Original Research

Real-World Effectiveness of Biologic Therapies in a Multimorbid Population of COPD Patients With Type 2 Inflammation

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***Running Head*: Biologic Therapies in COPD: Impact on Exacerbations**

***Keywords*:** COPD; biologic therapy; hospitalizations; exacerbations

Abbreviations: CAD (coronary artery disease), CVA (cerebrovascular accident), COPD (chronic obstructive pulmonary disease), GOLD (Global Initiative for Chronic Obstructive Lung Disease), ICS (inhaled corticosteroids), PFT (pulmonary function test), T2 (type 2)

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Abstract

Background

Chronic obstructive pulmonary disease exacerbations impair quality of life, accelerate disease progression and increase hospitalizations and mortality risk. Biologic therapies targeting type 2 inflammation have demonstrated efficacy in clinical trials, however real-world data in more diverse populations with greater comorbidity burden remain limited. We evaluated whether biologic therapy is associated with reductions in exacerbations in a real-world COPD cohort.

Methods

Retrospective review of the electronic medical record (2016-2023) was performed. Patients who had COPD that were treated with biologics were included. Demographics, comorbidities, imaging findings, eosinophil count, and pulmonary function testing were collected. The primary outcome was the change in moderate and severe exacerbations in the year before and after biologic initiation. Secondary outcomes included admissions requiring NIV, IMV or ICU care.

Results

56 patients (mean age 71±8.5, 50% female) were included. 55% had CAD, 71% hypertension, 14% stroke, 30% diabetes. Baseline FEV1 was 41±20, RV 159±48.8 and DLCO 42±18. Biologics reduced annual moderate exacerbations from 3.63±2.6 to 2.0±2.4(mean reduction 1.63, 95% CI 1.080-2.179, $p<0.001$) and hospitalizations from 1.34±1.92 to 0.48±1.14(mean reduction 0.86, 95% CI 0.420-1.295, $p < 0.001$). Reductions were not associated with emphysema severity or GOLD stage. Annual admissions requiring NIV decreased 0.13 to 0.02($p=0.033$). Annual ICU admissions trended down 0.18 to 0.05($p=0.163$) and IMV frequency was unchanged. There were no significant changes in pulmonary function.

Conclusion:

In a real-world cohort of COPD patients with T2 inflammation, biologics were associated with significant reductions in hospitalizations, exacerbations and NIV utilization, supporting their effectiveness outside clinical trial settings.

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Background

Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with impaired quality of life, increased hospitalizations, disease progression and increased mortality[1–5]. The cornerstone of guideline directed therapy in the last decades centered on inhaled bronchodilators, followed by inhaled corticosteroids (ICS) and azithromycin or roflumilast[6, 7]. In the last several years, more data has emerged assessing the role of type 2 inflammation (T2) in COPD, and the use of the peripheral blood eosinophil count as a surrogate of T2 inflammation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines recommends using the peripheral blood eosinophil count to guide therapy in patients with COPD at risk of moderate or severe exacerbations based on several studies demonstrating eosinophil count can predict response to ICS[6, 7].

Given the potential novel target of T2 inflammation, there has been increased interest in the use of biologics to treat type 2 inflammation nonresponsive to inhaled triple therapy in patients with COPD[8–11]. The initial four large prospective randomized trials that targeted the IL-5 pathway failed to reach their primary endpoint regardless of the biologic agent used[8, 10, 11]. In 2017, METREX showed that mepolizumab prolonged the time to moderate or severe exacerbations in patients with COPD and an eosinophilic phenotype without significant differences in rate of hospitalizations or improvements in lung function. The beneficial effect on exacerbation reduction was not observed in the METREO study when statistical analysis accounting for multiplicity was conducted[8]. The 2019 companion trials GALATHEA and TERRANOVA, that utilized benralizumab also did not show a significant difference in rate of exacerbations compared to placebo despite substantially reducing the level of blood eosinophils[9]. However, two large prospective and controlled multicentered clinical trials examining dupilumab vs

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placebo in patients with COPD enriched for type 2 inflammation, reported fewer exacerbations, improved lung function and quality of life[10, 11]. Most recently mepolizumab has been reevaluated, finding that COPD patients with an eosinophilic phenotype had reductions in annual moderate or severe exacerbations[12].

The results of randomized clinical trials are promising, however, more data reflective of real world populations are needed to assess for their external validity[13–15]. Issues with generalization of clinical trials include the relative poorer representation of minority populations[16, 17] and those with increased comorbid disease[18]. Prior studies have shown that as little as 3% of asthma patients and 17% of COPD patients would meet inclusion criteria for their respective clinical trials[19, 20]. While randomized clinical trials remain the gold standard of scientific research, assessing the effect of therapies on real world populations is also required. Our study aims to review the effects of biologics in a real-world population of patients with COPD to assess the benefits of these agents outside of a clinical trial setting.

