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RESEARCH ARTICLE
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THE EFFICACY OF BIOLOGICAL TREATMENT METHODS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS; SYSTEMATIC REVIEW

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by airflow obstruction and persistent inflammation, result in frequent exacerbations and reduced quality of life. Patients with moderate to severe COPD continue to experience disease progression with regular treatments. Biologic therapies to a specific immune pathways were developed through the identification of eosinophilic and type 2 inflammatory phenotypes. This study aims to evaluate the efficacy and safety of biologic therapies to decrease exacerbations and improve clinical outcomes in patients with moderate to severe COPD.

Methods: we conduct a systematic search in electronic databases (PubMed, Scopus, and Google Scholar) for randomized controlled trials (RCTs) published between 2014 and 2024. Studies included adult COPD patients (≥40 years) treated with biologics targeting IL-5, IL-4/13, IL-1, or TSLP. The Cochrane Risk of Bias 2 tool was used to assess study quality. Data extraction and screening were performed independently by two authors.

Results: Seven RCTs were included, examining biologic treatrmet (dupilumab, mepolizumab, benralizumab, tezepelumab, and MEDI8968). Dupilumab reduce exacerbation rates and improved lung function and quality of life in patients with type 2 inflammation. Mepolizumab showed modest benefit in eosinophilic COPD. Other treatments, including benralizumab and tezepelumab, failed to demonstrate consistent clinical efficacy.

Conclusion: Biologics treatment show a selective benefits in COPD patients with eosinophilic or T2-high inflammation, mainly with dupilumab. Further studies are needed to define optimal patient selection and assess long-term safety and cost-effectiveness.

Keywords: Chronic obstructive pulmonary disease; Biologic therapy; Eosinophilic inflammation; Dupilumab; Mepolizumab; Benralizumab; Tezepelumab

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating respiratory condition characterized by airflow limitation, persistent inflammation, and a high burden of morbidity and mortality worldwide (1). COPD treatment mainly focused on symptom control with bronchodilators (beta2-agonists and anti-muscarinic agents) which remain foundational in recent practice (1). Instead of improvements in bronchodilator formulations and inhaler devices, patients continue to develop acute exacerbations and disease progression (2).

The shift in COPD management has been driven by an expanding recognition of the disease's heterogeneity and the identification of distinct inflammatory phenotypes and endotypes, such as eosinophilic COPD (3). This phenotype had a favorable response to corticosteroids and opened the door for the use of targeted biologic therapies, mainly monoclonal antibodies that inhibit interleukin-5 (IL-5) and its receptor (4). Clinical trials have shown that these methods reduce exacerbation frequency, especially in patients with elevated blood eosinophils (5).

IL-4/IL-13 receptor antagonist (Dupilumab), was shown to be efficient in decreasing exacerbations and improving quality of life in patients having type 2 inflammation (6). Dupilumab advocate the precision medicine in COPD, where treatments are directed to specific inflammatory profiles and biomarker patterns (7). The introduction of biologics in COPD management represents a significant advance, which change focus from general symptom relief to inflammation-targeted therapy aimed at change disease progression.

The high cost of biologic therapies and the limited availability of predictive biomarkers prevent their widespread usage (7), and the patient-reported outcome measures are underutilized in assessing therapeutic impact (6). Biologic therapies offer a good options for specific subgroups of COPD patients, but we need further research to optimize patient selection and integrate these treatments into standard care (2). The evolution of COPD treatment indicate a shift toward precision and personalized medicine, with biologics at the most effective for those with eosinophilic or T2-high phenotypes (3).

Study aim

The aim of this systematic review is to evaluate the efficacy and safety of biologic therapies to reduce exacerbations and improve outcomes in COPD patients with severe to moderate disease, we a mainly focus on patients with eosinophilic inflammation.

Method

This study was conducted according to The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. We searched electronic databases (PubMed, Scopus, and Google scholar) for randomized controlled trials about the biological treatment of COPD, conducted in the period from 2014 to 2024.

