Pulm Ther (2025) 11:177–193
https://doi.org/10.1007/s41030-025-00291-5

REVIEW

Monoclonal Antibodies for the Treatment of Chronic Obstructive Pulmonary Disease

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Received: December 27, 2024 / Accepted: February 26, 2025 / Published online: March 23, 2025

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a common and complex disease characterized by persistent airflow limitation and the presence of exacerbations, resulting in significant morbidity and mortality. Although the pathogenesis of COPD is multifactorial, airway inflammation plays a significant role in disease progression. Despite the advantages of non-pharmaceutical and pharmaceutical interventions that have significantly improved the symptom burden and exacerbation frequency in COPD, there is a lack of disease-modifying therapies that target the underlying disease mechanisms. Monoclonal antibodies (mAbs), a drug class that has improved treatment in severe asthma by blocking mediators of the type 2 (Th2) and allergic inflammatory cascades, are currently under investigation for their efficacy in COPD. Our review summarizes the evidence for the use of monoclonal antibodies in COPD and discusses current limitations and promising advances. Although targeting Th1 inflammation has failed to improve COPD outcomes, recent clinical trials have shown beneficial effects of monoclonal antibodies targeting Th2 inflammation, providing evidence for a personalized approach in COPD treatment.

Keywords: COPD; Eosinophils; Biomarkers; Cytokines; Monoclonal antibodies

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Key Summary Points

Several biologic therapies evaluated in different randomized controlled trials (RCTs) in chronic obstructive pulmonary disease (COPD) have failed to demonstrate a significant beneficial effect.

Biologic therapies that act on Th2-mediated inflammation in a subset of patients with eosinophilic COPD may be useful for this specific group of patients.

The exquisite intricacy of COPD, including smoking status, the different exacerbation phenotypes, and the complex nature of disease pathology, may be implicated in suboptimal response to biologic therapies.

In the future, novel and emerging monoclonal antibody therapies should be evaluated in limited and targeted populations of patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a complex disease characterized by persistent airflow limitation and exacerbations, leading to impaired quality of life (QoL), increased morbidity, and mortality [1]. Over the past few decades, significant advances have been made in the pharmaceutical treatment of COPD, mainly with long-acting bronchodilators and inhaled corticosteroids, leading to improved symptoms, reduced exacerbation rates, and increased survival [2]. However, despite advances, current therapies offer an improvement of only 15–25% in exacerbation frequency, highlighting the need for further treatment alternatives [3].

COPD pathogenesis is characterized by the "classic triad" of inflammation, oxidative stress, and protease–antiprotease imbalance, mainly due to exposure to cigarette smoking [4]. However, a further multifactorial nature of COPD pathogenesis has been recognized, since genetic factors, early-life events, and aging (e.g., cell senescence) are found to contribute to disease progression [5]. The main anti-inflammatory agents in stable COPD are inhaled corticosteroids and phosphodiesterase-(PDE)-4 inhibitors. In recent years, novel and promising therapies targeting inflammation through monoclonal antibodies have been tested in COPD, with variable results [6]. Our review aims to summarize the current evidence for the therapeutic effect of monoclonal antibodies in COPD.

METHODOLOGY

We searched MEDLINE for the terms "monoclonal," "antibodies," "cytokines," and "COPD." We evaluated both original research papers and relevant reviews, and the initial set of relevant papers was short-listed to those of interest, based on the opinion and expertise of the authors. Only papers written in English were used. Every effort was made not to omit any significant study in the field, and no time frame was used for the literature search, although we focused mainly on recent advances. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

OVERVIEW OF INFLAMMATION IN COPD

COPD is characterized by the presence of airway and lung parenchymal inflammation, affecting both innate and adaptive immunity and contributing to chronic airway remodeling, small airway disease, and pulmonary emphysema [7]. In addition to stable disease, COPD exacerbations are associated with a further increase in pulmonary inflammation [8]. In contrast, systemic inflammation is also present in COPD and affects systemic manifestations of the disease and the presence of comorbidities [9].