Methods

Study description

This is a single-center retrospective review of the electronic medical record (EMR) between 1/1/2016 to 10/1/2023 for consecutive patients that were ever prescribed a biologic agent and carried a diagnosis code for COPD. This study was performed in accordance with the ethical standards of the Helsinki Declaration of 1975 and Western Institutional Review Board (Protocol #31820). Patients and/or the public were not involved in the design of this study.

Patient population

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The initial EMR query identified patients >40 years of age, with a history of COPD diagnosis, who were prescribed biologic therapy, including mepolizumab, benralizumab and dupilumab. Review of the EMR was performed to confirm the clinical diagnosis, biologic indication and initiation of therapy. The diagnosis of COPD reflected the interpretation of the treating pulmonologist based on clinical history, pulmonary function testing and radiographic evidence of disease. Pulmonary function testing was obtained as clinically indicated, and not in a protocolized manner. Patients were excluded if their primary pulmonologist indicated a diagnosis solely of asthma, without evidence of COPD.

Patients were also excluded if they had been on multiple biologics, had a history of interstitial lung disease, or were on biologics for alternate therapies such as for dermatologic disease. Patients were also excluded if they were missing office appointments or PFTs, one year prior and one year post initiation of therapy. Initiation and maintenance of biologic therapy was determined through longitudinal review of chart documentation. Patients that were prescribed a biologic, but never had documented treatment were excluded.

The study was conducted prior to the FDA approval of biologic therapies for COPD, and usage of these agents was off label. Initiation of these therapies were at the discretion of the treating clinician, based on inadequate control of COPD despite optimal therapy.

Data collected

Data collected included the type and number of comorbidities, prescribed inspired oxygen at rest, degree of emphysema quantitated on HRCT imaging, peripheral blood eosinophil count at initiation and nadir.

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Chart review was performed to quantify the number of moderate exacerbations, number of COPD-related hospitalizations, number of ICU admissions, and inpatient utilization of noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV). Pulmonary function test data was recorded and included the FEV1, FVC, TLC, RV and DLCO % predicted.

Endpoints

The primary end point was the annual number of moderate and severe exacerbations after therapy with biologic agents. Moderate exacerbations were defined as treatment with oral corticosteroids and severe exacerbations were defined by COPD related hospitalizations. ICU utilization was also compared, along with annual admissions requiring NIV or IMV. Pulmonary function test data was compared before and after initiation of therapy.

Statistical Analysis

All continuous variables are presented as mean (standard deviation) or median (interquartile range) unless otherwise stated. Paired samples t-tests were used to compare clinical outcomes before and after initiation of biologic therapy including exacerbations, hospitalizations, ICU admissions, NIV and IMV utilization. Linear regression and univariate ANOVA were used to evaluate associations between baseline clinical characteristics and changes in outcomes following biologic therapy. Statistical analyses were performed using SPSS version 25, New York, USA. Statistical significance was defined as a p value less than 0.05 and a confidence interval that did not cross 0.

Results

Patient demographics

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1,241 patients were obtained from initial query of EMR. 668 patients remained after duplicate entries were removed. Of 192 patients with clinically confirmed COPD treated with biologic therapy, 56 patients had complete pre and post initiation office visits and PFTs were included in the final analysis (Figure 1).

The mean (±SD) age of patients was 71 ± 8.5 yrs. Patients were equally split between male and female patients (50%, n=28 in each group), and with a high proportion of non-white patients (33.9%, n=19) (Table 1). There were no active smokers at the time of biologic initiation. In terms of comorbid disease, 55.4% of patients had CAD, 25% had heart failure, 71.4% had hypertension, 14.3% had prior CVA, and 30.4% had diabetes. 40 patients had structural evidence of emphysema on chest CT imaging. Patients had a prior history of frequent and severe exacerbations.

Baseline Pulmonary Function Testing, Imaging, Exacerbations and Eosinophil Counts

Baseline FEV1 % predicted was 41 ± 20. Patients in our study on average had significant gas trapping (RV% Predicted 159 ± 48.8) and moderately reduced DLCO (42 ± 18.8), without hyperinflation (TLC % Predicted 107 ± 24.8). CT evidence of emphysema was seen in 40 (71.4%) of patients. The mean number of moderate exacerbations in the year prior to initiation of biologic therapy was 3.63 ± 2.6. The mean number of severe exacerbations in the year prior was 1.3± 1.9. The mean eosinophil count was 414 ± 296 cells/µL.

Comparison of Baseline Characteristics to Clinical Trial Participants

Patient demographics were compared to prior clinical trials for biologic therapy in COPD including METREX, GALATHEA and TERRANOVA, BOREAS and NOTUS, and MATINEE (Table 2). Compared to previously conducted clinical trials, our study cohort had a higher

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proportion of older and female patients (50% compared to 29.3-35%) and non-white patients (33.9% compared to 10.4 to 15.9%). African American patients made up a larger proportion of patients who received biologic therapy for their COPD in this cohort (17.9% as compared to 0.5-2.6%). Baseline FEV1% predicted in our patients was similar to previously reported trials. Other measures, such as lung volumes and DLCO were not reported in the clinical trials. CT proven emphysema was reported in 70% of our patients. Only GALATHEA AND TERRANOVA reported imaging based emphysema (by CXR or CT) in 53-56% of their patients. NOTUS reported emphysema in 30.4% of their patients, however this was as reported by the investigator.

