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ORIGINAL RESEARCH

Biological Anti-IL-5/IL-5R Therapeutics for Chronic Obstructive Pulmonary Disease (COPD) with Specific Treatable Traits: A Real-World Retrospective Analysis

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Introduction: We describe the use of anti-IL-5 monoclonal antibodies from a COPD clinic, a source other than traditional clinical trials. The objectives were to characterize the patient subgroup prescribed anti-IL-5 monoclonal antibodies and to report potential benefits.

Methods: This is a retrospective case series study of 17 patients treated in a COPD subspecialty clinic. All patients had a diagnosis of COPD (post-bronchodilator FEV1/FVC <0.7) and had been prescribed an anti-IL-5 biologic for at least 8 months. Acute exacerbations of COPD (AECOPDs) were collected as reported in electronic medical records.

Results: All patients (17) enrolled were treated with biologics for ≥8 months, and 13 (76%) for ≥1 year. Patients were characterized by severe disease traits, FEV1 <50% predicted, recurrent exacerbations (3.5 moderate-to-severe AECOPDs in the year before treatment), high peripheral blood eosinophil counts (≥250 cells/μL in the previous year), all on inhaled triple therapy, and only 1 patient with a diagnosis of asthma prior to smoking. There was a statistically significant decrease in the exacerbation rate compared with baseline after 8 and 12 months of anti-IL-5 treatment, respectively, yielding the equivalent of a 2–3x reduction in exacerbation rate. Absolute FEV1 decreased, and the decline in FEV1 % of predicted reached statistical significance ($p<0.05$); CAT score improved ($p<0.05$).

Discussion: This real-world evidence data aligns with existing studies suggesting the potential benefit of anti-IL-5 treatment for specific patients with COPD and therefore advocates for further investigation of RCTs on the use of anti-IL-5 biologics for well-characterized patients with COPD.

Keywords: COPD, biologics, anti-IL5 therapy, blood eosinophil count, RWE, RWD

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous disease with a possible common feature across phenotypes of frequent and severe acute exacerbations of COPD (AECOPDs). AECOPDs are detrimental to overall health status, and can lead to accelerated deterioration of lung structure, extended or recurrent hospitalizations, and premature death.[1] Moreover, AECOPDs tend to present in clusters, such that the strongest predictor of an AECOPD is a recent history of adverse lung events.[1] Recent randomized clinical trials (RCTs) have shown that individuals with moderate or severe disease who are at high risk of AECOPD benefit from being treated with single inhaler triple therapy.[2,3] This is the basis for the recommendations that these patients be treated with single inhaler triple therapy because of its many proven benefits, including the reduction of moderate and severe AECOPDs and most importantly, a significant reduction in mortality.[4]

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There is a need to better define patient characteristics for personalizing interventions beyond optimal inhaled therapy for those who continue to experience exacerbations and to further improve patient outcomes. Among other potential therapies, there has been increased interest in the potential role of biological treatments (so-called 'biologics'). Though RCTs have failed to show efficacy of biologics such as anti-IL-5 for relatively non-specific COPD cohorts,[5] post-hoc analysis has identified a subpopulation of patients with COPD with an eosinophilic phenotype for whom this therapy could be effective in reducing annual moderate and severe exacerbations.[6] Furthermore, anti-IL-5 biologics may also decrease oral corticosteroid use in patients with COPD as recently shown in a retrospective case series.[7] Collectively, these studies suggest that biological therapies could be impactful as personalized interventions to reduce AECOPDs and improve health status in COPD patients with demonstrated high peripheral blood eosinophil counts and severe disease traits. More research is required to investigate this therapeutic possibility, including data from real-life clinical practice, which would allow us to support this finding and move toward implementing potential targeted case-finding strategies and planning for additional RCTs.