COPD pathogenesis is characterized by the upregulation of a "network" of cytokines that are potential targets for monoclonal antibodies [10]. Upon epithelial injury due to cigarette smoking and other injurious factors, innate

immunity is activated by infiltration of the macrophages and neutrophils and activation of the inflammasomes, including interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-8 [10] expression. Subsequently, the Th1 adaptive immune response is activated, alongside Th17+ cells, with sequestration of T cytotoxic cells [7] and chronic airway inflammation with lymphoid follicle formation in the airway wall [11]. Thus, COPD is "classically" associated with Th1 immunity and neutrophilic inflammation. The expression of alarmins by an "injured" epithelium, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), also plays a significant role in the amplification of airway inflammation in COPD [12]. Nevertheless, eosinophilic/Th2 inflammation is also implicated in COPD pathogenesis. Although the prevalence of eosinophilic COPD depends on the cutoff values used [13], data from the ECLIPSE cohort have shown that ~37.4% of patients with COPD have persistent eosinophilic inflammation, as defined by > 2% of eosinophils in the peripheral blood [14]. Eosinophilic inflammation in COPD is characterized by alterations in innate and adaptive immunity and by upregulation of Th2 cytokines such as IL-4, IL-5, and IL-13 [10]. Recruitment of eosinophils in the airways is mediated by eosinophilic chemoattractants, such as C–C chemokine receptor type 3 (CCR3) chemokines and prostaglandin (PG)-D2, whereas, similarly to asthma, activation of innate lymphoid cells (ILC)-2 cells can also mediate Th2 inflammation in COPD [10]. Interestingly, a group of patients with COPD presented with intermittent eosinophilic inflammation, highlighting the instability of the phenotype and the need for continuous phenotyping and endotyping, a phenomenon also observed in severe asthma [15].

OVERVIEW OF MONOCLONAL ANTIBODY MECHANISMS OF ACTION

Monoclonal antibodies (mAbs) have emerged as an important drug class for the treatment of inflammatory and immunological diseases. With the use of mAbs, specific molecules of interest can be targeted, including cytokines, growth factors, cytokine receptors, clusters of differentiation, and others such as immunoglobulin E (IgE) and complement [16]. Monoclonal antibodies can exert their therapeutic effect through multiple mechanisms, mainly through ligand or receptor blockage, but also through receptor downregulation, depletion of targeted cells, or signaling induction [17]. In respiratory medicine, monoclonal antibodies are utilized for the treatment of various conditions, including lung cancer and infectious diseases [18], and for the treatment of airway diseases, mainly for severe allergic and/or eosinophil asthma [6].

Antibodies Targeting IL5/IL5R

Anti-IL-5/5R mAbs are currently the most commonly used biologics in severe asthma, depending on the phenotype of each patient. Blood eosinophils are one of the most predominant biomarkers that guide clinicians in prescribing an anti-IL-5 agent. Since COPD shares common pathophysiological features with asthma, the question immediately arises as to whether these biologics have a place in specific COPD phenotypes [10, 19]. Several randomized controlled trials (RCTs) have sought to evaluate their potency in a clinical setting.

Mepolizumab

Two phase 3 parallel double-blind RCTs, METREX and METREO (with the difference between them being that METREX used mepolizumab at a dose of 100 mg whereas METREO used either the 100 mg or the 300 mg dose), recruited over 2000 patients with COPD who had a history of moderate to severe exacerbations under triple therapy and evaluated the efficacy of once-monthly mepolizumab add-on treatment over 52 weeks. The primary endpoint of both trials was the annual exacerbation rate (AER).

The use of 100 mg mepolizumab monthly in the METREX study was associated with a statistically significant (p-value = 0.04) reduction in the AER versus placebo (1.40 versus 1.71) in the modified intention-to-treat population with

an eosinophilic COPD phenotype. On the contrary, the results of the METREO study on the primary endpoint were not statistically significant. However, a trend favoring mepolizumab in the regime of 100 mg per month was also observed [20]. The benefit of mepolizumab was greater in patients with a higher blood eosinophil count (BEC). In a meta-analysis of the intention-to-treat population of both trials, it was demonstrated that as the blood eosinophil number increased, patients receiving 100 mg mepolizumab had a lower AER versus placebo, and the margin of this effect was almost linearly proportional to patients' BEC [21]. Similar to the excellent safety profile demonstrated by mepolizumab in asthmatic patients [22], no safety concerns were raised in COPD patients. These two trials demonstrated for the first time that eosinophilic inflammation is an important feature in specific COPD phenotypes, and targeted therapy could benefit patients in establishing disease control and reducing exacerbations [20]. On the other hand, changes in health-related QoL, as assessed by the St George's Respiratory Questionnaire (SGRQ) score and the COPD Assessment Test (CAT), did not differ between the mepolizumab and placebo arms.