Combined moderate and severe exacerbations were higher at 4.8 ± 4.13 in our study compared to 2.1-2.5 reported by prior clinical trials. Baseline mean number of moderate exacerbations, mean number of severe exacerbations and % of patients with a severe exacerbation in the previous year were variably reported in the clinical trials (Table 2). Baseline eosinophil levels were similar to prior studies.

Moderate Exacerbations and Hospitalizations

Before initiation of biologic, patients experienced a mean 3.63 ± 2.6 moderate exacerbations compared to 2 ± 2.4 post treatment. There was a mean reduction of moderate exacerbations in the first year after initiation of biologic therapy of 1.63 (95% CI 1.080-2.179, $p<0.001$) (Figure 2).

The reduction in moderate exacerbations when stratified for presence of emphysema ($p=0.603$) or GOLD staging ($p=0.338$) did not show statistically significant differences. Baseline serum

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eosinophils prior to initiation of biologic therapy were not associated with a greater reduction of exacerbations.

COPD related hospitalizations were reduced post therapy (1.34 ± 1.92 to 0.48 ± 1.14), with a mean reduction of 0.86 hospitalizations in the first year after initiation of biologic therapy (95% CI 0.420-1.295, $p < 0.001$) (Figure 3).

Mean annual ICU admissions decreased from 0.18 to 0.05 ($p= 0.163$), admissions requiring NIV decreased from 0.13 to 0.02 ($p=0.033$), while annual rates of IMV was unchanged (mean 0.04) (Figure 4)

Lung Function

There was no significant difference in pulmonary function tests before and after initiation of biologic therapy. %Predicted values for FEV1, FVC, TLC and DLCO at one year were similar to values prior to initiation.

Discussion

In a real-world population of patients with COPD and T2 inflammation, treatment with biological agents was associated with a statistically significant decrease in both moderate exacerbations, and hospitalizations on follow up at 1 year. In addition, biologic therapy was associated with a decrease in the most severe hospitalizations, with a trend towards decreased ICU admissions, and significant reductions in NIV utilization. Importantly, this cohort of patients was treated prior to the FDA approval of biologic therapies for COPD, and these agents were prescribed off label. The decision to initiate biologics was at the discretion of the treating clinician, in patients who were determined to require escalation of therapy despite existing therapy. The findings from this real-world cohort support recent clinical trials showing that there

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is a role for biologics in patients that present with a T2 inflammatory endotype and that these findings suggest sustained benefits to less restrictive and more diverse patient populations.

We believe our cohort is more reflective of real-world populations, and is better representative of women and minority patients, which is shown in the comparison to the previous COPD and biologic therapy clinical trials (Table 2). Increasing women and minority enrollment in clinical trials has been an ongoing priority since the 1990s, and the extent of the disparity is still unknown. A recent study in 2022 analyzing all US clinical trials from 2000-2020 showed that only 43% of the included studies reported any race/ethnicity data[16] however this is expected to improve over time as in 2017 the NIH required race/ethnicity reporting, if the data was collected, in all trials submitted to ClinicalTrials.gov[21]. Until clinical trials become more reflective of the general population, real world data remains necessary to supplement their findings and assess external validity.

In addition, our study was able to reaffirm continued success of biologic therapies even in a group of patients with significant additional comorbidities. In the GOLD guidelines, it is noted that patients with COPD often have additional comorbidities and that there is no evidence multimorbid patients should manage their COPD differently[6]. Importantly, the guidelines do note that most evidence comes from trials in patients where COPD is their only significant disease, however on average, a patient with COPD has five significant comorbidities[22]. It is therefore crucial to evaluate if real world patients continue to derive substantial clinical benefit to avoid exposure to polypharmacy if there is no advantage. Our study demonstrated that real world patients, with a significant number of comorbidities, benefited from biologic therapy with a durable effect of reductions in exacerbations and hospitalizations.

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In comparison to the clinical trials, our patients had higher rates of exacerbations at baseline than those included in clinical trials. At baseline, our patients had 4.8 combined moderate and severe exacerbations in the year prior, compared to 2.1-2.5 in the trial patients. When separated out, moderate and severe exacerbations were variably reported, however appear higher in our patients (Mean moderate exacerbations 3.63 vs 1.8, mean severe exacerbations 1.3 vs 0.3). Over 50% of our patients also had at least 1 hospitalization, prior to therapy, as compared to rates of 21-40% in the clinical trials. While it is challenging to compare groups, it is encouraging that our patients still derive benefit, despite higher baseline metrics of COPD severity. There was also no significant difference in terms of exacerbation reduction, in patients with radiologic evidence of emphysema, and those of different GOLD grades, suggesting sustained benefits in these groups.