In the current study, we present real-world data (RWD) from a subspecialty COPD clinic in which anti-IL-5 monoclonal antibodies have been prescribed in a carefully selected subpopulation of patients. The objectives were to characterize the patient subgroup prescribed anti-IL-5 monoclonal antibodies and to report on potential benefits with respect to specific outcomes, primarily AECOPDs. Secondary outcomes, including lung function and patient reported outcomes such as patient health status, were also investigated.

Methods

Study Design

This is a retrospective, longitudinal case series study of patients treated at the COPD subspecialty clinic of the McGill University Health Centre (MUHC)/Montreal Chest Institute (MCI), a clinic with a current caseload of ~500 patients. The COPD clinic is a referral clinic of a tertiary care center, with patients usually referred for ongoing management for complicated management issues or outcomes. This retrospective study using chart review as part of the project "Individual variability to make management decisions to prevent COPD exacerbations" has been approved by the McGill University Health Centre (MUHC) Research Ethic Board July 11, 2019, and renewed until July 11, 2022 (project number 2020–5844). This research relied exclusively on secondary use of anonymous information, without possibility of data linkage and dissemination of results that could not generate identifiable information.(https://ethics.gc.ca/eng/policy-politique_tcps2-eptc2_2022.html).

Study Participants

Eligible patients were required to have a formal diagnosis of COPD (defined as post-bronchodilator $FEV_1/FVC < 0.7$)[4] and have been prescribed an anti-IL-5 biologic between June 2018 and July 2022, for a duration of treatment of at least 8 months.

Data Collection

All data were collected retrospectively from electronic medical records. For each patient, a review of their records was conducted to collect baseline demographic information and relevant clinical data before and during treatment, including characteristics of acute exacerbation, spirometry, and disease-specific health status.

Treatment

Treatment was defined as having been prescribed an anti-IL-5 biologic. Duration of treatment was defined as the duration between the time of anti-IL-5 treatment initiation until either: cessation of treatment, patient death, date of last clinic visit, or if treatment remained ongoing, date of data collection.

Outcomes

AECOPDs were collected as reported in the electronic medical record (telephone or in-person visit, acute ambulatory care or emergency visit, or hospital admission). AECOPDs were categorized as moderate, defined by the requirement of oral corticosteroids and/or antibiotics, or severe if the event required hospitalization. To distinguish between previous AECOPDs and isolated events, the operational definition for an isolated event was the use of corticosteroids and/or

antibiotics at least four weeks after the last course of treatment (antibiotics/corticosteroids). If an intervention for AECOPD was required within the four weeks succeeding a previous event, it was considered an extension of the previous incident, not an isolated event. Forced Expiratory Volume in 1 second (FEV_1) was obtained from the spirometry test performed in the outpatient clinic visit closest to the time of IL-5 initiation. Health status was assessed using the COPD Assessment Test (CAT).

Statistical Analysis

Statistical analysis was performed using GEE model with type III likelihood ratio statistics via normal distribution with a log link function for continuous variables, and binomial distribution with an identity link function for binary variables for pre-/post-initiation comparison to estimate β (95% CI) and risk difference (95% CI), respectively. An exchangeable correlation structure and robust standard errors were used to account for correlation between pre-/post-initiation measures. For the proportion with 100%, the risk difference and 95% CI were estimated using the method suggested by Newcombe.[8] Poisson distribution was used to estimate exacerbation rate ratio. Significance was considered at alpha <0.05. Statistical analyses were performed in SAS (version 9.4).

Results

Between June 2018 and July 2022, 21 patients were prescribed anti-IL-5 biologics at the MCI COPD subspecialty clinic; 17 patients were included, 3 patients were excluded because they did not receive the biologic of interest and 1 patient because of insufficient data. All patients enrolled were treated with biologics for ≥8 months, and 13 (76%) for ≥1 year. Participants prescribed anti-IL-5 therapy were characterized by the traits described in Table 1. Participants primarily had

Table 1 Patient Characteristics 8 Months ± 2 Days Prior to Initiation of Treatment (n=17 Unless Otherwise Specified)

