

Anti-IL5/IL5R Treatment in COPD: Should We Target Oral Corticosteroid-Dependent Patients?

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Introduction: Monoclonal antibodies targeting interleukin 5 (IL5) or its receptor (IL5R) are frequently used in severe asthma, in which they reduce exacerbations rate and oral corticosteroids (OCS) exposure. Anti-IL5/IL5Rs have been studied in patients with chronic obstructive pulmonary disease (COPD) without convincing benefits. However, these therapies have been used in clinical practice in COPD with apparently good results.

Purpose: To describe the clinical characteristics and therapeutic response of COPD patients treated with anti-IL5/IL5R in a real-world setting.

Patients and Methods: This is a retrospective case series of patients followed at the Quebec Heart and Lung Institute COPD clinic. Men or women, with an established diagnosis of COPD, and treated either with Mepolizumab or Benralizumab were included. Demographics, disease and exacerbation-related data, airway comorbidities, lung function, and inflammatory profile were extracted from patients' hospital files at baseline visit and 12 months post-treatment. Therapeutic response to biologics was assessed by measuring change in annual exacerbation rate and/or OCS daily dose.

Results: Seven COPD patients treated with biologics were identified (5M:2F). All were found to be OCS-dependent at baseline. Radiological evidence of emphysema was found in all patients. One case was diagnosed with asthma before age 40. Residual eosinophilic inflammation was found in 5/6 patients (blood eosinophils count $237 \pm 225 \times 10^6$ cells/L) despite chronic OCS use. After 12 months of anti-IL5 treatment, mean OCS dose dropped from 12.0 ± 7.6 to 2.6 ± 4.3 mg/day, representing a 78% decrease. Annual exacerbations rate was reduced by 88%, from 8.2 ± 3.3 to 1.0 ± 1.2 per year.

Conclusion: Chronic OCS use is a common characteristic of patients treated with anti-IL5/IL5R biological therapies in this real-world setting. In this population, it may be effective in decreasing OCS exposure and exacerbation.

Keywords: COPD, treatment, anti-IL5, monoclonal antibodies, exacerbations, oral corticosteroids

Plain Language Summary

Chronic obstructive pulmonary disease (COPD) is a lung disease most often caused by tobacco smoking. It generally involves airway inflammation, which is triggered by the immune system activation. There are different types of inflammation and one involves the participation of immune cells called eosinophils. Eosinophilic inflammation is most often found in asthma, another airway disease, but some patients with COPD have clinical evidence of it. Biologic therapies have been developed to target specific immune cells or molecules causing inflammation, such as eosinophils.

Biologics targeting eosinophilic inflammation have revolutionized asthma management. They have been studied in COPD without convincing benefits. However, they are sometimes used by clinicians in a selected COPD population with apparently good results. We explored characteristics and response of such COPD patients treated with anti-eosinophilic biologic therapies in a tertiary center. Seven patients were identified and all of them were chronically treated with oral corticosteroids (OCS), a drug known to suppress eosinophilic inflammation. Biologic treatment allowed for a 78% reduction in chronic OCS dose and 88% reduction in flare-up frequency. This magnitude of response is comparable to the effects seen in OCS-dependent asthma. These findings suggest that, as shown in asthma, chronic OCS use might predict response to biologic therapies in COPD. However, OCS-dependent patients are

currently excluded from biologic trials in COPD as it is not a recommended treatment in this disease. Our findings might help design future trials studying biologics in COPD.

Introduction

During the past two decades, monoclonal antibodies development and commercialization have revolutionized severe asthma management. By targeting precise elements of inflammatory cascade, biological agents neutralizing immunoglobulin E (IgE), interleukin 5 (IL5), its receptor (IL5R) or the receptor of interleukin 4 (IL4R) allow for an important reduction in exacerbations and oral corticosteroids (OCS) exposure in severe asthmatics with a T_2 inflammation profile.^{1–3} IL5 is involved in the recruitment, activation, maturation and survival of eosinophils,⁴ leading to an increased and sustained eosinophilic infiltration in blood and pulmonary tissues of asthmatics which contributes to disease severity.⁵ Of the five monoclonal antibodies currently approved in Canada for severe asthma, three target signaling pathways of IL-5 or its receptor (IL5R): Mepolizumab, Benralizumab and Reslizumab. Mepolizumab and Reslizumab target circulating IL5 while Benralizumab binds to the IL5 receptor alpha (IL5R α) subunit expressed on eosinophils and basophils.⁴ Now considered revolutionary, these drugs were initially considered clinically ineffective when studied in an unselected asthmatic population.⁶ This highlights the importance of careful selection of patients in a heterogeneous disease like asthma, especially when studying treatments targeting precise elements of the inflammatory cascade.