Our study showed a mean reduction of 0.857 yearly hospitalizations in patients who, on average, had 1.34 hospitalizations in the year preceding treatment. Reductions in exacerbations are so critical, again, due to the association with poorer quality of life, sustained reduction in lung function and overall mortality[1–5]. In some of the prospective clinical trials, a reduction in exacerbations has been demonstrated, but reducing hospitalizations has not. Hospitalizations, along with having the strongest associations with negative patient outcomes, also significantly drives health care expenditure. Despite accounting for a relatively low proportion of total exacerbations, hospitalizations can cost upwards to 60-70% of estimated COPD healthcare-associated costs[23]. Significantly reducing hospitalization in COPD patients is paramount to improving both patient centered targets and decreasing health care utilization.

Our study also aimed to examine the highest severity of hospitalizations, those that require ICU admissions, NIV utilization or IMV. There was a trend towards decreased ICU admissions, from 0.18 to 0.05 annually, however this did not reach statistical significance (p=0.163). NIV

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utilization did however significantly decrease (0.13 to 0.02, p=0.033), while IMV was similar (mean 0.04). This suggests that this trend towards less ICU utilization may be driven mainly by reductions in patients needing NIV. This has important implications as ICU admissions significantly drive resource utilization and costs for patients with COPD[24]. In addition, reductions in NIV utilization are clinically significant, as patients who require NIV represent a higher risk trajectory for mortality, one that approximates that of patients who require IMV, with a 1 year mortality greater than 40%[25].

There was no significant improvement in measures of pulmonary function testing, including FEV1. This is similar to the findings in GALATHEA/TERRANOVA, METREX/METREO and MATINEE but different from BOREAS/NOTUS. This may be attributable to our patient population, which had on average, lower FEV1 at baseline (Table 2). The clinical trials also do not report other measures such as lung volumes or diffusion capacity for comparison. This is a retrospective study and PFTs were not obtained in a protocolized manner, which makes comparison to the trials challenging. While most trials did not report this statistic, 70% of our patients also had CT proven emphysema. NOTUS reported 30.4% of their patients had emphysema and MATINEE had rates of 49%, however this was based off clinician reporting, not imaging findings. GALATHEA AND TERRANOVA reported emphysema rates of 53-56% based on prior XR or CT. Our patients may represent an overall more severe cohort of COPD patients which may not have reflective improvement in FEV1.

Limitations from this study include its retrospective design which opens the results to biases including selection bias. Inclusion required complete clinical documentation and pulmonary function testing within 1 year, which may have preferentially selected patients who tolerated treatment. Patients who discontinued treatment early due to lack of benefit, adverse effects, or

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death may be underrepresented however complete longitudinal data was important to establish disease severity and assess for clinical improvement following initiation of therapy. Our study required the use of retrospective chart review and are subject to errors in documentation. Certain elements such as follow up pulmonary function testing were not obtained at predetermined time periods and may be affected by the patient's clinical situation at the time. The final sample size of the study was also relatively small.

In addition, the diagnosis of COPD with T2 inflammation was based on the treating pulmonologist's interpretation of clinical history, imaging, and diagnostic testing and was subject to interobserver variability. Patients considered to have primary asthma without COPD were excluded, but it remains a challenge in both clinical trials and real-world practice to definitively distinguish COPD with T2 inflammation from asthma in patients with overlapping features. In these patients, we cannot exclude that an underlying concomitant asthmatic phenotype contributed to the response. Despite this heterogeneity, these findings remain relevant as they reflect the ambiguity that occurs when applying clinical trial data to real-world patients. In clinical practice, there will be variable interpretations of a true diagnosis of COPD and if there is any overlap syndrome, and it is crucial to see if these patients continue to respond to the selected therapy. Moreover, there is growing evidence that targeting an endotype may be more effective in deciding therapy. Different biologic agents were used in our patients but were not compared to one another given the small sample size and retrospective design of the study, however descriptive analysis demonstrated reductions in moderate and severe exacerbations across all three treatment groups.

Overall, the combination of the results from clinical trial data along with our real-world data is encouraging in the use of biologic therapies in COPD patients with T2 inflammation. Biologics

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continue to be investigated in COPD patients, with prospective studies reassessing the initial biologic agents, along with newer therapies targeting novel pathways, and it will be important to better define the full benefits of these therapies in real-world patients, along with identifying which patients are most likely to respond.

In conclusion, in a real-world population of patients with COPD, with evidence of T2 inflammation, biologic therapy was associated with a reduction in moderate exacerbations and hospitalizations.