In a meta-analysis of these trials, mepolizumab at a dose of 100 mg versus placebo reduced the AER by 23% in patients with more than 300 eosinophils/μL. However, the opposite was also true, since mepolizumab add-on therapy in patients with less than 150 eosinophils/μL exhibited a trend towards higher AER versus placebo treatment [23]. The role of anti-IL-5 treatment in COPD remains unclear, and future studies may need to recruit patients with a higher number of blood eosinophils, even if the recruitment process will be far more challenging.

Benralizumab

The first randomized trial that studied the impact of anti-IL-5R in COPD was conducted in 2014 by Brightling et al. [24], who recruited 101 patients and randomly assigned them to either placebo or benralizumab treatment in a 1:1 ratio. Among the inclusion criteria, patients were required to have a sputum specimen with at least 3% eosinophils in the past year and at least one acute exacerbation during the same time period. The AER, lung function, and QoL endpoints were unmet in the total population recruited. However, the subgroup analysis of patients with a higher BEC (at least 200/μL) demonstrated a trend favoring benralizumab treatment, although the results were not statistically significant [24].

Two phase 3 parallel, double-blind RCTs sought to evaluate the effectiveness of benralizumab in patients with COPD with frequent exacerbations under guideline-based inhaled treatment. Patients were recruited in a 2:1 ratio based on their BEC, with the threshold being 220 eosinophils/μL for each group. The first study ran under the name GALATHEA and used either the 30 mg or the 100 mg dosing regimen of benralizumab. The second study, which ran under the name TERRANOVA, also used a dose of 10 mg in addition to the two doses mentioned above. Patients in both trials received the first three doses monthly, followed by a dosing scheme every 8 weeks, and the follow-up period was 56 weeks. The primary endpoint was the AER reduction in patients with > 220 eosinophils per cubic millimeter [25].

In the GALATHEA study, only the 100 mg benralizumab dose produced a non-statistically significant sign of superiority versus placebo in reducing the AER, while the 30 mg benralizumab group demonstrated an almost identical AER to the placebo group. In the TERRANOVA study, the 10 mg benralizumab group exhibited the lowest AER among the three treatment groups and the placebo group; however, no treatment arm managed to achieve statistically significant results [25].

A possible explanation for the negative results of these trials is that patients, unlike the twin studies for mepolizumab, could be enrolled even under dual inhaled therapy; therefore, up to 9% of patients in these studies were not under inhaled glucocorticoids. Moreover, the concomitant presence of asthma was under 10% in the benralizumab studies, whereas its prevalence in the twin mepolizumab studies was less well characterized and possibly higher. Nonetheless, benralizumab did not demonstrate a statistically significant reduction of the AER in patients with COPD

despite the eosinophilic phenotype of their disease [20, 25].

Benralizumab has also been tested as a treatment option in eosinophilic exacerbations (> 300 eosinophils/μL) of asthma or COPD. Interestingly, patients receiving benralizumab had a lower percentage of treatment failure at 90 days than a group receiving prednisolone alone, with no safety concern raised [26]. This study however included mainly patients with asthma (56%), whereas 32% of patients had a diagnosis of COPD and 12% of both.

Meta-Analyses on the Effect of Mepolizumab and Benralizumab in COPD

Two meta-analyses compared the effect of mepolizumab and benralizumab in patients with COPD, deriving data from all the RCTs previously reported. In a systematic Cochrane meta-analysis, mepolizumab at a dose of 100 mg was shown to decrease exacerbations by 19% in patients with more than 150 eosinophils/μL. However, with the inclusion of patients with COPD with less than 150 blood eosinophils/μL, this percentage dropped to 8%. The group with high eosinophil count experienced a longer time until the first exacerbation compared to placebo, with high certainty of evidence. Lung function and QoL were not found to be ameliorated. As for benralizumab, the dose of 100 mg was found to reduce the number of severe exacerbations requiring hospitalization with high certainty of evidence in the group of patients with more than 220 blood eosinophils/μL. The same group of patients also experienced a statistically significant improvement in the SGRQ total score under benralizumab add-on treatment; however, the improvement did not reach clinical significance [27]. Similar results were reported in another recent meta-analysis, including the five RCTs mentioned earlier. It was shown again that patients who benefit the most from anti-IL-5 treatment are those with severe eosinophilic inflammation (in this meta-analysis, the cutoff value was set at 300 eosinophils/μL) [28].