Chronic obstructive pulmonary disease (COPD) is another heterogenous inflammatory airway disease characterized by persistent respiratory symptoms and airflow limitation. In contrast to asthma, it appears after years of cigarette smoking or noxious environmental exposures, leading to permanent structural changes and irreversible airflow obstruction.⁷ By promoting neutrophils infiltration in pulmonary tissues, tobacco smoke leads to a neutrophil-predominant disease.⁸ However, a small subset of COPD patients displays eosinophilic inflammation. This phenotype has been associated with a higher risk of exacerbations^{9–11} and better response to oral and inhaled corticosteroids.^{12–17}

Given that eosinophilic inflammation may lead to exacerbations in a number of COPD patients, anti-IL5/5Rs have been studied in eosinophilic COPD in four Phase 3 trials: METREX and METREO studied Mepolizumab and GALATHEA and TERRANOVA studied Benralizumab.^{18,19} They failed to show convincing benefits despite inclusion criteria similar to asthma trials.^{1–3} An incorrect selection of the studied population may however have accounted for these inconclusive results.

In clinical practice, physicians occasionally see COPD patients with evidence of significant eosinophilic inflammation contributing to repeated exacerbations. Anti-IL5s are sometimes tried in this population, after informed consent, when the drugs cost can be covered by the patient insurance plan. The benefits seen in clinical practice seem better than what have been reported in clinical trials. We therefore aim to describe the characteristics and therapeutic response of COPD patients treated with anti-IL5 monoclonal antibodies in the real-world setting of a tertiary care center.

Materials and Methods

Study Design

This is a retrospective, longitudinal case series study of patients treated at the Quebec Heart and Lung Institute COPD clinic and who initiated anti-IL5 treatment between March 2017 and March 2021. Data were extracted from the patient's hospital files before treatment initiation (V_0 ; baseline visit) and after 12 months (\pm 3 months) of treatment (V_1). If less than 12 months had elapsed after the first treatment injection, the last available visit was used for V_1 .

All patients signed a consent form allowing research staff to access their medical record for research purposes. Written consent to publish the case details has also been obtained from each of the 7 patients. The study was approved by the Quebec Heart and Lung Institute – Laval University ethics committee (CÉR 22093).

Study Participants

Men and women aged 40 years and over, with an established diagnosis of COPD, and who had received at least 3 doses of anti-IL5 therapy (Mepolizumab or Benralizumab) were included in the study. Exclusion criteria were confounding comorbidities such as eosinophilic granulomatosis with polyangiitis (EGPA) or hypereosinophilic syndrome. Anti-IL5s

were administered as a subcutaneous injection, according to the approved Canadian dosing scheme for asthma (Mepolizumab 100 mg every 4 weeks, or Benralizumab 30 mg every 4 weeks for 3 doses, then every 8 weeks).

Data Collection

Demographics including age, sex, body mass index (BMI), smoking history and number of pack-year were recorded at baseline visit. Disease and exacerbation-related data, airway comorbidities, lung function and inflammatory profile were collected at V_0 and V_1 . COPD exacerbations were defined as an acute worsening of respiratory symptoms that resulted in additional systemic therapy such as antibiotics and/or oral corticosteroids (OCS).

Study Outcomes

Treatment efficacy was assessed using the reduction in annual exacerbation rate and/or OCS daily dose in OCS-dependent patients, between V_0 and V_1 . Secondary outcomes included change in forced expiratory volume in one second (FEV_1) and inflammatory biomarkers (blood eosinophils, sputum eosinophils and FeNO) between V_0 and V_1 . Cases are presented using descriptive statistics. Continuous variables are presented as means (\pm SD or range) and categorical variables are presented as numbers (%). Although statistical analysis of results such as paired T-tests would have been interesting, the small sample size provided by our case series did not allow for them to be appropriately performed.