We include randomized controlled trials (RCTs) of adult patients aged ≥40 years, diagnosed with COPD based on GOLD criteria or similar diagnostic standards, includes sever to moderate COPD (GOLD stage II–IV), both male and female participants. Treatment with a biologic agent targeting: Interleukin-5 (Mepolizumab, Benralizumab), Interleukin-4/13 (Dupilumab), Interleukin-1 receptor (MEDI8968), and thymic stromal lymphopoietin (Tezepelumab). We exclude observational studies, case reports, or reviews, studies focusing on asthma without COPD, studies not reporting clinical outcomes of interest, conference abstracts without full-text publication, and studies with intervention duration <6 months.

Two independent authors conducted the literature search, screen titles and abstracts, and assess full-text articles for eligibility (Fig 1). Data extraction was performed independently by two authors using a standardized form. Discrepancies at any stage was resolved through discussion or by consulting a third author. One additional author assist in resolving conflicts, verifying extracted data, and check methodological accuracy.

Risk of bias assessment was performed using Cochrane Risk of Bias (RoB 2) Tool (Table 1). The tool assess the quality according to randomization bias, deviations from intended interventions, missing data bias, measurement bias, and selection of reported results. Three studies had high quality, 4 studies had moderate quality and one study with low quality.

Table 1: risk of bias assessment according to Cochrane Risk of Bias (RoB 2) Tool

Study	Randomization Bias	Deviations from Intended Interventions	Missing Data Bias	Measurement Bias	Selection of Reported Results	Overall Risk of Bias
Criner et al. (2019) (8)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Moderate Quality
Pavord et al. (2017) (9)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Quality
Singh et al. (2024)	Some Concerns	High Risk	Low Risk	Some Concerns	High Risk	Low Quality
Bhatt et al. (2024)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Quality
Calverley et al. (2017)	Low Risk	Some Concerns	Low Risk	Low Risk	Some Concerns	Moderate Quality
Bhatt et al. (2023)	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	High Quality
Brightling et al. (2014)	Some Concerns	Some Concerns	Low Risk	Some Concerns	Some Concerns	Moderate Quality

Results

We included 7 randomized controlled trials (RCTs) in this systematic review examined the efficacy of different biologic therapies for inflammation in patients with chronic obstructive pulmonary disease (COPD), and eosinophilic inflammation. Criner et al. (8) examined Benralizumab in two large Phase III trials (GALATHEA and TERRANOVA) over 56 weeks. They include 3,842 patients with severe to moderate COPD and a history of exacerbations. Despite the biologic targeting IL-5 receptor α, no significant decrease in exacerbation rates was observed in comparison to the placebo group. Lung function and quality of life improvements were also not clinically significant. Mepolizumab studied by Pavord et al. (9) which is anti-IL-5 monoclonal antibody, in the METREX and METREO trials. They include 1,510 patients, who received treatment for 52 weeks. Mepolizumab reduced exacerbation rates significantly in patients with eosinophilic phenotype (blood eosinophils ≥150 cells/μL). In COPD population without eosinophilic phenotype, no significant benefit was seen.

Singh et al. (10) conducted the COURSE trial to examine Tezepelumab, a TSLP inhibitor, in 333 patients during 52 weeks. They found no significant reduction in exacerbation rates when compared to placebo. The study discussed outcomes based on baseline blood eosinophil counts but they did not find a clear subgroup with greater responsiveness. Bhatt et al. (2024) (11) collected data from the BOREAS and NOTUS trials, evaluating IL-4/IL-13 inhibitor (Dupilumab), in 1,874 patients with COPD and type 2 inflammation. The treatment result in a significant decrease in exacerbation rates (30% reduction) in compareson to placebo. Lung function improved (FEV1 increase of 160 mL), and patients reported better quality of life.

