life, and reducing exacerbations.

Material and methods: We compared the efficacy of omalizumab, mepolizumab, and dupilumab in patients with severe asthma on active pharmacological treatment.

Results: Forty-nine patients with a mean age of 49 years were analyzed, 53.1% women and 46.9% men. 22.4% were ex-smokers compared to 8.2% active smokers. Notable medical history included atopy (42.9%), polyposis (38.8%), sensitization to olive pollen (38.8%), AERD (22.4%), drug allergy (16.3%), and mental health history (10.2%).

Regarding the severe asthma phenotype, they presented a T2 allergic phenotype (57.1%), high T2 (34.7%), and non-T2 (8.2%). It was observed that in all biological drugs, the need to go to the emergency room and the use of oral glucocorticoids was reduced by half in the two years after their administration.

We obtained a naive subgroup of 38 patients without previous biological treatment. The improvement is notable in terms of a lower number of visits to the emergency room and cycles of systemic corticosteroids in the first year of treatment. Improvement in the percentage of FEV1 after one year of treatment in the three groups, but only in a statistically significant way in the Dupilumab treatment group.

Conclusion: Clinical improvement is observed in patients with severe asthma after one year of treatment with different biological drugs, although statistical significance is only obtained in the improvement of functional capacity in the Dupilumab treatment group.

Background

Currently, it is estimated that only a small percentage of asthmatic patients do not achieve adequate control of the disease despite maintaining high doses of inhaled corticosteroids and assuming that they have a correct adherence and inhalation technique [1,2]. In fact, severe asthma currently accounts for 5-10% of all asthma cases and is often driven by type 2 inflammatory mediators. Exacerbations are frequent and sometimes severe in these patients, resulting in a high economic impact due to both direct and indirect costs associated with the disease. Beyond recurrent exacerbations, underlying T2 inflammation can lead to airway remodeling and permanent loss of lung function [3,4].

For them, treatment with monoclonal antibodies targeting underlying inflammatory pathways can improve disease control [5]. There are currently multiple monoclonal antibodies approved for the treatment of asthma. These therapies target key points of the T2 inflammatory pathway, including immunoglobulin E (IgE) (omalizumab) which was the first successful biological target used in patients with allergic disease and asthma [6], interleukin 5 (IL-5) (mepolizumab, reslizumab) or

its receptor (benralizumab), thymic stromal lymphopoietin (TSLP) (tezepelumab) and interleukin 4 receptor subunit alpha (IL4rα) (dupilumab), a common receptor for IL-4 and interleukin 13 (IL-13) signaling [2,5].

While all biologics have individually demonstrated good efficacy and safety profiles, there is a notable absence of head-to-head comparisons of the biologics approved to date, limiting opportunities to optimize patient selection for these expensive treatments [3,6,7].

The treatment choice may be straightforward for individuals who qualify for only one type of therapy. However, there is still uncertainty regarding the most suitable biologic therapy for patients with moderate to severe asthma who exhibit multiple phenotypes simultaneously, such as allergic and eosinophilic asthma, or for those who meet the criteria for several biologic treatments [7,8]. Since these medications have overlapping functions, it is ultimately the responsibility of clinicians treating patients with severe asthma to select the appropriate therapy in the absence of head-to-head effectiveness data from clinical trials [1,3,9].

Furthermore, the potential costs of selecting a less effective biologic drug, sometimes driven by price, in an individual with severe asthma are substantial. Delaying treatment could increase the already high burden of asthma-related morbidity and mortality [7,10,11].

In this context, our study provides valuable data to assist in clinical decision-making. We conducted a retrospective cohort study to evaluate the effectiveness of omalizumab, dupilumab, and mepolizumab in reducing asthma-related exacerbations and improving lung function among our asthma patients in a real-life setting.