Results

Participants

Seven COPD patients (5M:2F) received an anti-IL5 in our COPD clinic. Baseline characteristics are shown in Table 1. All had radiological evidence of emphysema and had a severely impaired lung function with a mean FEV_1 of $34.6 \pm$

Table 1 Participants Characteristics at Baseline (V_0)

	Total Cases (N = 7)	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age — years	64.0 \pm 5.1	69	68	60	58	68	58	67
Sex	5M:2F	Male	Female	Female	Male	Male	Male	Male
Smoking history		Former	Former	Active	Former	Never*	Former	Former
Number of pack-years	32.5 \pm 15.4	20	25	40	60	N/A	20	30
Age of COPD diagnosis — years	56.1 \pm 5.7	54	64	50	51	60	52	62
COPD Phenotype								
Emphysema	7 (100)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chronic bronchitis	2 (29)	No	No	No	Yes	No	Yes	No
Number of exacerbations in previous year								
Total	7.3 \pm 3.9	7	1	9	8	9	4	13
Hospitalizations	1.0 \pm 1.4	1	1	1	0	4	0	0
Comorbidities								
Asthma diagnosis before 40 years of age	1 (14)	No	No	No	No	No	Yes	No
Bronchiectasis	6 (86)	Yes	Yes	Yes	Yes	Yes	Yes	No
Oral corticosteroids dose — mg/day	11.4 \pm 6.9	10.0	15.0	5.0	10.0	10.0	5.0	25.0
Skin prick tests	3 (50)	N/A	Positive	Negative	Positive	Positive	Negative	Negative
Total serum IgE — IU/mL	78.5 \pm 53.6	22.0	14.0	106.0	148.0	34.2	113.0	112.0
Blood eosinophils — $\times 10^6$ cells/L	237 \pm 225	600	N/A	100	220	0	100	400
Sputum eosinophils — %	49.7 \pm 11.1	N/A	N/A	N/A	N/A	N/A	41.8	57.5
FEV_1 — liters	0.98 \pm 0.29	1.44	1.06	0.68	0.92	1.11	0.56	1.08
FEV_1 — % of predicted value post-bronchodilator	34.6 \pm 13.2	48.3	53.8	25.8	26.0	37.8	16.5	34.1
Historical data								
Maximal recorded blood eosinophils — $\times 10^6$ cells/L	729 \pm 315	600	800	300	800	1100	1100	400
Maximal recorded sputum eosinophils — %	54.3 \pm 4.6	N/A	N/A	N/A	N/A	N/A	51.0	57.5
Maximal recorded reversibility — liters	0.17 \pm 0.09	0.11	0.16	N/A	0.29	0.11	0.10	0.26
Maximal recorded reversibility — % change	16.5 \pm 10.3	7.9	15.0	N/A	35.0	7.0	14.0	20.0

Notes: Plus–minus values are means \pm SD. *This patient was diagnosed with a genetic form of COPD based on the presence of severe and progressive emphysema without relevant exposure/history.

Abbreviations: N/A, Unavailable or not applicable; COPD, chronic obstructive pulmonary disease; IU, international unit; FEV_1 , forced expiratory volume in one second; L, liter.

13.2%. One patient was a never smoker (case 5) but was diagnosed with a genetic form of COPD. One patient had a previous diagnosis of asthma (before age 40) and two had a historical FEV₁ reversibility of more than 200 mL, but less than 400 mL.

All patients were OCS-dependent at baseline. Despite chronic use of OCS, 6/7 patients remained frequent exacerbators (exacerbation rate 7.3 ± 3.9) and 5/6 had evidence of residual eosinophilic inflammation (blood eosinophil levels $237 \pm 225 \times 10^6$ cells/L). Before chronic OCS use, the mean blood eosinophils count was $729 \pm 315 \times 10^6$ cells/L. Sputum eosinophils were only available for cases 6 and 7 and were respectively 41.8% and 57.5%.