	Mean ± SD /n (%)
Socio-demographics	
Age, in year	67.8 ± 11.5
Gender: Male gender	10 (59%)
BMI	26.5 ± 4.9
Smoking Status	
Never smoker	1 (6%)
Current smokers	4 (23%)
Former smokers	12 (71%)
Pack-years (n=13)	40.5 ± 20.1
Severity of Airflow Obstruction by Spirometry	
FEV1 (L)	1.0 ± 0.6
FEV1 (% Predicted)	37.8 ± 18.2
Severity of Airflow Obstruction by GOLD Classification	
GOLD 4	8 (47%)
GOLD 3	4 (24%)
GOLD 2	5 (29%)
GOLD 1	0 (0%)

(*Continued*)

Table 1 (Continued).

	Mean ± SD /n (%)
Symptoms and Health status	
MRC Score	3.8 ± 0.8
CAT Score (n=7)	24.9 ± 7.7
Exacerbation Events	
≥1 moderate or severe exacerbation, n (%)	17 (100%)
≥2 moderate or severe exacerbation, n (%)	14 (82%)
≥1 severe exacerbation, n (%)	14 (82%)
Respiratory Medication	
Triple Therapy: ICS/LABA/LAMA	17 (100%)
Peripheral Blood Eosinophil Count (Highest in Previous Year)	
200–250 cells/uL	0 (0%)
251–300 cells/uL	5 (29%)
≥300 cells/uL	12 (71%)
Peripheral Blood Eosinophil Count (Highest in Previous 5 Years)	
200–250 cells/uL	0 (0%)
251–300 cells/uL	2 (12%)
≥300 cells/uL	15 (88%)
History of Asthma Prior to Smoking	
Yes	1 (6%)
Comorbidities	
Total number	3.2 ± 1.6
1–2 comorbidities	3 (18%)
3+ comorbidities	14 (82%)

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index; FEV_1, Forced Expiratory Volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council Dyspnea Scale; CAT, Chronic Obstructive Pulmonary Disease (COPD) Assessment Test; ICS, Inhaled Corticosteroid; LABA, Long-Acting β_2-Agonist; LAMA, Long-Acting Muscarinic Antagonist.

GOLD 3 (severe) or GOLD 4 (very severe) airflow obstruction, and all experienced ≥1 moderate or severe, mostly recurrent exacerbations and a high symptom burden in the year before treatment. All participants were on triple inhaled therapy and had a peripheral blood eosinophil count ≥250 cells/μL in the previous year, with about three-quarters ≥300 cells/μL. In the previous 5 years, 88% had an eosinophil count of ≥300, and only 1 patient had a diagnosis of asthma prior to smoking. Additionally, patients generally demonstrated improvement within 48–72 h of their acute symptoms to short courses of systemic corticosteroids, but recurrence of exacerbations usually occurred within 4 weeks of treatment withdrawal. None were on oral corticosteroids as maintenance therapy.

Table 2 presents the results on the primary outcome of exacerbation rate ratio as well as the secondary outcomes of changes in lung function and disease-specific health status. There was a statistically significant overall decrease in the exacerbation rate among all patients compared with baseline after 8 and 12 months of anti-Il-5 treatment, respectively,

Table 2 Comparison of the Primary Outcome Exacerbations, and Secondary Outcomes Lung Function, and Symptom Burden at Baseline (Pre) and During Anti-IL-5 Therapy (Post) (n=17 Unless Otherwise Specified)