Material and Methods

This is a retrospective and observational study. Patients diagnosed with severe asthma who were being followed up in our Allergy Unit at the Virgen del Rocío University Hospital were recruited. At the time of inclusion, dated March 2024, they were being treated with biological drugs with different mechanisms of action: mepolizumab, omalizumab, or dupilumab. Data were taken only from these 3 biological drugs since they were the ones from which we were able to obtain the most data. These drugs had been prescribed according to step 6 of the GEMA guide. All patients had been on their current treatment for at least one year and the results were analyzed at the start of treatment, at 12 months and 24 months if they had been on treatment for more than 2 years. A follow-up period of at least one year was used so that exacerbations were not influenced by the seasons of greatest frequency of infectious or allergic episodes.

Some of these patients had previously received treatment with another biological drug, so a second study was carried out on the subgroup of these patients who were naive and had not received previous treatment.

In this case, data were obtained from the medical records of patients who attended our hospital. This is a retrospective, non-interventional study. All patients were actively receiving biological treatment at the time of inclusion of the data. Data were collected retrospectively on the efficacy of these drugs over at least one year of treatment.

Demographic data, as well as comorbidities recorded at diagnosis, were collected from the clinical history upon arrival at the allergy clinic, before the start of treatment. FeNO, differential blood cell counts, forced expiratory capacity in 1 s (FEV1%), and Tiffeneau (FEV1/FVC%) were obtained as part of routine follow-up care. The lung function was assessed using standardized ERS/ATS spirometry [12]. Asthma control was assessed using the Asthma Control Test (ACT) [13]. Medication changes, exacerbation rates, and ACT scores were reassessed at the start of biologic therapy, at 12 and 24 months. Exacerbation rates were recorded from the medical record in the 12 months before the start of therapy. We defined exacerbations as an acute worsening of asthma symptoms requiring *de novo* OCS or an increase in OCS dose for at least 3 days [14]. Smoking status and comorbidities related to atopic and eosinophilic phenotype were also assessed from the computerized medical record at baseline. Response to biologic therapy was calculated for each patient based on changes recorded during the year before and after the start of therapy in lung function, ACT, OCS dose, and exacerbation rate.

Statistical Study

Data were collected from the patient's medical history or from information stored in the patient's digital history. The variables were collected in a computerized database designed for this project. This database will not store personal data, as they will be encoded in the data collection process from medical history.

Quantitative and qualitative independent variables were studied. The analyses were performed using Jamovi statistical software and IBM SPSS version 29. Descriptive statistics were used, using tables, representing the absolute and relative values of the qualitative variables, as well as measures of central tendency and variability for the quantitative variables. The assumption of normality of the quantitative variables was verified using the Shapiro-Wilk test. The changes in the quantitative variables at the different measurement times were modeled using generalized mixed linear models, trying to control the variability of the individuals. Statistical significance was established for p-value <0.05.

The study has been designed following the ethical principles outlined in the Declaration of Helsinki. It will also adhere to Good Clinical Practice standards and comply with all relevant legal regulations throughout its duration. Furthermore, the privacy and protection of the data collected during the study will be strictly maintained.

Results

Sample overview

Data from 49 patients with a median age of 49 years (15-72 years) at the time of the first consultation were analyzed. The baseline characteristics of all patients, regardless of treatment, were similar in terms of gender distribution (women 53.1% and men 46.9%) and with a similar mean and median BMI of 26 (**Table 1**).

When obtaining data from allergy consultations, most patients had a diagnosis of T2 allergic phenotype (57.1%) and elevated T2 (34.7%).

The median total IgE was 205 kU/L (15-4804 kU/L) and although 42.9% were atopic, only 28.6% of them had clinical relevance compatible with their asthma pathology. In 30% of patients, this information was not collected.

Table 1.