Therapeutic Response

Five patients had completed 12 months of anti-IL5/IL5R treatment at the time of data extraction. In these patients, the mean OCS dose was reduced from 12.0 ± 7.6 to 2.6 ± 4.3 mg/day, corresponding to a 78% decrease from baseline (Figure 1). Three patients completely stopped using OCS. Despite the reduction in OCS dose, patients' annual exacerbation rate was decreased by 88%, from 8.2 ± 3.3 to 1.0 ± 1.2 (Figure 2). Post-treatment outcomes are presented in Table 2.

Other Outcomes

After one year of biological treatment, the mean blood eosinophils count was reduced from 237 ± 225 to $0.0 \pm 0.0 \times 10^6$ cells/L (Figure 3). One case had residual blood eosinophil inflammation (100×10^6 cells/L) but had not completed 12 months of anti-IL5 at the time of data collection (Table 2). Sputum eosinophils change could not be evaluated because of insufficient data. There was a non-clinically significant increase in mean FEV₁ from 0.98 ± 0.29 to 1.07 ± 0.30 L between V₀ and V₁.

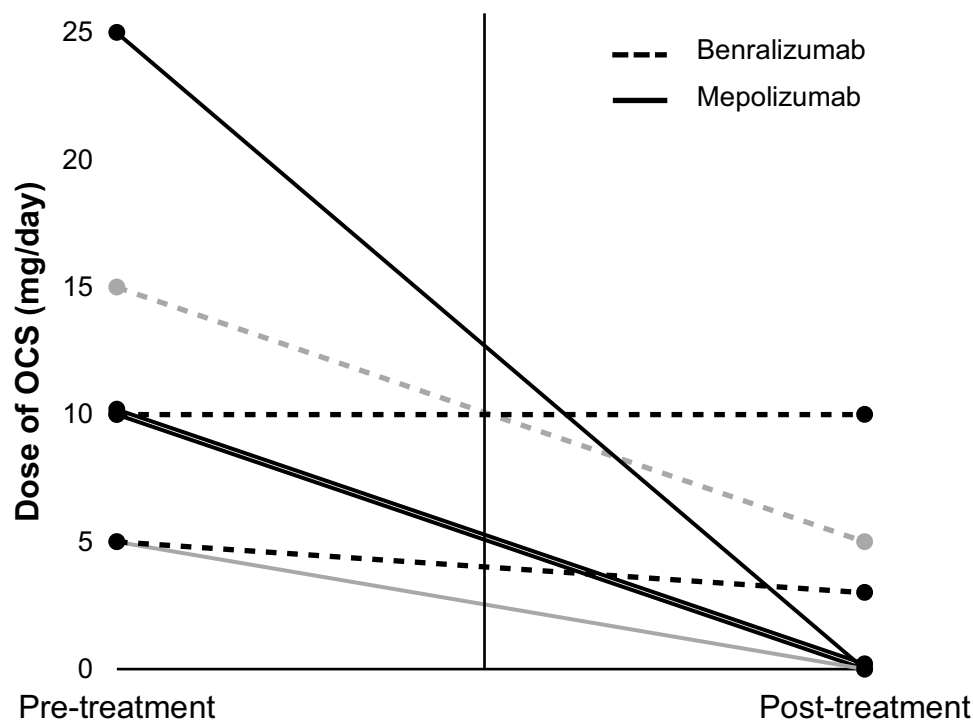


Figure 1 Daily oral corticosteroids intake.

Notes: Cases that had not completed 12 months of anti-IL5/5R treatment at the time of data collection are represented by grey lines. Oral corticosteroids intake for cases 2 and 3 were collected respectively at 5 and 6 months (time of the last visit available) after the initiation of the biologic.

Abbreviation: OCS, oral corticosteroids.