Brightling et al. (12) examined Benralizumab in 101 patients with COPD and sputum eosinophilia. The drug effectively reducing blood and sputum eosinophils, but there is no significant exacerbations reduction. Improvements in FEV1 were noted in patients with higher eosinophil counts. Calverley et

al. (13) studied IL-1 receptor inhibitor (MEDI8968) in 324 patients with severe to moderate COPD. There was no significant improvements in exacerbation rates, lung function, or quality of life during the 56 weeks study period. Bhatt et al. (2023) (14) additionally tested Dupilumab in 939 patients with elevated blood eosinophil counts. The study confirmed Dupilumab efficacy, with fewer exacerbations, improved lung function, and enhanced quality of life. Characteristics and main findings of the included studies presented in (Table 2). Study aim, population characteristics and methodology presented in (Table 3).

Table 2: characteristics of the included studies

Study	Study Design	Study Duration	Sample Size	Demographic Characteristics	Treatment Modality	Main Findings
Criner et al. (2019)	Randomized controlled trial	56 weeks	GALATHEA: 1,607; TERRANOVA: 2,235	Severe to moderate COPD patients with eosinophilic inflammation	Benralizumab (30 or 100 mg) vs. placebo	Benralizumab did not significantly reduce exacerbation rates in COPD
Pavord et al. (2017)	Randomized controlled trial	52 weeks	METREX: 836; METREO: 674	Patients with COPD and eosinophilic phenotype	Mepolizumab (100 mg or 300 mg) vs. placebo	Reduction in exacerbation rates in eosinophilic COPD but not in general COPD population
Singh et al. (2024)	Randomized controlled trial	52 weeks	333	Severe to moderate COPD patients	Tezepelumab (420 mg) vs. placebo	No significant reduction in COPD exacerbations
Bhatt et al. (2024)	Randomized controlled trial	52 weeks	1,874	COPD with type 2 inflammation (eosinophilic COPD)	Dupilumab (300 mg) vs. placebo	Significant reduction in exacerbation rate and improved lung function
Calverley et al. (2017)	Randomized controlled trial	56 weeks	324	Moderate-to-very severe COPD patients	MEDI8968 (anti-IL-1 receptor 1) vs. placebo	No significant improvements in exacerbation rates, lung function, or quality of life
Bhatt et al. (2023)	Randomized controlled trial	52 weeks	939	Patients with COPD and elevated blood eosinophil counts	Dupilumab (300 mg) vs. placebo	Fewer exacerbations, improved lung function, better quality of life
Brightling et al. (2014)	Randomized controlled trial	56 weeks	101	COPD patients with eosinophilia	Benralizumab vs. placebo	No significant exacerbations reduction, but some improvement in FEV1

Table 3: study aim and population characteristics of the included studies

Study	Study Aim	Population Characteristics	Methodology
Criner et al. (2019)	To evaluate the efficacy and safety of Benralizumab in COPD patients with eosinophilic inflammation	Severe to moderate COPD patients with eosinophilic inflammation	Randomized, double-blind, placebo-controlled trial over 56 weeks (GALATHEA & TERRANOVA)
Pavord et al. (2017)	To assess the impact of Mepolizumab in reducing exacerbations in eosinophilic COPD	Patients with COPD and eosinophilic phenotype	Randomized, placebo-controlled trial over 52 weeks (METREX & METREO)
Singh et al. (2024)	To evaluate the efficacy of Tezepelumab in reducing COPD exacerbations	Severe to moderate COPD patients	Randomized, placebo-controlled trial over 52 weeks (COURSE)
Bhatt et al. (2024)	To assess Dupilumabs effect on COPD with type 2 inflammation	COPD patients with type 2 inflammation (eosinophilic COPD)	Randomized, placebo-controlled trial over 52 weeks (BOREAS & NOTUS)
Calverley et al. (2017)	To evaluate the role of IL-1 receptor inhibition in COPD management	Moderate-to-very severe COPD patients	Randomized, placebo-controlled trial over 56 weeks
Bhatt et al. (2023)	To determine the effects of Dupilumab on COPD with elevated blood eosinophil counts	Patients with COPD and elevated blood eosinophil counts	Randomized, placebo-controlled trial over 52 weeks (BOREAS)
Brightling et al. (2014)	To analyze Benralizumabs impact on COPD exacerbations and lung function	COPD patients with eosinophilia	Randomized, placebo-controlled trial over 56 weeks