Antibodies Targeting IL4/13R (Dupilumab)

The Th2 cytokines IL-4 and IL-13 are central drivers of Th2 inflammation in asthma and other Th2 airway inflammatory diseases, such as chronic rhinosinusitis with nasal polyps and allergic rhinitis, displaying overlapping and distinct roles in their pathophysiology and clinical manifestations [29]. IL-4 and IL-13 are closely linked, as they both activate the Th2 receptor complex IL-4Rα/IL-13Rα1, expressed in the airway epithelium, smooth muscle cells, eosinophils, and mast cells, responsible for the activation of several distinct and overlapping signaling pathways [30]. IL-4 also binds the type 1 receptor complex, consisting of IL-4Rα and a γ chain, resulting in the upregulation of Th2 responses and eosinophil accumulation and the downregulation of type 1 responses [31].

Both IL-4 and IL-13 are pleiotropic cytokines produced by a large number of effector cells including Th2 cells, activated group 2 ILC2, mast cells, basophils, and CD8+ and B cells [32]. IL-4 primarily upregulates B-cell class switching and increased IgE synthesis by plasma cells [33]; however, it also promotes T helper (Th)2 differentiation from naïve helper T cells (Th0), driving the generation of other pro-allergic cytokines and chemokines such as IL-5, IL-9, IL-13, and eotaxins [34]. In addition, IL-4 can direct eosinophil chemotaxis to inflammatory loci through the increased expression of eotaxin and vascular cell adhesion molecule 1; at the same time, it also increases the survival of eosinophils in tissues by inhibition of their apoptosis [35]. Similarly, IL-13 is believed to be a central regulator of IgE synthesis, triggering airway hyperresponsiveness [36]. In contrast, IL-13 induces goblet cell hyperplasia and mucus production, airway smooth muscle cell hyperplasia, proliferation and contractility, fibroblast activation, and collagen deposition [37]. Moreover, IL-13 is also involved in the epithelial barrier damage and airway obstruction associated with the development of mucus plugs [38] and in the upregulation of nitric oxide production from airway epithelial cells [39].

Dupilumab is a fully human recombinant IgG4 antibody directed against the

alpha-subunit of the IL-4 receptor, capable of inhibiting the signaling of both IL-4 and IL-13 and emerging as one of the most successful therapies targeting the IL-4/IL-13 axis [40]. Dupilumab has been shown to decrease the levels of Th2 biomarkers, such as exhaled nitric oxide (FeNO) and serum IgE, although blood eosinophil levels seem to remain unchanged or even increase [41]. Dupilumab indications are increasingly expanded and include skin diseases such as allergic contact dermatitis and spontaneous chronic urticaria, eosinophilic gastrointestinal disorders, particularly eosinophilic esophagitis, and food allergy, as well as respiratory diseases such as allergic rhinitis with or without nasal polyposis, allergic bronchopulmonary aspergillosis, and chronic eosinophilic pneumonia [42]. In addition, dupilumab was approved in 2018 as an add-on maintenance treatment for patients with severe uncontrolled asthma characterized by baseline blood eosinophils > 150 cells/mm^3 and FeNO levels higher than 25 ppb [43].

As eosinophils are a significant source of IL-4 and IL-13, neutralization of the IL-4/IL-13 axis in the recognized population of patients with COPD with evidence of Th2 high inflammation seems an obvious target, with potential benefits in airway obstruction, mucus production, and eosinophil-mediated inflammation [44]. However, the role of the IL4/IL-13 axis in COPD needs to be better described. In an in vitro model, Doyle et al. [45] demonstrated in a transgenic mouse model that eosinophil-derived IL-13 plays a role in alveolar destruction and development of emphysema by promoting the production of matrix metalloprotease (MMP)-12 from alveolar macrophages. At the same time, in sputum samples from patients with eosinophilic COPD, increased MMP-12 levels were predictive of emphysema and were positively associated with pulmonary eosinophilia while correlating negatively with FEV_1 [45]. Similarly, in an animal model of mice with pathology resembling asthma and COPD, viral infection activated CD4 natural killer T cells to persistently recruit and activate macrophages to produce IL-13, driving inflammation, mucus production, and airway hyperresponsiveness even after the complete clearance of the virus, thus contributing to the chronicity of disease [46]. In addition, BAL lymphocytes from patients with COPD were found to have higher percentages of IL-4 + CD4, IL-4 + CD8, and IL-13 + CD8 T cells compared to non-COPD smokers or healthy controls, tending to present a Th2 pattern of intracellular cytokine expression that was inversely related to the degree of airflow obstruction [47].