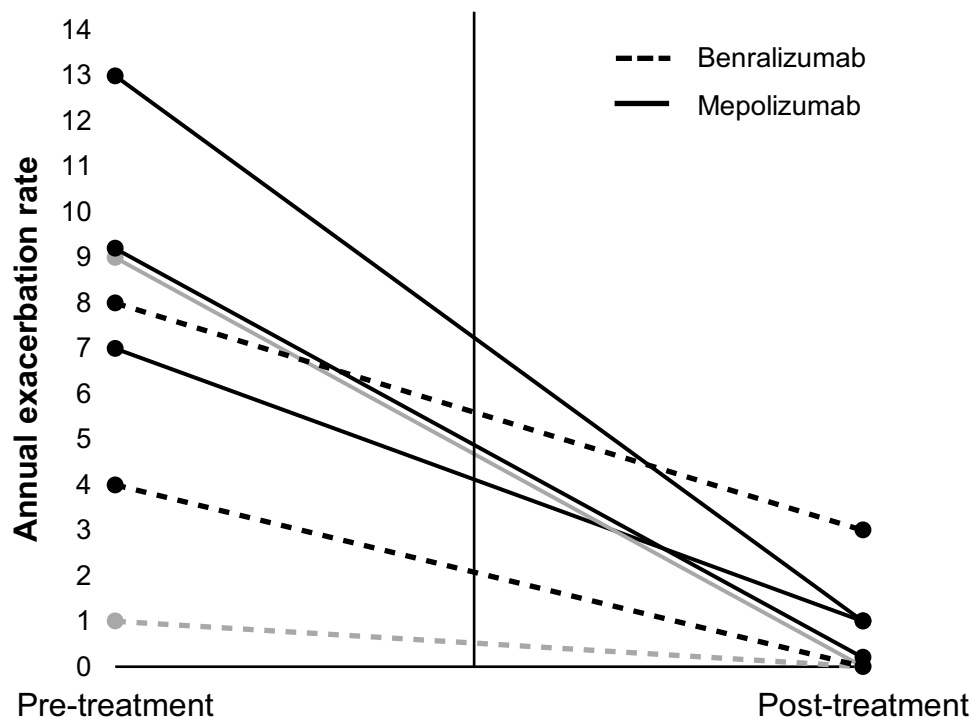


Figure 2 Annual exacerbation rate.

Notes: Cases that had not completed 12 months of anti-IL5/5R treatment at the time of data collection are represented by grey lines. Annual exacerbation rate for cases 2 and 3 were collected respectively at 5 and 6 months (time of the last visit available) after the initiation of the biologic.

Discussion

To our knowledge, this case series is the first to report the benefits of anti-IL5/IL5R therapies in COPD patients chronically treated with OCS. In this real-world setting study, COPD patients selected for treatment with anti-IL5 were all OCS-dependent and displayed significant blood and/or sputum eosinophilic inflammation, either on OCS or prior to their initiation. These observed improvements parallel the benefits demonstrated in OCS-dependent asthma, decreasing OCS use and exacerbation rates.¹⁻³

Four phase 3 parallel-group trials have reported results of anti-IL5/IL5R therapy in eosinophilic COPD patients.^{18,19} In these trials, the eosinophilic phenotype was defined using blood eosinophils counts: $\geq 150 \times 10^6$ cells/L at screening or $\geq 300 \times 10^6$ cells/L during the previous year for Mepolizumab trials (METREX and METREO),¹⁸ and $\geq 220 \times 10^6$ cells/L

Table 2 Post-Treatment Outcomes (V₁)

	Total Cases (N = 7)	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
	Biological Agent	Mepo	Benra	Mepo	Benra	Mepo	Benra	Mepo
Oral corticosteroids dose — mg/day	2.6 ± 3.8	0	5*	0*	10	0	3	0
Number of exacerbations on biologic								
Total	0.7 ± 1.1	1	0*	0*	3	0	0	1
Hospitalizations	0.1 ± 0.4	0	0*	0*	1	0	0	0
Blood eosinophils — X10 ⁶ cells/L	16.7 ± 40.8	0	0*	100*	0	0	0	N/A
Sputum eosinophils — %	1.0 ± 1.4	0	N/A*	2.0*	N/A	N/A	N/A	N/A
FEV ₁ — liters	1.0 ± 0.3	1.43	1.05*	0.70*	0.96	1.05	0.57	1.33
FEV ₁ — % of predicted value post-bronchodilator	36.5 ± 13.0	49.8	53.3*	26.8*	30.0	36.1	16.9	42.5

Notes: Plus-minus values are means ±SD. *Post-treatment outcomes for cases 2 and 3 were collected respectively at 5 and 6 months (time of the last visit available) after the initiation of the biologic.

