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SHORT REPORT

The Response to Biologics is Better in Patients with Severe Asthma Than in Patients with Asthma–COPD Overlap Syndrome

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Abstract: Although biologics have demonstrated to be effective in T2-high asthma patients, there is little experience with these drugs in asthma–COPD overlap (ACO). The aim of this study was to compare the effectiveness of biologics in these two conditions. We included 318 patients (24 ACO and 297 asthma) treated with monoclonal antibodies and followed for at least 12 months. Omalizumab was the most frequently employed biologic agent both in patients with ACO and asthma. Asthma control test (ACT) scores after at least 12 months of biologic therapy were not significantly different between groups. The percentage of patients with ≥1 exacerbation and ≥1 corticosteroid burst was significantly higher in ACO patients (70.8 vs 27.3 and 83.3% vs 37.5%, respectively), whereas the percentage of "controlled" patients (with no exacerbations, no need for corticosteroids and ACT ≥ 20) was significantly lower (16.7% vs 39.7%). In conclusion, this report suggests that patients with ACO treated with biologics reach worse outcomes than asthma patients.

Keywords: asthma, asthma–COPD overlap, COPD

Asthma–COPD overlap (ACO) is the coincidence of two complex conditions in a single individual. Or it can be considered as a part of the chronic airway disease continuum (Dutch hypothesis), being placed somewhere between the "pure" forms of asthma and COPD.[1] Whichever the case, ACO is challenging for the clinician.[2] To choose the best therapeutic option is particularly difficult, given the lack of specific studies and the fact that most clinical trials for asthma excluded patients with features of COPD, and vice versa. Although biologics have demonstrated to be effective in T2-high asthma patients,[2] there is little experience with these drugs in ACO.

The aim of this study was to compare the effectiveness of biologics in asthma and ACO. Data were sourced from the GEMA-DATA register, a national (Spain), multicenter (40 Asthma Units), observational initiative with retrospective and prospective data collection. This study was conducted in accordance with the Declaration of Helsinki, ethical governance was provided by Santa Creu i Sant Pau Hospital (Barcelona) and subjects signed informed consent prior to study commencement. Data collection started in October 2017 and is currently ongoing. GEMA-DATA includes ≥18-year-old patients diagnosed with asthma according to Global Initiative for Asthma (GINA) criteria and who receive treatment according to GINA Step 5 or experience uncontrolled asthma at Step 4.[3] Only patients who received a monoclonal

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antibody and have been followed up for a period longer than 12 months were included. Demographic and spirometric data, as well as T2 biomarker values, were collected from the first recorded visit. Data concerning clinical outcome were extracted from the last recorded visit.

For the purpose of this study, only patients with ≥ 12 months follow-up and with no missing data on crucial variables (smoking history, spirometry, monoclonal antibodies use, ACT, systemic corticosteroids use, exacerbations) were analyzed. The flowchart (Figure 1) represents the consecutive stages of the patient inclusion.

Patients were classified into non-smokers or smokers (current or past smokers with a smoking history of ≥10 pack-years). ACO was diagnosed in those smokers who showed bronchial obstruction (FEV1/FVC <70%) despite maintenance treatment with bronchodilators or systemic corticosteroids. This definition fits in well with GINA´s proposal (history of smoking and/or other toxic exposures, any asthma features and persistent expiratory airflow limitation with or without bronchodilator reversibility).[3] Asthma control test (ACT),[4] severe exacerbations (admissions, emergency room visits, or the need for oral steroids for ≥3 days) in the preceding 12 months, unscheduled medical visits during this period, the need for regular systemic corticosteroids and the number of corticosteroids´ bursts were used to assess clinical outcome. "Clinical control" was defined as absence of severe exacerbations in the previous year, ACT ≥20 and non-use of systemic corticosteroids. Analyses were performed using Chi-squared or Fisher's exact test for categorical data and Student's *t* test or Wilcoxon rank sum test for continuous data as appropriate. A p-value <0.05 was considered significant. All analyses were conducted using SPSS software v22 (IBM Corporation, Armonk, NY, USA).