The recently published phase-3, double-blind, randomized BOREAS study [48] evaluated the efficacy, safety, and tolerability of dupilumab as an add-on treatment in patients with moderate to severe COPD and evidence of Th2 inflammation (absolute BEC of at least 300 cells/μL at screening visit), that had an elevated exacerbation risk despite triple therapy. In this study, patients who received dupilumab presented a reduced exacerbation rate, compared to those that received a placebo, with no significant safety concerns. Interestingly, dupilumab significantly reduced FeNO levels compared to placebo, suggesting a favorable biologic effect. Similar results emerged from the NOTUS study [49], a phase 3, double-blind randomized trial in which 935 patients with COPD with BEC of ≥ 300 cells/mL were randomized to receive subcutaneous administration of dupilumab (300 mg) or placebo every 2 weeks for 1 year. Dupilumab was associated with fewer exacerbations compared to placebo. However, regarding other endpoints, including lung function and patient-reported outcomes (QoL, as assessed by the SGRQ score), the effect of dupilumab was inconclusive. Improvement in FEV_1 was below the minimal clinically important difference in both the BOREAS and the NOTUS trial, whereas a signal, albeit modest and below clinical importance, for improved QoL in the BOREAS trial was not reproduced in the NOTUS trial.

Monoclonal Antibodies Against IL-17

IL-17 is a cytokine produced mainly by Th17 cells, a subset of T cells implicated in the induction of neutrophilic inflammation and airway remodeling in stable COPD [50]. Although in vivo experimental studies have shown a beneficial effect of blocking the IL-17 pathway in animal models of COPD [51], clinical evidence

is sparse and unsupportive. Eich et al. performed a phase 2 study with CNTO-6785, an anti-IL17 mAb, in patients with moderate to severe COPD either with ≥ 2 exacerbations in the last 2 years or with sputum production. The study failed to show a significant change in the primary outcome, which was a change in percent-predicted FEV_1 from baseline [52]. The results of IL-17 blockage are further confounded by the described antimicrobial function of IL-17, which may result in conflicting results in COPD exacerbations and an immunosuppressive effect of anti-IL-17 treatment [53].

Anti-TNF-α

TNF-α, formerly known as cachectin because of its capacity to cause tissue depletion (cachexia), is a cytokine that is typically described as having a primary proinflammatory role in endotoxin-induced septic shock as well as in a number of chronic inflammatory diseases, including rheumatoid arthritis, psoriasis, Crohn's disease, asthma, COPD, and acute lung injury [54]. In COPD, TNF-α plays a major role in the development of lung inflammation, with its primary function being the maintenance of neutrophilic inflammation both locally in the airways and lung parenchyma and systemically through "inflammatory" weight loss [55]. Patients with COPD with weight loss have shown markedly greater levels of circulating TNF-α than patients with COPD with stable weight or whose age and gender were the same as healthy volunteers [56]. Since circulating TNF-α levels were found to be negatively correlated with oxygen saturation and to increase with the degree of dyspnea, TNF-α may also be a factor in the progression and impairment of COPD [57, 58]. Finally, in a recent systematic review and meta-analysis, TNF-α levels were found to be higher in patients with COPD than in healthy controls, suggesting a relationship between TNF-α level and COPD [59]. Etanercept and infliximab are two anti-TNF antibodies available on the market that have been used in clinical trials for treating COPD [60].

In June 2005, the first study assessing the effect of the anti-TNF-α drug infliximab in patients with COPD was published [61]. It was an exploratory single-center, double-blind, placebo-controlled, randomized, phase 2 trial including 22 current smokers with mild to moderate COPD, with the percentage of sputum neutrophils being the primary endpoint. Infliximab did not show a positive short-term effect on airway inflammation, lung function, resting energy expenditure, or QoL in this short-term trial, and no significant safety issues were observed. In a nested case–control observational analysis of individuals with COPD who received anti-TNF-α biologic therapy for rheumatoid arthritis, anti-TNF-α decreased the number of COPD hospitalizations (adjusted rate ratio, 0.62) [62]. This reduction was more prominent in patients treated with etanercept than infliximab (rate ratio, 0.49 and 0.95, respectively). However, it was questionable whether all the patients had available lung function test results and a COPD diagnosis confirmed by a physician, since all study participants were chosen from an insurance claim database.