Descriptive				
	Minimum	**Maximum**	**Average**	
				Desv. Error
BMI	17.22	40.51	26.5624	.77092
Age	15	72	48.45	2.032
IGE	15.0	4804.0	461.822	136.8964
FENO	16.0	70.0	33.288	6.0332
FENO postl	5.0	58.0	24.100	7.7861
FENO post2	25	41	33.00	8.000
Eosinophils	0	2430	504.77	65.492
Eosinophils postl	40	1280	346.11	87.295
Eosinophils post2	40	1380	323.33	144.251
Emergency/year	0	11	2.15	.409
Emergency/year postl	0	3	.18	.087
Emergency/year post2	0	1	.10	.066
Corticosteroid /year	0	12	4.00	.515
Corticosteroid/year postl	0	12	.73	.347
Corticosteroid/year post2	0	12	.64	.545
ACT	5	25	13.70	.858
ACT postl	8	25	20.18	.876
ACT post2	15	25	21.11	1.136
FEVI	30	106	75.06	6.378
FEVI postl	52.0	118.0	82.940	2.6922
FEVI post2	58.5	117.0	84.170	6.0544
FEVI/FVC	51	78	66.25	5.662
FEVI/FVC postl	60	103	75.40	7.339
FEVI/FVC post2	60.57	91.68	78.2370	3.72961
SNOT22	63	89	76.00	7.506
SNOT22 postl	11	92	41.00	13.835
SNOT22 post2	0	18	.90	.900

When analyzing the comorbidities that patients presented before biological treatment, we see that 8.2% of the patients were active smokers and 22.4% ex-smokers. That is, 30.6% of the patients had or previously had contact with tobacco.

Chronic rhinosinusitis with nasal polyposis (RNSwPN) was found in 38.8% of patients, aspirin-exacerbated respiratory disease (AERD) in 22.4%, inducible laryngeal obstruction (OLI) in 38.8%, drug allergy in 16.3%, and psychological or psychiatric history in 10%.

As for the rest of the comorbidities, only 2% had a diagnosis of obstructive sleep apnea (OSA) or thyroid pathology, and only 6.1% had gastroesophageal reflux (GER).

A diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was found in 4.1% of patients. No patient was diagnosed with allergic bronchopulmonary aspergillosis (ABPA).

Patients are currently treated with dupilumab (30.6%), mepolizumab (46.9%), and omalizumab (22.4%). 22.4% of patients had previously received other biologics, with omalizumab being the most common at almost 20%. We were unable to analyze the pre- and post-FeNo data since it was only recorded in 16% of cases. Only 6% had SNOT 22 recorded at the start of the study, so a comparison could not be made either.

As for the comparison of the data of all patients treated with biologics at the start and later, we see that the mean eosinophilia at the start was 504.77 cells/microliter in absolute value. The mean at one and two years of treatment is around 300 cells/microliter.

The mean number of visits to the emergency room before starting treatment was 2.15 times per year with an average use of 4 corticosteroid cycles per year. After one year of therapy, emergency room visits were significantly reduced (0.18 and 0.10 at two years of

treatment). The corticosteroid cycles per year decreased to a mean of 0.73 per year (p<0.001).

The previous ACT started at a mean of 13.70, improving to 20.18 after one year of biological treatment (p: 0.007) and 21.11 after the second year.

Regarding lung function, an improvement was observed. The mean average FEV1 percentage before starting biological treatment was 78.041%, reaching 82.989% after the first year of treatment and more than 84% after the second.

Description and comparison of naive patients.

Of all the patients we have on treatment with monoclonal agents, a subgroup of patients was obtained who had not previously received another biological one before the current one. These are 38 naive patients who started biological treatment without having received another previous one and continued the same drug for at least one year: omalizumab (28.9%), mepolizumab (44.7%) and dupilumab (26.3%).

Half of all these patients had an allergic T2 phenotype and 39.5% had a high T2 phenotype. As we can see in **Table 2**, if we look at each of the treatment groups, 72.7% of the patients receiving omalizumab had an allergic T2 phenotype and 60% of the patients who were on treatment with dupilumab had a non-allergic high T2 phenotype. As for the patients treated with mepolizumab, the phenotype was more homogeneous, with 47.1% having high T2 and 41% having allergic T2.