Twenty-four patients diagnosed with ACO and 297 with asthma were included. Demographic and clinical characteristics are summarized in Table 1. ACO was more frequently diagnosed in males, reflecting the fact that smoking is more prevalent in males and, remarkably, bronchiectasis were more frequent in this group, maybe limiting the scope for improvement. As it should be expected, FEV1 was significantly lower in ACO patients than in asthma. However, biomarkers of T2 inflammation showed similar values in both groups, in consonance with the finding that the proportion of patients with atopy, chronic rhinosinusitis and nasal polyps did not differ significantly between ACO and asthma patients.

Omalizumab was the most frequently employed biologic agent both in patients with ACO and asthma. ACT scores after at least 12 months of biologic therapy were not significantly different between groups. The number of severe exacerbations, hospitalizations and unscheduled visits were significantly higher in ACO patients whereas the percentage of "controlled" patients was significantly lower (Table 1 and Figures S1–S4).

This study offers a real-life snapshot of the effectiveness of biologic therapy in patients with ACO. Not surprisingly, the outcome variables showed better results for asthmatics, but it must be mentioned that 16% of the biologic-treated patients with ACO attained clinical control. Only 39.7% of the asthmatics were controlled with monoclonal antibodies, but this figure is in line with those reported in other real-life studies, which reflected that the majority of the patients achieve "partial response".[4]

There is little experience with the use of biologic agents in ACO patients. Omalizumab improved asthma control and quality of life, without significantly improving lung function, in 11 current or ex-smokers with severe allergic asthma and ACO (FEV1 <80%) enrolled in the Australian Xolair Registry.[5] However, it should be noted that mean ACQ score persisted above 2 after 6 months of treatment. Besides, a *post-hoc* analysis of the PROSPERO[6] study found that 50 patients with ACO (defined as medical history of asthma, a postbronchodilator FEV1/FVC <0.7 and smoking history ≥10 pack-years), treated with omalizumab had similar clinical outcomes to patients with asthma and with ACO in terms of exacerbation frequency and ACT scores. Nonetheless, FEV1 did not significantly increase and mean ACT clearly remained below 20.[7] These studies assessed how much the patients improved after therapy compared to their values before therapy, whereas our study focused on outcome variables that reflect the level of control achieved after biologic treatment. Another difference is that prior reports were restricted to the use of omalizumab while in this study different monoclonal antibodies were employed. All these drugs have demonstrated effectiveness in patients with asthma[2] but, in COPD patients, only mepolizumab and benralizumab were tested to date.[8] Mepolizumab 100 mg reduces the rate of moderate or severe exacerbations by 19% in COPD patients with an eosinophil count of at least 150/μL and benralizumab 100 mg reduces the rate of severe exacerbations requiring hospitalization in patients with ≥220/μL blood eosinophils (benralizumab 10 mg probably has the same effect on this specific subset).[9] Given that biologic therapy is not part of

Figure 1 Stages of the patient inclusion.

Table 1 Demographic and Clinical Characteristics of Biologic-Treated Severe Asthma and Asthma–COPD Overlap Patients. Parameters of Clinical Response