Exacerbations: 8 Months ±2 Days (n=17)	**Pre**	**Post**	**Pre vs Post: Proportion Difference/RR (95% CI)[†]**	**P-value**
≥1 moderate or severe exacerbation, n (%)[#]	17 (100%)	9 (52%)	47.1% (23.3%, 70.8%)	0.003*
≥2 moderate or severe exacerbation, n (%)[&]	14 (82%)	3 (18%)	64.7% (36.7%, 92.7%)	<0.001*
≥1 severe exacerbation, n (%)[&]	14 (82%)	6 (35%)	47.1% (23.3%, 70.8%)	0.001*
Moderate or severe exacerbation rate, (no./patient-year)[$]	4.06	1.15	3.54 (2.02, 6.20)	<0.001*
Exacerbations: 12 months (n=13)	Pre	Post	Pre vs post: Risk difference/RR (95% CI)[†]	P-value
≥1 moderate or severe exacerbation, n (%)[#]	13 (100%)	8 (62%)	38.5% (12.0%, 64.9%)	0.039*
≥2 moderate or severe exacerbation, n (%)[#]	13 (100%)	6 (46%)	53.9% (26.8%, 81.0%)	0.005*
≥1 severe exacerbation, n (%)[&]	10 (77%)	5 (39%)	38.5% (12.0%, 64.9%)	0.004*
Moderate or severe exacerbation rate, (no./patient-year)[$]	3.54	1.46	2.42 (1.31, 4.48)	0.005*
Lung Function and Symptom Burden: 8 months	Pre	Post	Pre vs post: β (95% CI)[‡]	P-value
FEV1 (L), mean ± SD	1.0 ± 0.6	0.8 ± 0.4	0.23 (−0.02, 0.48)	0.072
FEV1 (% predicted), mean ±SD	37.8 ± 18.2	32.5 ± 14.5	5.29 (2.05, 8.54)	0.001*
CAT Score, mean ± SD	24.9 ± 7.7 (n=7)	20.6 ± 5.9 (n=9)	5.72 (1.01, 10.44)	0.017*

Notes: *Statistically significant with p<0.05. [†]RR=exacerbation rate ratio. [#]Risk difference and 95% CI estimated using method suggested by Newcombe was used for the proportion with 100%. [&]Risk difference and 95% CI was obtained by performing GEE model with binormal distribution and an identity link function for binary variables, accounting for the correlation between pre-post measures. [$]RR and 95% CI was obtained by performing GEE model with Poisson regression, accounting for the correlation between pre-post measures. [‡]β and 95% CI was obtained by performing GEE model with normal distribution, accounting for the correlation between pre-post measures. **Abbreviations**: FEV1, Forced Expiratory Volume in 1 second; CAT, Chronic Obstructive Pulmonary Disease (COPD) Assessment Test.

yielding the equivalent of a 2–3x reduction in exacerbation rate. Absolute FEV_1 was observed to decrease, and the decline in FEV_1% predicted reached statistical significance (p<0.05). There was a statistically significant improvement in the CAT score (p<0.05).

Discussion

The results of this RWD study showed that the patient subgroup prescribed anti-IL-5 monoclonal antibodies is generally characterized by severe disease traits, including severe airflow obstruction (FEV_1 < 50% predicted) and recurrent exacerbations (overall 3.5 moderate-to-severe AECOPDs in the year before treatment), high peripheral blood eosinophil counts and marked response to systemic corticosteroids for the treatment of AECOPD. Patients were all on maximal inhaled triple therapy and had multiple comorbid conditions but rarely a diagnosis of asthma prior to smoking. The prescription of an anti-IL5 biologic in these patients was associated with a marked reduction in both the frequency and severity of COPD exacerbations (equivalent to a 2–3x reduction), and a significant improvement in disease-specific health status despite a reduction in FEV_1 which remains unexplained.