The patients in the omalizumab group were the youngest, with a mean age of 40.09 years **(Figure 1)**. Although women predominated in most groups (55-58%), in the dupilumab group 60% were men.

The BMI of the 3 groups was similar, with a mean of 25-26 **(Figure 2)**.

The mean IgE before starting treatment was higher in the omalizumab group (1257.583 kU/L). 7.9% of the patients were smokers and 23.7% were ex-smokers. In terms of treatment groups, patients on mepolizumab led the percentage of patients with the most contact with tobacco, since 11.8% of these patients were active smokers and 35.3% were ex-smokers. 36.8% of patients presented nasal polyposis, and 47% of patients on mepolizumab. 18.4% had AERD (allergic diagnosis either by anamnesis or provocation).

The mean eosinophil count at the start of treatment was higher with mepolizumab (673.75 cells/microliter). After the first year of treatment, they were also the ones that decreased the most (233.33 cells/microliter) significantly (p: 0.003).

The average number of visits to the emergency room in the year before treatment with omalizumab was 1.56, for mepolizumab 2.35 and dupilumab 2.50. The number of visits to the emergency room decreased significantly in all treatment groups (p<0.001) **(Figure 3)**.

The cycles of oral corticosteroids in the year before treatment were around 3 in all the three treatment groups, and in all cases, the cycles decreased significantly (p<0.001) one year after treatment **(Figure 4)**. The ACT also improved in all treatment groups with biologicals.

Regarding the lung function of the patients, they went from an average percentage of FEV1 of 84.76% to 77.4% in omalizumab; Compared to mepolizumab, it went from 82% to 87.86% and in the case of dupilumab it improved significantly from 67.150% to 87.87% **(Figure 5)**.

Table 2.