Abbreviations: N/A, Unavailable or not applicable; Mepo, Mepolizumab; Benra, Benralizumab; IU, international unit; FEV₁, forced expiratory volume in one second; L, liter.

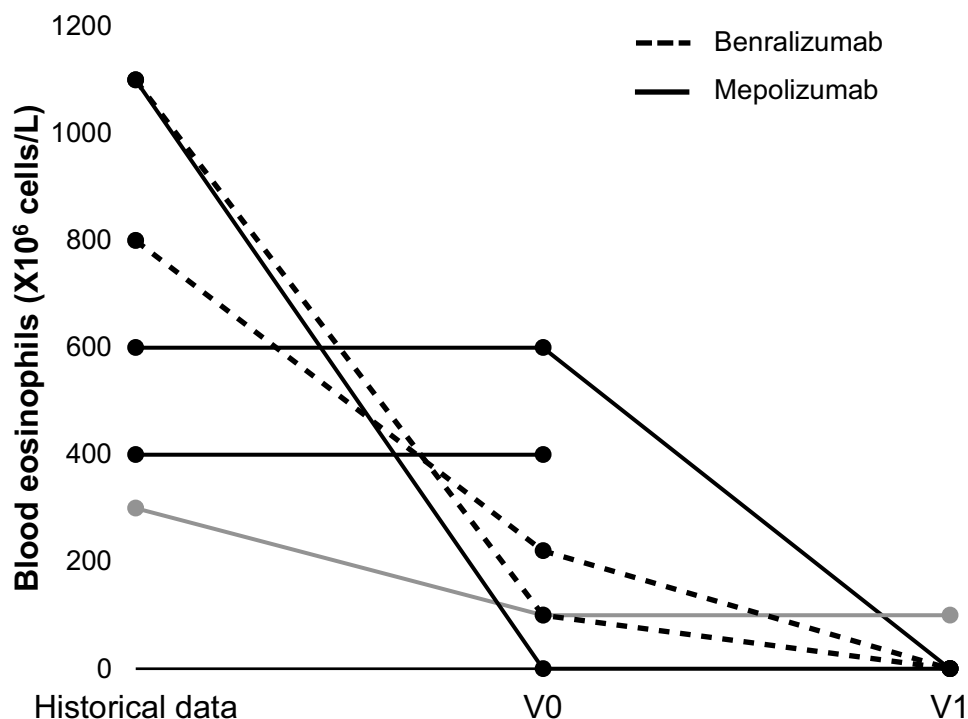


Figure 3 Blood eosinophils levels.

Notes: Historical blood eosinophil level was measured in the last 3 years before baseline visit (V₀). Cases that had not completed 12 months of anti-IL5/5R treatment at the time of data collection are represented by grey lines. Blood eosinophil levels for cases 2 and 3 were collected respectively at 5 and 6 months (time of the last visit available) after the initiation of the biologic.

at screening for Benralizumab trials (GALATHEA and TERRANOVA).¹⁹ In these selected populations, only the METREX trial, studying Mepolizumab, reached statistical significance in an efficacy endpoint, reducing exacerbations by 18% compared to placebo. These results are far from the 50% exacerbation rate reduction seen in asthma with these therapies.^{20,21} However, with an exacerbation rate reduction of 88%, our case series suggests that, when appropriately selected, COPD patients may have a similar response to asthmatics with anti-IL5s.

Asthma is an eosinophil-predominant disease, which is not the case of COPD. Using an imperfect albeit convenient biomarker such as blood eosinophils may result in more misclassification (false positive or false negative) of eosinophilic-driven disorders in low prevalence diseases such as COPD. Indeed, studies have shown that the correlation of blood to sputum eosinophils is weaker in COPD when compared to asthma, suggesting that blood eosinophils are a less efficient biomarker to identify patient with an eosinophilic phenotype in this disease.²² Therefore, selecting the COPD study population for anti-IL5 trials based on the same eosinophils criteria as asthmatics may have contributed to the deceiving results of these drugs in COPD. More specific predictors of eosinophilic disease in COPD are required to identify patients that may respond to biologic therapy.