Four RCTs have investigated the efficacy of anti-IL-5 therapeutics for COPD: GALTHEA and TERRANOVA for benralizumab,[9] and METREX and METREO for mepolizumab.[10] These failed to show significant benefits. Not targeting a well-selected group of patients, with high peripheral eosinophilia and severe disease, may have accounted for the failure to show conclusive results. A recent RCT demonstrated the efficacy of an anti-IL4/IL-13 biologic—dupilumab—in patients with COPD characterized by high peripheral blood eosinophilia count (≥300/μL) and severe disease traits with increased risk of exacerbation despite maximal inhaled therapy.[11] Following initiation of treatment, the intervention (anti-IL4/13 dupilumab) group exhibited a decreased annualized rate of moderate or severe AECOPDs; 0.78 events/year (95%

CI 0.64–0.93) compared with 1.10 events/year (95% CI, 0.93–1.30) when compared with placebo. This population also reported a greater improvement in pre-bronchodilator FEV_1 and improvement in disease-specific health status (measured using the St. George's Respiratory Questionnaire (SGRQ)) score compared with placebo. Such improvements were sustained through week 52.

A small benralizumab trial found a numerical reduction in rates of AECOPDs in patients characterized by eosinophilia (≥200 cells/μL) but not specific to disease severity (~50% GOLD I/II, 50% GOLD III/IV).[12] Moreover, the METREX study with mepolizumab found no significant reduction in rates of AECOPDs in a general population characterized by severe disease (94% GOLD D), but no eosinophilia necessarily.[10] Only when examining a population characterized by both severe disease and eosinophilia (≥150/μL at screening or ≥300/μL in the prior year), as was done in a post-hoc analysis of the METREX/METREO trials, was a significant reduction (by 18%) in rates of exacerbations reported (p=0.006).[13] This meta-analysis also demonstrated greater treatment effects with mepolizumab versus placebo with increasing screening blood eosinophil counts for exacerbations treated with systemic glucocorticoids but not in patients whose exacerbations were treated with antibiotics. This differential response to mepolizumab according to the trigger of exacerbation (microbial or non-microbial) may be of interest and will require further study.

Another recent real-world evidence case series included 7 COPD patients all with radiological evidence of emphysema and maintenance oral corticosteroid (OCS) treated either with mepolizumab or benralizumab, with only 1 patient known to have asthma before the age of 40 years, with blood eosinophils count of 237 ± 225 cells/μL despite chronic OCS use.[7] After 12 months of anti-IL-5 treatment, mean OCS dose was reduced from 12.0 ± 7.6 to 2.6 ± 4.3 mg/day and annual exacerbation rate decreased from 8.2 ± 3.3 to 1.0 ± 1.2, representing a 78% and 88% decrease, respectively. Thus, our results are in concordance with the currently available RWD in the literature in that anti-IL-5 treatment may potentially reduce the frequency of AECOPDs in a subpopulation of patients with COPD, especially those with recurrent moderate to severe exacerbations despite optimal combined inhaled therapy, and high blood eosinophil counts.

A strength of this study is that we were able to describe the potential use and efficacy of anti-IL-5 therapy for "real-world" patients with COPD. These new results allow us to better plan the design of a new RCT that could confirm the efficacy of anti-IL-5 in subgroup of COPD patients. Despite this optimism, there are limitations to this study, including the lack of a concomitant control group, the absence of randomization and the small sample size, all of which hinders our ability to investigate the impact of therapy beyond exacerbations. This study is not an RCT and therefore should be interpreted ultimately as exploratory and hypothesis generating.

This RWD study of anti-IL-5 monoclonal antibodies for patients with COPD demonstrated that strategies targeting "treatable traits" such as recurrent AECOPDs may be beneficial in the treatment of phenotypically heterogeneous diseases, such as COPD. The conclusions of this research align with existing studies suggesting the potential of anti-IL-5 treatment for specific patients with COPD and therefore advocate for further investigation of RCTs on the use of anti-IL-5 biologics and/or other biologics for well-characterized patients with COPD. Targeting eosinophilic inflammation has been successful in managing severe eosinophilic asthma and may hold promise in certain phenotypes of COPD. Given that there have been few trials for anti-IL-5, further studies with well-characterized patients with COPD, especially those with recurrent moderate to severe exacerbations despite optimal combined inhaled therapy, and high blood eosinophil counts may ultimately lead to the establishment of this therapeutic and other biologics for COPD, as currently, none are.[14]

Disclosure

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