Discussion

The therapeutic methods of COPD has developed recently with the biologic agents, specially, those targeting eosinophilic inflammation and type 2 immune pathways. This systematic review aimed to analyze the findings from 7 RCTs, discussed the clinical outcomes and barriers of biologic treatment in COPD. Among the biologics studied, dupilumab show consistent and clinically significant benefits. Bhatt et al. studies (11,14) examined dupilumab in patients with severe to moderate COPD and eosinophilic inflammation (eosinophils ≥300 cells/μL). dupilumab reduced the annualized rate of severe to moderate exacerbations and improved lung function (FEV_1) and quality of life, which support its role in targeting the IL-4/IL-13 pathway. These findings consistent with Hu et al. (2025) study (15), whcih confirm dupilumab's benefits over other biologics in reducing exacerbations, especially in eosinophilic subpopulations (rate ratio 0.70, 95% CI 0.58–0.84).

Anti-IL-5 receptor monoclonal antibody (benralizumab) had mixed outcomes. Criner et al. (2019) (8) found no significant decrease in exacerbation rates or improvements in lung function. These outcomes supported by Brightling et al. (2014) (16), which failed to demonstrate a clinical benefit. Calverley et al. (2017) (13) also found no efficacy in IL-1 receptor blockade, which highlight the mismatch between biomarker modulation and clinical outcomes in COPD.

Mepolizumab, targeting IL-5, show intermediate results. Mepolizumab reduce exacerbations in patients with elevated eosinophil counts (≥150 cells/μL) but not effective in the general COPD population (9). This suggests a key role for patient stratification based on inflammatory biomarkers. Similarly, Kersul et al. emphasized that efficacy in biologic therapy is closely related to the identification of treatable traits, with patients with eosinophilia (17).

Anti-TSLP monoclonal antibody (tezepelumab), had no significant improvements in exacerbation rates or lung function. Also it target an upstream cytokine involved in epithelial inflammation, tezepelumab failed to deliver measurable clinical benefits, due to the complex and heterogeneous nature of COPD pathophysiology (10). Suresh et al. (2007), study show that IL-13 increases nitric oxide production through inducible nitric oxide synthase (iNOS) in airway epithelial cells. This support the relevance of IL-13 as a therapeutic target and helps explain the effectiveness of dupilumab

in COPD patients with T2 inflammation (18). IL-13's had a potential role in airway remodeling and inflammation, with a strong rationale for targeting the IL-4/IL-13 axis in T2-high COPD phenotypes (16).
There is a lack of long-term efficacy data and real-world application of biologics in COPD. Also there is a significant economic effect and a need for more precise phenotyping tools, such as blood biomarkers, exhaled nitric oxide, and genetic profiling, to improve patient selection and outcomes (15,19).

Limitations
Our study had some limitations, the included trials vary in patient characteristics, baseline eosinophil counts, smoking history, and COPD severity. This heterogeneity limits the generalizability of pooled findings. The studies assess different biologics (benralizumab, mepolizumab, dupilumab, tezepelumab, MEDI8968), each targeting different inflammatory pathways, which result in clinical and mechanistic variability, making comparison through meta-analysis difficult. The studies had some variations in the definition and measurement of exacerbations, lung function improvement and quality of life outcomes. Based on the Cochrane RoB 2 assessment, some studies had high risk of bias in intervention adherence and reporting. The included trials have a duration of around 52–56 weeks, which limits understanding of the long-term efficacy and safety of biologic therapies in COPD.

Conclusion
Our review supports a selective benefit of biologics mainly, dupilumab in COPD patients with T2 inflammation and eosinophilia. Other biologics such as mepolizumab offer modest benefits, while benralizumab and tezepelumab have yet to show consistent efficacy in this setting. The findings underscore the importance of precision medicine and the need for further RCTs to find the long-term effectiveness, safety, and cost-efficiency of biologic therapies in COPD patients.

Conflict of interest
None

Ethical approval
Not applicable

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PRISMA consort chart of selected studies