On the contrary, a double-blind, randomized controlled trial found that etanercept had no benefit for the treatment of acute exacerbations of COPD (AECOPDs), although patients receiving etanercept and with baseline eosinophil counts under 2% responded more favorably than those receiving prednisone [63]. In 2007, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-finding study including patients with moderate to severe COPD receiving infliximab ($n = 157$) or placebo ($n = 77$) evaluated the efficacy, health status, and safety of infliximab for a period of 44 weeks [64]. Similar findings in all treatment arms showed no changes in exacerbation frequency, symptoms, health-related QoL, or lung function. Notably, more adverse events, such as pneumonia (10 versus 1) and cancer incidence (12 versus 3), were observed in individuals in the infliximab group. In 2012, the multicenter observational Remicade Safety Under Long-Term Study in COPD (RESULTS COPD) was published. This trial collected malignancy and mortality data every 6 months for 5 years from patients who had received one study agent dose in the previous phase 2 study [65]. The prolonged patient follow-up after therapy termination showed no

evidence of increased malignancy risk during the study period. In an additional two-center, randomized, double-blind, placebo-controlled study evaluating the effects of infliximab in 16 patients with moderate to severe COPD suffering from cachexia compared to 25 control subjects, infliximab did not cause an observable reduction in local inflammation in this particular population of patients with COPD and had minor effects on systemic inflammation [66]. Specifically, exhaled breath condensate (EBC) levels of inflammatory markers were unchanged in patients receiving infliximab, and systemic levels of acute-phase proteins (C-reactive protein, fibrinogen, and lipopolysaccharide-binding protein), IL-6, and soluble TNF receptor (sTNFR) showed no change during the study period.

The question is why TNF-α inhibitors seem to be ineffective in COPD. One possible explanation is that COPD is a heterogeneous disease with characteristics that occur with different phenotypes. However, it remains poorly characterized, and little is known about the underlying pathobiology contributing to it. Another reason could be that proinflammatory cytokines other than TNF-α drive the inflammatory process in this entity [67]. According to preclinical studies, TNF-α inhibitors have the potential to reverse corticosteroid insensitivity by restoring corticosteroids' broad attenuating effects on inflammation and airway remodeling, as well as through their synergistic effects with corticosteroids in regulating airway remodeling [68, 69]. Therefore, TNF-α treatment should not be abandoned, but there is a need for further exploration, probably in a more carefully selected population of patients with COPD.

Anti-IL-1, Anti-IL-8, and Anti-IL-6

IL-1 is a proinflammatory cytokine produced by numerous cell types, including monocytes, macrophages, and fibroblasts, affecting a variety of cells and organs [70, 71]. Its primary mechanism of action is stimulation of the activity of innate immune system cells, including eosinophils, mast cells, neutrophils, and basophils, thus promoting both systemic and local inflammation. IL1A and IL1B, two related but different IL-1 genes, encode IL-1α and IL-1β. The IL-1 receptor type 1 (IL-1RI), a cell surface receptor found on almost all cells, is the binding site for all IL-1s. When IL-1 binds to its receptor, a series of inflammatory mediators, chemokines, and other cytokines are released [70]. Thus, it was speculated that specific pharmacological blockade of IL-1 activity in inflammatory diseases such as COPD might be beneficial.

In a phase II randomized controlled trial, 324 patients with a history of frequent COPD exacerbations received a new anti-IL-1R1 human monoclonal antibody (MEDI8968), which blocks the activation of both IL-1α and IL-1β [72]. All study participants were randomized 1:1 to receive placebo or MEDI8968 300 mg (600 mg intravenous loading dose) subcutaneously once monthly for 52 weeks. Unfortunately, this specific biologic did not achieve a statistically significant improvement in the primary outcome, which was the frequency of moderate or severe exacerbations. The same was seen in the secondary outcomes, showing no improvement in lung function or health status in patients with COPD. A further post hoc analysis of patient subgroups (based on neutrophils) did not change the study outcome. No differences in adverse events were observed between the study groups.

Canakinumab, an anti-IL-1β monoclonal antibody, has recently been studied in inflammatory diseases like COPD [73]. It binds to human IL-1β with great specificity and neutralizes its signaling, suppressing inflammation in individuals with autoimmune disorders. Another randomized, double-blind, placebo-controlled exploratory study assessed the safety and efficacy of multiple doses of canakinumab in 147 patients with COPD with moderate to very severe disease [74]. At the end of the study, no statistical analysis was offered; however, reported changes in lung function were quite comparable between the two treatment arms. There are currently no other active studies evaluating the possible therapeutic role of anti-IL-1 therapy in patients with COPD.