Variable	Asthma n = 297	ACO n = 24	*p* value
Male, frequency (%)	80 (26.9)	14 (58.3)	0.002
Age, median (IQR)	57.4 (45.5–65.7)	59.9 (52.7–64.7)	0.26
Non-smokers, frequency (%) Ex-smokers, frequency (%) Current smokers, frequency (%) Smoking history (pack-yrs), median (IQR)	261 (87.9) 36 (12) 0 5.0 (4.0–9.0)	0 20 (83.3) 4(16.6) 20.0 (11.3–30.0)	 <0.001
Diagnosis < 12 yrs (%)	22.7	4.3	0.036
Atopy (%)	70.5	77.3	0.627
Comorbidities (%) -Rhinosinusitis. -Nasal Polyps. -Bronchiectasis. -Obesity. -Gastroesophageal reflux. -Anxiety/depression	 65.0 36.4 18.2 8.2 20.5 25.3	 66.7 25.0 37.5 0.0 12.5 4.2	 >0.99 0.375 0.031 <0.005 0.435 0.706
Post-bronchodilator FEV1/FVC (%), median (IQR)	71.0 (61.5–77.1)	57.4 (43.6–66.1)	<0.001
Post-bronchodilator FEV1 (% predicted), median (IQR)	80.5 (63.2–95.5)	66.3 (50.4–80.7)	<0.001
Post-bronchodilator FVC (% predicted), median (IQR)	94.9 (82.3–108.2)	94.6 (72.2–111.5)	0.287
FENO (ppb), median (IQR)	39.0 (20.0–66.2)	33.7 (10.8–58.3)	0.327
IgE (IU/mL)	236.5 (91.0–532.8)	451.0 (193.0–630.0)	0.140
Blood eosinophils (cells/mm^3) -Last recorded value, median (IQR) -Maximum historical value, median (IQR)	 110.0 (22.5–310.0) 670.0 (330.0–1100.0)	 109.0 (37.6–307.5) 500.0 (200.0–1000.0)	 0.902 0.08
High-dose ICS/LABA (%)	100	100	
LAMA (%)	54.2	87.5	<0.05
Biologic therapy -Omalizumab, n (%). -Mepolizumab, n (%). -Reslizumab, n (%). -Benralizumab, n (%). -Dupilumab, n (%).	 132 (44.4) 108 (36.3) 28 (9.4) 28 (9.4) 1 (0.3)	 15 (62.5) 5 (20.8) 1 (4.2) 3 (12.5) 0	
Parameters of clinical response			
ACT, median (IQR) ACT<20 (%)	22.0 (17.0–24.0) 36.5	18.5 (14.0–23.3) 59.1	0.096 0.109
≥1 severe exacerbation (%)	27.3	70.8	<0.001
≥1 hospitalization (%)	8.1	29.2	0.004
≥1 unscheduled visit	19.2	54.2	<0.001
Corticosteroid bursts, median (IQR) ≥ 1 burst (%)	0.0 (0.0–1.0) 37.5	2.0 (1.0–4.0) 83.3	<0.001 <0.001

(*Continued*)

Table 1 (Continued).

Variable	Asthma n = 297	ACO n = 24	*p* value
Maintenance corticosteroids (%)	22.2	12.5	0.437
Corticosteroids´ dose (prednisone equivalent, mg), mean (SD)	12.5 (17.8)	10.0 (5.0)	0.594
Clinical control (%)	39.7	16.7	0.028

Notes: Atopy: Positive skin prick test or serum specific IgE. Clinical control: absence of severe exacerbations in the prior 12 months, ACT ≥ 20 and no need for systemic corticosteroids.

Abbreviations: ACO, asthma–COPD overlap; ACT, asthma control test; FENO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, Forced vital capacity; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.

standard of care for ACO, the discussion about which biologic to preferentially use is merely speculative, but it seems reasonable to choose a drug with proved efficacy in asthma and probable benefit in eosinophilic COPD patients.

The study has obvious limitations due to its retrospective design. Since many patients entered the register already receiving treatment with a biologic medication it is not possible to assess how much they improved with respect to baseline. Besides, a relatively small number of ACO patients were included, as a consequence of the strict definition adopted in this paper and reflecting the fact that this therapy is not officially indicated for this condition. Moreover, only nine patients were treated with anti-IL-5 biologics, and it cannot be excluded that results would have differed with a higher prevalence of this agents.

In conclusion, this report suggests that patients with ACO treated with biologics reach worse outcomes than asthma patients in terms of spirometric parameters, exacerbations, symptoms and OCS use. Nevertheless, it should be interpreted as hypothesis generating and more studies are needed in order to clarify the role of these drugs in this clinical setting.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

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