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Declarations

Ethics approval and consent to participate: This study was performed in accordance with the Declaration of Helsinki. This human study was approved by Temple University Institutional Review Board - approval: Protocol #31820. Adult participant consent was not required because this was a retrospective chart review involving minimal risk to participants and a waiver of informed consent was granted by the IRB.

Consent for publication: Not applicable

Clinical Trial Number: Not applicable

Availability of data and materials: The data that supports the findings of this study are not publicly available due to privacy restrictions related to protected health information, but are available from the corresponding author upon reasonable request

Competing Interests: No competing interests exist for all authors

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Authors' contributions: TH is the guarantor of the article, taking responsibility for the integrity of the work from inception to the published article. TH, SD, and GC designed the research study. TH, AM, and SD performed data-analysis. SD performed statistical analysis. AM, SD and GC helped revise the manuscript.

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Table 1: Demographics and Clinical Characteristics of the Patients at Baseline and Treatment Group

Variable	N=56
Age, years (mean ± SD)	71 ± 8.5
Female no. (%)	28 (50)
Male no. (%)	28 (50)
Race or Ethnic Group no. (%)	
Caucasian/White	37 (66.1)
African American/Black	10 (17.9)
Hispanic	6 (10.7)
Other	3 (5.3)
Pulmonary Function Tests mean ± SD	
FEV1% Pred	41 ± 20
FVC % Pred	75 ± 17.6
FEV1/FVC	41.6 ± 15.3
TLC % Pred	107 ± 24.8
RV % Pred	159 ± 48.8
DLCO % Pred	42 ± 18.8
GOLD Grades no. (%)	
GOLD 1	4 (7.1)
GOLD 2	9 (16.1)
GOLD 3	25 (44.6)
GOLD 4	18 (32.1)
Moderate Exacerbations in Year Prior (Mean ± SD)	3.63 ± 2.6
Severe Exacerbations in Year Prior (Mean ± SD)	1.34 ± 1.9
Combined Moderate and Severe Exacerbations in Year Prior (Mean ± SD)	4.8 ± 4.13
Eosinophils at Initiation - cells/µL (Mean ± SD)	414 ± 296
CT Evidence of Emphysema no. (%)	40 (71.4)
Comorbid Diseases no. (%)	
Coronary Artery Disease	31 (55.41)

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Heart Failure	14 (25)
Hypertension	40 (71.4)
Stroke History	8 (14.3)
Diabetes Mellitus	17 (30.4)
Background COPD Therapy	
Triple Inhaled Therapy	52 (92.9)
Chronic Azithromycin or Roflumilast	40 (71.4)
Biologic Therapy Group no. (%)	
Mepolizumab	37 (66.1)
Benralizumab	13 (23.2)
Dupilumab	6 (10.7)

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Table 2: Comparison of Real-World Cohort of Patients with T2 Inflammation in relation to COPD biologic clinical trials

Variable	Real-World Cohort (N=56)	METREX-eos (Mepolizumab) (N= 462)	GALATHEA (Benralizumab) (N=1120)	TERRANOVA (Benralizumab) (N=1545)	BOREAS (Dupilumab) (N=939)	NOTUS (Dupilumab) (N = 935)	MATINEE (Mepolizumab) (N = 804)
Age, years mean ± SD	71 ± 8.5	65 ± 8.5	65.6 ± 8.25	65.2 ± 8.33	65.1 ± 8.1	65 ± 8.3	66.2±8.0
Female no. (%)	28 (50)	163 (35)	328 (29.3)	521 (33.7)	319 (34)	303 (32.4)	253 (31)
Race or Ethnic Group no. (%)							
Caucasian/White	37 (66.1)	NR	988 (88.2)	1211 (78.4)	790 (84.1)	838 (89.6)	673 (84)
African American /Black	10 (17.9)	NR	18 (1.6)	40 (2.6)	5 (0.5)	12 (1.3)	10 (1)
Hispanic	6 (10.7)	NR	NR	NR	261 (27.8)	300 (32.1)	NR
Other	3 (5.3)	NR	114 (10.2)	294 (19)	144 (15.3)	85 (9.1)	121 (15)
Pulmonary Function Tests mean ± SD							
FEV1% Pred	41 ± 20	44.2 ± 14.8	43.1 ± 12.2	42.9 ± 11.9	50.6 ± 13.1	50.1 ± 12.6	48.2 ± 15.8
FVC % Pred	75 ± 17.6	NR‡	NR	NR	NR	NR‡	NR‡
FEV1/FVC	41.6 ± 15.3	45 ± 11	43±12	45 ± 11	50 ± 10	50 ± 10	49 ± 12
TLC % Pred	107 ± 24.8	NR	NR	NR	NR	NR	NR
RV % Pred	159 ± 48.8	NR	NR	NR	NR	NR	NR
DLCO % Pred	42 ± 18.8	NR	NR	NR	NR	NR	NR
Moderate Exacerbations in Year Prior mean ± SD	3.63 ± 2.6	NR	NR	NR	NR	1.8 ± 1	NR
Severe Exacerbatio	1.34 ± 1.9	NR	NR	NR	0.3 ± 0.7	0.3 ± 0.6	NR