IL-8 is a proinflammatory chemokine with a central role in neutrophil chemotaxis which has been found to be increased in the airways of patients with stable COPD and during exacerbations [75]. The therapeutic potential of an

Table 1 Monoclonal antibodies in the treatment of COPD

Monoclonal antibody	Target	Study design	Patient characteristics	Main outcome	Ref
Itepekimab	IL-33	Phase 2a multicenter, randomized, double-blind, placebo-controlled trial (343 patients)	Current or former smokers, symptomatic (CAT ≥ 10), FEV_1 30–70%, ≥ 2 moderate or 1 severe exacerbation within previous 1 year	No effect on exacerbation rate in the overall population. Reduced exacerbations in former smokers	[79]
Astegolimab	ST-2 (IL-33 receptor)	Phase 2a single-center, randomized, double-blind, placebo-controlled trial (81 patients)	Current or former smokers, exertional dyspnea (mMRC ≥ 2), FEV_1 < 70%, ≥ 2 exacerbations within previous 1 year	No effect on exacerbation rate, improvement in QoL	[80]
Tezepelumab	TSLP	Phase 2a multicenter, randomized, double-blind, placebo-controlled trial (337 patients)	Current or former smokers, FEV_1 20–80%, ≥ 2 moderate or severe exacerbations within previous 1 year, on triple therapy	No effect on exacerbation rate	[81]
Mepolizumab	IL-5	Two phase 3 multicenter, randomized, placebo-controlled, double-blind, parallel-group trials (METREX 837 patients, METREO 675 patients)	FEV_1 20–80%, ≥ 2 moderate or 1 severe exacerbation within previous 1 year, on inhaled glucocorticoid–based therapy	Exacerbation reduction, no effect on lung function or QoL	[20]
Benralizumab	IL5R	Two phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials (GALATHEA 1120 patients, TERRANOVA 1545 patients)	Current or former smokers, mMRC ≥ 1 at screening, > 220 eosinophils/μL, FEV_1 20–65%, ≥ 2 moderate exacerbations within previous 1 year, under dual or triple therapy	No reduction in exacerbations	[25]
CNTO-6785	IL-17	Phase 2 multicenter, randomized, placebo-controlled, double-blind, parallel-group trial (187 patients)	FEV_1 40–80%, chronic bronchitis, ≥ 2 exacerbations within previous 2 years or able to produce sputum during screening	No change in pre- bronchodilator percent-predicted FEV_1	[52]

Table 1 continued

Monoclonal antibody	Target	Study design	Patient characteristics	Main outcome	Ref
Dupilumab	IL-4/IL-13 receptor	Phase 3 multicenter, double-blind, randomized, placebo-controlled trial (939 patients)	Current or former smokers, MRC ≥ 2, chronic bronchitis, BEC > 300/μL, FEV_1 30–70%, with ≥ 2 moderate or 1 severe exacerbation within previous 1 year, under triple therapy	Reduced exacerbation rate, improvement in lung function and QoL below clinically important difference	[48]
Dupilumab	IL-4/IL-13 receptor	Phase 3 multicenter, double-blind, randomized, placebo-controlled trial (935 patients)	Current or former smokers, MRC ≥ 2, chronic bronchitis, BEC > 300/μL, FEV_1 30–70%, with ≥ 2 moderate or 1 severe exacerbation within previous 1 year, under triple therapy	Reduced exacerbation rates, improvement in lung function below clinically important difference	[49]

Summary of the main studies on the efficacy of monoclonal antibodies in patients with COPD. The "target pathway," study design and population, and its main findings are presented for each study. *BEC* blood eosinophil count, *CAT* COPD Assessment Test, *FEV_1* forced expiratory volume at the first second, *mMRC* modified Medical Research Council Dyspnea Scale, *QoL* quality of life, *COPD* chronic obstructive pulmonary disease

anti-IL-8 monoclonal antibody (ABX-IL-8) in symptomatic patients with COPD was investigated in a small 3-month phase 2 study, showing an improvement in dyspnea, as assessed by the transition dyspnea index score (increase > 1 point), with no difference in other outcomes [76]. Finally, although IL-6 is a proinflammatory cytokine also implicated in systemic inflammation in COPD [77], and neutralizing antibodies against IL-6 are commercially available, no study to our knowledge has evaluated the efficacy of blocking IL-6 in COPD.