Our small study suggests that, as shown in asthma, OCS use could be a predictor of response to anti-IL5 therapies in COPD.²³ Patients treated with daily OCS are however systematically excluded from trials studying monoclonal antibodies in COPD, including those currently ongoing. One should understand that, although OCS is a recognized treatment for severe asthma, they are not recommended for daily use in COPD due to a lack of clear demonstrated benefits and potential for harm.²⁴ There is however a role for chronic OCS in COPD with eosinophilic airway inflammation as shown in a 2007 study by Siva et al.¹² In this randomized control trial (RCT), 40% of COPD patients received regular OCS to reduce their sputum eosinophils and this strategy was associated with a 62% reduction in severe exacerbations. Even though guidelines do not recommend it, regular OCS are sometimes used in clinical practice in selected COPD patients with recurrent exacerbations needing frequent OCS bursts to reduce the overall steroid burden. Long-term OCS use have however been associated with an increased mortality risk in COPD and strategies are therefore

needed to replace its use, even if already limited in this disease.²⁵ Including these patients in future anti-IL5 trials should be considered.

The impressive reduction in exacerbations with anti-IL5 in our patients suggests that most of their exacerbations were eosinophilic. This would be an unusual finding as most COPD patients have a heterogeneity in the nature of their exacerbation. A study investigating biomarkers expression in acute exacerbation of COPD identified four biologic clusters population for exacerbation events: bacterial-predominant, viral-predominant, eosinophilic-predominant or paucii-inflammatory.²⁶ Among the twenty-five percent of COPD patients identified with eosinophilic-predominant exacerbations, only 60% of their exacerbations were eosinophilic. This intra-patient variability in exacerbations nature potentially limits the maximal benefit of anti-IL5s in COPD. However, with an 88% reduction in exacerbations twelve months after anti-IL5 initiation, our study population seemed to display more homogeneous eosinophilic exacerbations. Once again, their OCS-dependent status is probably responsible as clinicians are probably more likely to continue long-term OCS in COPD patients who improve dramatically after their introduction. It is yet unclear whether this chronic OCS response should be used to identify COPD patients with eosinophilic exacerbations who might be candidate for biologics, but according to our study results, it certainly deserves further consideration.

One could wonder if the OCS-dependent COPD patients of our case series are not merely severe asthmatics, explaining the good response to OCS and anti-IL5 therapy. Distinguishing asthma from COPD is indeed challenging in older individuals with a history of smoking, as typical features of asthma are also more prevalent in COPD. For example, a significant bronchodilator response is found in up to 50% of COPD patients, without necessarily indicating an overlap.²⁷ All our cases had radiological emphysema, confirming a COPD component to their airway disease. Although one patient was a never smoker, he suffered from severe and progressive panlobular emphysema in the absence of relevant exposure/history and a lung resection specimen from a lung volume reduction surgery revealed no pathological disease other than emphysema. Alpha-one antitrypsin deficiency (AATD) screening was negative, but the patient had a familial history of premature emphysema, suggesting an unidentified non-AATD genetic COPD. The COPD diagnosis in this never smoker therefore seems appropriate. Only one patient had a previous diagnosis of asthma, hence a definitive asthma-COPD overlap (ACO). No other patient of our series met the criteria for ACO, as defined by an international panel of expert in 2016.²⁸ We can then safely assume that, except for one patient with ACO, our case series was mainly composed of COPD patients.

Limitations

This series being retrospective in nature and involving a small sample size, its results must be taken cautiously. A selection bias may have occurred as COPD patients treated with anti-IL5/5Rs in our institution were first offered to enroll in ongoing clinical trials studying biological therapies in COPD. To be included in this case series, they either refused to participate in the trials or did not meet the inclusion criteria. Another selection bias was introduced by the need for the drug to be covered by the patients' insurance plan.

The nature of the exacerbations was not assessed, therefore any results involving exacerbation are affected by the clinician evaluation and ensuing choice of treatment. It however reflects the current real-world use of biologic therapy in COPD patients. It is yet unknown if the benefits reported in this study are sustainable over time.

Conclusion

In conclusion, our case series suggests that monoclonal antibodies targeting IL5 or its receptor may be effective in decreasing OCS exposure and exacerbation rate among eosinophilic COPD patients treated with chronic OCS. These findings need further validation but may serve to better select the population to be included in clinical trials studying biologic therapy in COPD.

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