| TREATMENT	Beginning			12 months		
	OMALIZUMAB	MEPOLIZUMAB	DUPILUMAB	OMALIZUMAB 1	MEPOLIZUM	DUPILUMAB
Patients	11 (28.9%)	17 (44.7%)	10(26.3%)			
Age (years)	40.09	49.59	52.3			
Female	6 (54.50%)	10 (58.80%)	4 (40%)			
Male	5 (45.50%)	7(41.2%)	6(60%)			
BMI	25.21	26.85	26.15			
Allergic phenotype T1	8 (72.7%)	7 (41.2%)	4 (40%)			
Phenotype T2	1 (9.10%)	8 (47.10%)	6 (60%)			
IgE	1257.583	414.117	236.575			
Smoker	1 (9.10%)	2 (11.80%)	0			
Ex-smoker	1 (9.10%)	6 (35.30%)	2 (20.00%)			
CRSwNP	2 (18.20%)	8 (47.10%)	4 (40.00%)			
AERD						
Eosinophils	331.25	673.75	397	405	233.33	450
Emergency	1.56	2.35	2.5	0.44	0.17	0
Corticosteroids	3	3.47	3.7	0.44	0.33	0
ACT	13	13.57	13.67	20.25	18.33	23.57
FEV1(%)	84.763	82	67.15	77.4	87.863	87.871
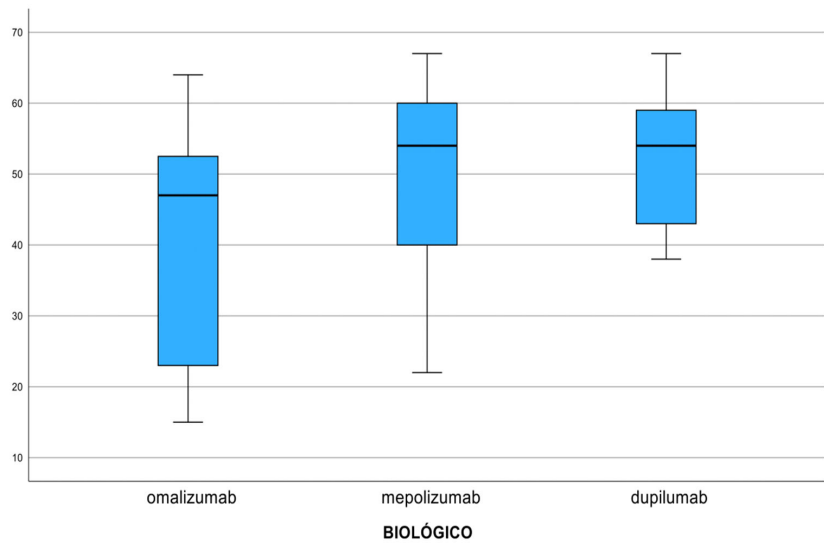
Figure 1. Age and biologics.
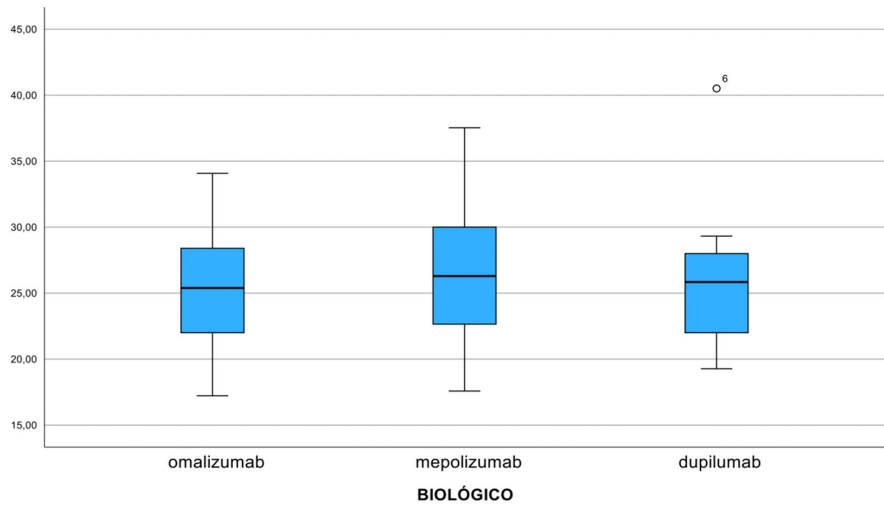
Figure 2. BMI and biologics.
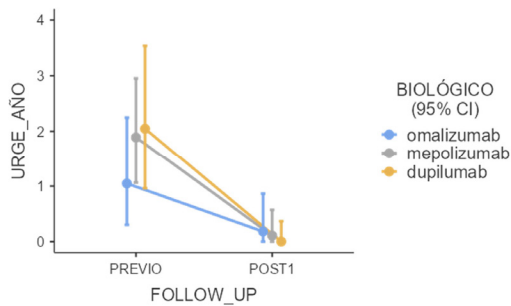

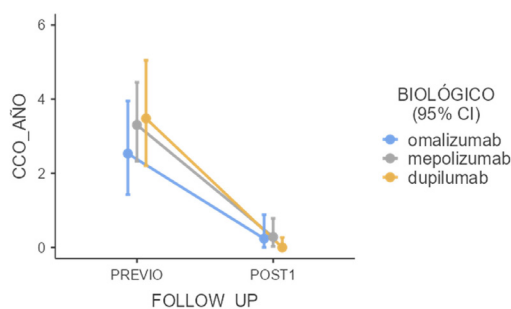**Figure 3.** Emergency/year and biologics.

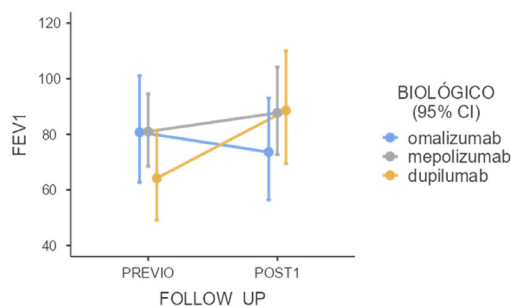**Figure 4.** Corticosteroid/year and biologics.

Figure 5. FEV1 and biologics.