Monoclonal Antibodies Against Alarmins (IL-33 and TSLP Pathways)

Both IL-33 and TSLP are "alarmins" expressed by the pulmonary epithelial cells upon injurious stimuli, such as viruses, oxidative stress, and pollutants [10]. Both alarmins contribute to innate and adaptive immunity and have been associated with Th2 inflammation through their effects on immune cells, such as dendritic cells and ILC2 cells [78]. Emerging data have also implicated alarmins in non-Th2 inflammation. For example, active cigarette smoking shifts the IL-33 pathway toward a Th1 response [78]. Rabe et al. reported that itepekimab, a mAb that targets IL-33, had no significant effect on the exacerbation rate in patients with COPD with at least two moderate or at least one severe exacerbation within 1 year before screening [79]. Interestingly, a reduced exacerbation rate and improved lung function were observed in subgroup analysis for former smokers, in contrast to active smokers. Similarly, astegolimab, an anti-ST2 (receptor of IL-33) antibody, failed to reduce the exacerbation rate in patients with moderate to very severe COPD and a history of frequent exacerbations, compared to placebo; however, it resulted in improved QoL, as assessed by the SGRQ, although below the cutoff for a clinically important difference [80]. Recently, the phase II COURSE trial also failed to show an improvement in the annualized rate of moderate or severe COPD exacerbations in patients receiving tezepelumab (an anti-TSLP monoclonal antibody), compared to placebo [81].

Inhaled Monoclonal Antibodies

A promising aspect of monoclonal antibody treatment for COPD is their administration through the inhaled route [82]. Direct intrapulmonary delivery offers significant advantages over systemic administration, such as the specific targeting of the airway epithelium, with smaller doses and fewer adverse effects [83]. Currently, evidence in obstructive airway diseases is minimal, possibly due to the technical challenges associated with the development of inhaled monoclonal antibodies, such as the size and stability of the protein complex [84]. Moreover, the safety of inhaled monoclonal antibody delivery must be further explored [85].

CONCLUSION

As the chronic inflammatory response that characterizes COPD is complex and heterogeneous, there is an unmet need for effective targeted anti-inflammatory medications for the treatment of patients, with monoclonal antibodies against cytokines and chemokines or their receptors standing as a potential approach in this direction. As summarized in Table 1, the various biologic therapies evaluated in different RCTs for COPD failed to demonstrate a significant beneficial effect, except those that act on Th2-mediated inflammation in a subset of patients with eosinophilic COPD.

The reasons for this poor response to biologics in COPD remain unclear. This uncertainty may reflect the exquisite intricacy of COPD, in which no single cytokine or chemokine has a dominant role. Moreover, the impact of smoking, the different exacerbation phenotypes regarding the need for treatment with either oral corticosteroids or antibiotics or both, and the complex nature of disease pathology, which may affect both the airways and the parenchyma, including irreversible remodeling i.e. emphysema and chronic bronchitis, may also be implicated in suboptimal response to biologic therapies. Furthermore, variability in study design, heterogeneity in inclusion criteria (symptoms, smoking

history, exacerbation history, baseline maintenance therapy, lung function impairment staging, inflammatory sub-phenotypes) may limit the external validity of current evidence of mAbs in COPD. Finally, although current studies do not raise safety concerns on the use of mAbs in patients with COPD, the economic burden of such therapies in the national health systems worldwide must be further studied. Therefore, in the future, novel and emerging monoclonal antibody therapies should be evaluated in limited and targeted populations of patients with COPD, based on biomarkers that may enable a better precision medicine approach.

Author Contributions. Software, validation, analysis, and formal analysis: Dimitrios Toumpanakis, Konstantinos Bartziokas, Agamemnon Bakakos, Evangelia Fouka, Petros Bakakos, Stelios Loukides, Paschalis Steiropoulos and Andriana I Papaioannou. Investigation, resources and data curation: Dimitrios Toumpanakis, Konstantinos Bartziokas and Agamemnon Bakakos. Writing—original draft: Dimitrios Toumpanakis, Konstantinos Bartziokas, Agamemnon Bakakos and Evangelia Fouka. Visualization and supervision: Petros Bakakos, Stelios Loukides and Andriana I Papaioannou. Project administration: Dimitrios Toumpanakis and Andriana I. Papaioannou. All authors read and approved the final manuscript.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data Availability. All data used are available in the references provided.

Declarations

Conflict of Interest. Paschalis Steiropoulos is an Editorial Board member of Pulmonary Therapy. Paschalis Steiropoulos was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Dimitrios Toumpanakis, Konstantinos Bartziokas, Agamemnon Bakakos, Evangelia Fouka, Petros Bakakos, Stelios Loukides and Andriana I Papaioannou have no conflict of interest to disclose.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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