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ns in Year Prior mean ± SD							
Patients with ≥1 hospitalization in the year prior %	52.6	34.6	40.4	33.9	25.9	NR	21
Combined Moderate and Severe Exacerbations in Year Prior mean ± SD	4.8 ± 4.13	2.5 ± 1.3	2.33 ± 1.25	2.28 ± 1.01	2.3 ± 1.0	2.1± 0.9	2.3 ± 0.9
Eosinophils at Initiation - cells/µL (Mean ± SD) ¶	414 ± 296	260/290	453.2 ± 280.25	504.5 ± 393.08	401 ± 298	407 ± 336	480
CT Evidence of Emphysema no.(%)	40 (71.4)	NR	628 (56.1)	824 (53.3)	NR	284 (30.4) †	395 (49) †
Comorbid Disease no.(%)							
Coronary Artery Disease	31 (55.41)	NR	NR	NR	NR	NR	NR¥
Heart Failure	14 (25)	NR	NR	NR	NR	NR	NR
Hypertension	40 (71.4)	NR	NR	NR	NR	NR	NR
Stroke History	8 (14.3)	NR	NR	NR	NR	NR	NR
Diabetes Mellitus	17 (30.4)	NR	NR	NR	NR	NR	NR

¶Data for METREX and MATINEE presented as geometric mean. METREX data separated for mepolizumab/placebo respectively

† As reported by provider

‡FVC reported in L, not %predicted

¥ % Any Hx of Cardiac Disease History Reported

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Figure 1: Diagram for patients with COPD who met final inclusion criteria