Discussion

An increasing number of new biological therapies are appearing for the treatment of severe asthma. However, due to their broad spectrum of action, the exact indications for each of them are still lacking. We also lack direct comparisons between previously approved monoclonals. All these factors limit the opportunities to optimize the selection of candidate patients for these therapies [6]. Given the high cost of these products [7,15].

We wanted to do a descriptive study of our population with severe asthma treated with omalizumab, mepolizumab, and dupilumab. The rest of the biological drugs had been followed for less than a year or did not have a sufficiently large population to compare them. In our sample, it is confirmed that middle-aged obese women predominate with severe asthma, and, like they are followed exclusively in allergy consultations, the high T2 phenotype predominates. Neither tobacco nor other associated comorbidities, except RNSwPN, have influenced our sample. We did not establish differences based on the level of eosinophils in blood.

It is important to highlight the high percentage of patients with RNSwPN and OLI (38.8%), as well as AERD (22.4%). The choice of the most appropriate medication for severe asthma in patients who present multiple phenotypes simultaneously is a challenge. Sometimes the decision is not always entirely clinical and is conditioned by the availability, reimbursement, or costs of the medication. Therefore, cost-effective algorithms would be of great help in this decision-making process. To do this, we have analyzed the characteristics of each of the treatment subgroups separately and compared them with each other.

All the biologics examined were associated with a significant improvement in exacerbation rates one year after treatment compared to the start of treatment. The individual efficacy of each biological treatment in moderate-severe asthma has already been demonstrated in multiple studies. All the groups studied significantly improved emergency room attendance and decreased the need for annual cycles of systemic corticosteroids, regardless of eosinophilia. They also significantly improved ACT and lung function.

By analyzing each naive group separately and comparing them with each other, we were able to observe certain characteristics of our sample:

- Omalizumab: the vast majority had an allergic T2 phenotype and were younger patients. We found a deterioration in lung function in the first year of patients treated with omalizumab. This has not been observed with other biologicals. Although it has been observed in a recently published study [16].

- Mepolizumab: Without a clear difference in terms of phenotypes, we are struck by the fact that it was the group with the highest percentage of smokers. A higher number of patients with chronic rhinosinusitis with nasal polyposis is observed. They were the group with the highest number of eosinophils at the start of treatment and those with the highest depletion after one year of treatment.

- Dupilumab: the majority had a high T2 phenotype and a greater tendency to be male. In patients treated with dupilumab compared to the other groups, even though those patients were older, with a greater need for emergency care and oral corticosteroids per year and had a more depressed lung function at the start than the rest, a statistically significant improvement in lung function was observed one year after treatment. This significance was not observed in the

other groups. Our findings add to other recent studies that have made indirect comparisons of biological treatments and have shown that dupilumab may be more effective in improving lung function. However, they did not find statistical significance as in our sample [7,16-21] There is a shortage of previous studies that compare the different types of biological treatments for severe asthma.

Although indirect comparisons can be useful when there is no evidence from comparative trials, the results can be limited by differences in the treatments of the study populations being compared and by the lack of availability of individual patient data [7].

The advantages of this work were that we have been able to conduct a real-life study without being influenced by the choice of one treatment or another, and where we can better reflect how these biological products work in a routine healthcare setting rather than in a monitored trial setting.

We have also been able to map the characteristics of our population of patients with severe asthma receiving treatment with biological drugs, see the characteristics of the patients who were receiving one or the other treatment as well as compare the results obtained in each of the subgroups.

Our study has limitations, the main one being the relatively small sample size. Our results should be interpreted with caution since these analyses have limitations as we have said some data are missing, indirect comparisons cannot replace clinical trials that compare these 3 drugs directly.

Conclusions

In our sample, the three biologic drugs compared demonstrated improvements in exacerbation rates, ACT, and systemic corticosteroid use. Mepolizumab and dupilumab demonstrated improvements in lung function compared to the start of treatment one year earlier, although only dupilumab achieved statistical significance.

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