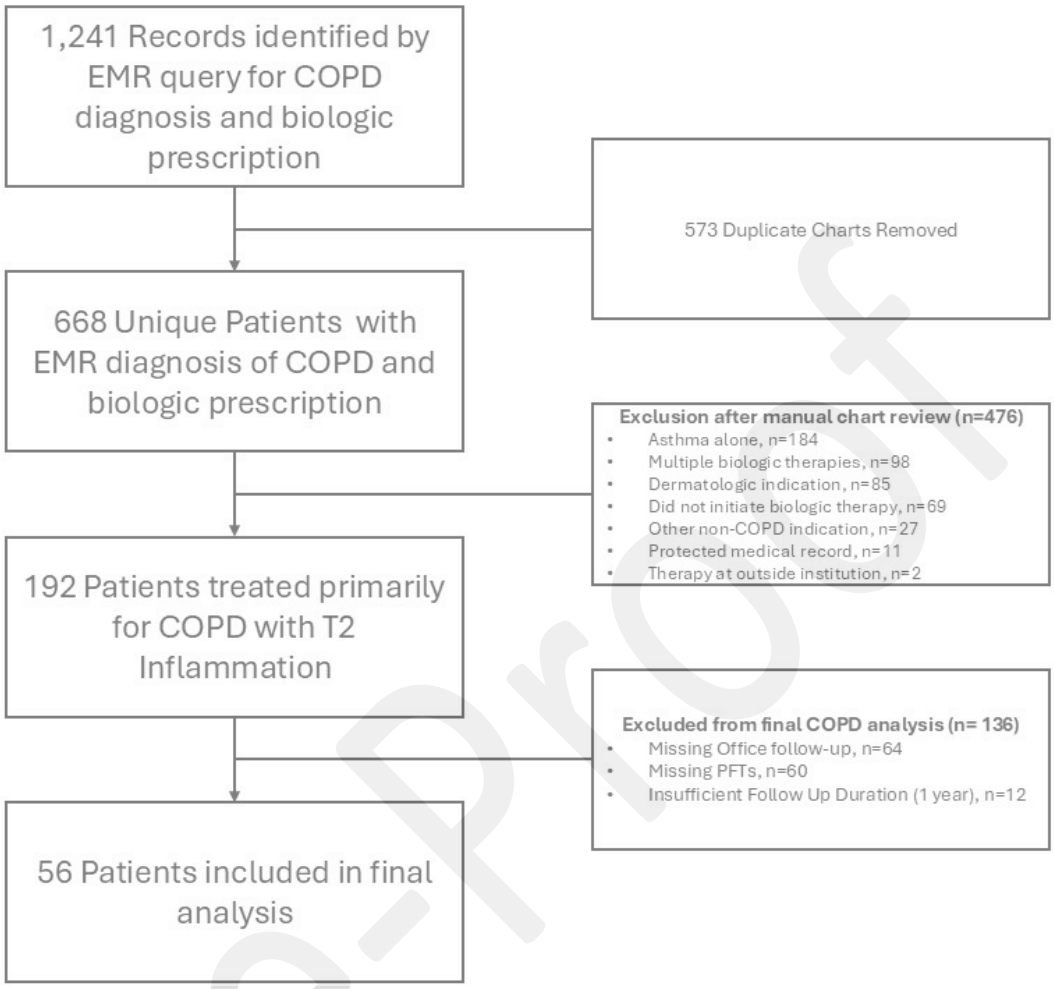

Figure 2: Comparison of Moderate Exacerbations pre and post biologic therapy

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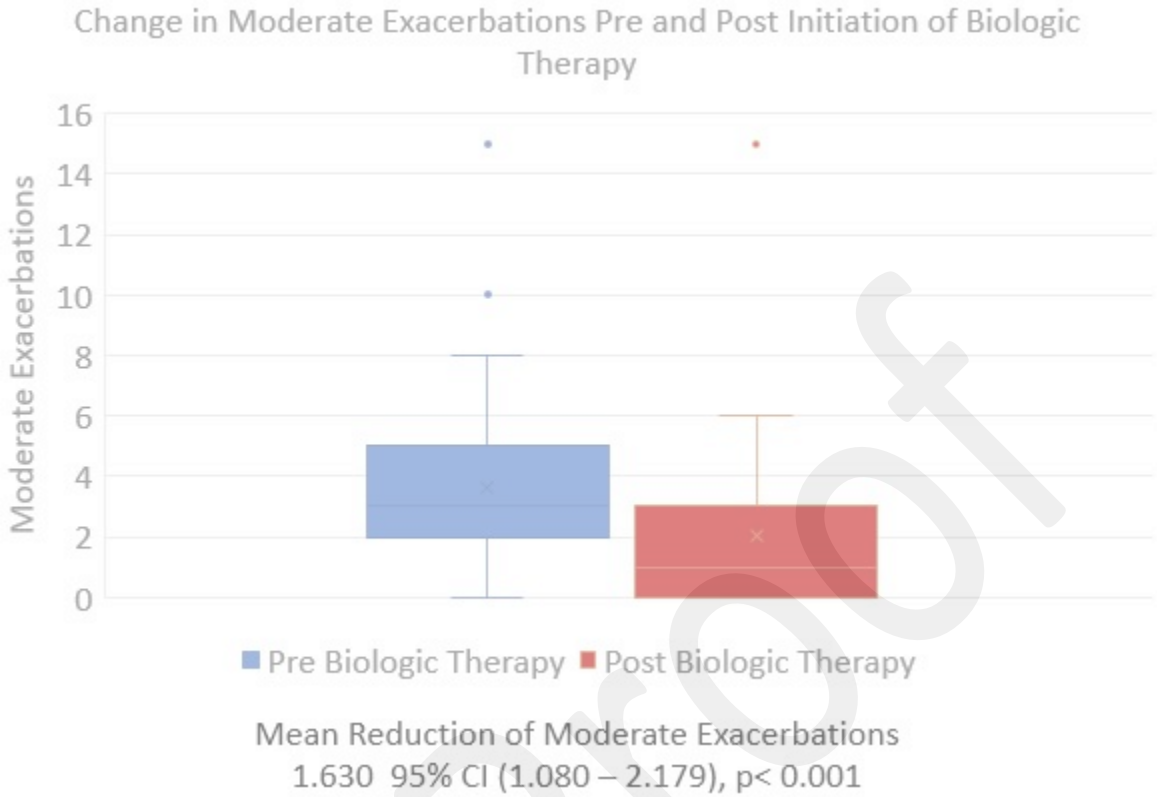

Figure 3: Comparison of Hospitalizations pre and post biologic therapy

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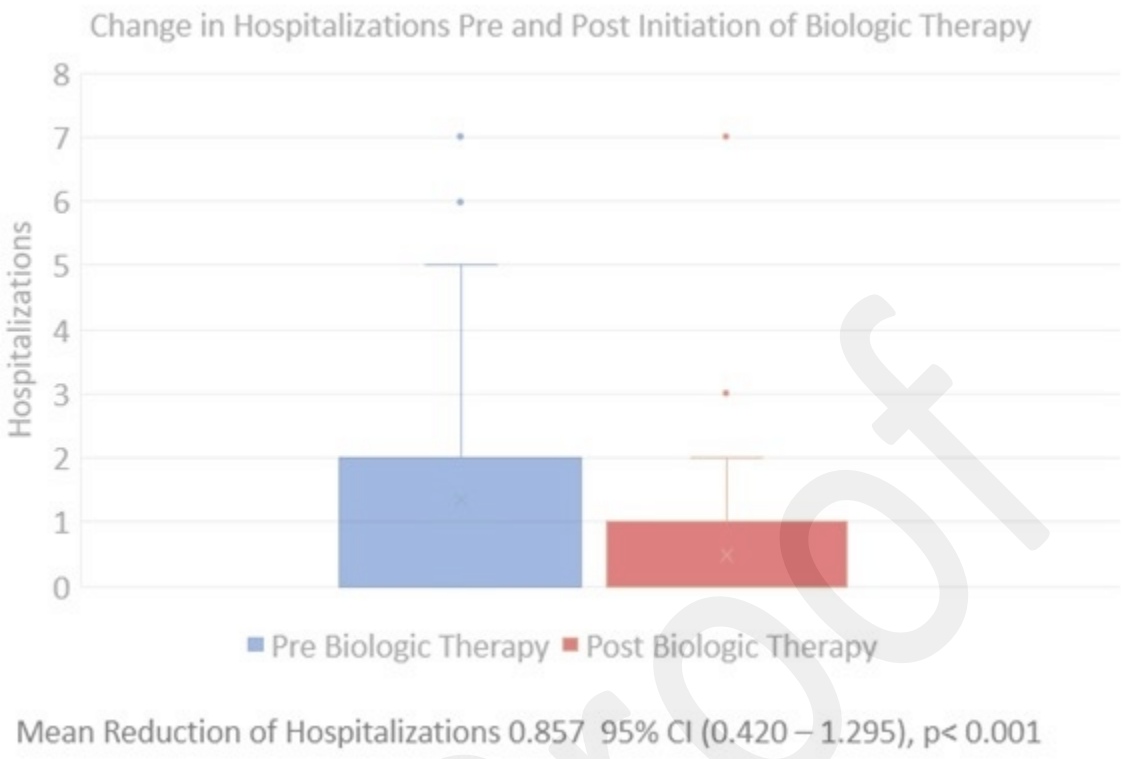

Figure 4: Annual rates of admissions requiring NIV, IMV and ICU utilization in the year prior and year post initiation of biologic therapy

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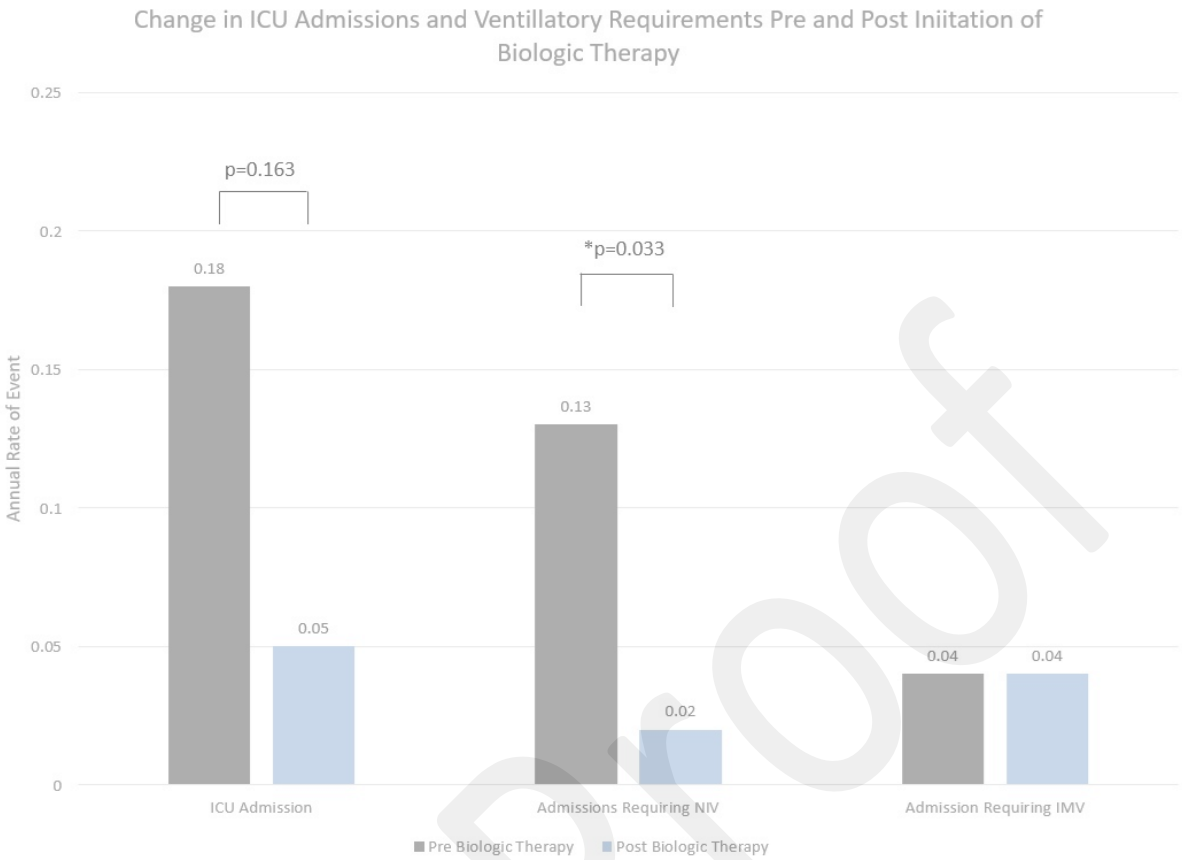

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