

T2 Biologics for Chronic Obstructive Pulmonary Disease



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Learning objectives:

1. To describe the pathophysiology of chronic obstructive pulmonary disease (COPD).
2. To describe the role of type 1/2 pathways in the pathogenesis of COPD.
3. To describe the trials of biologics in COPD and explain the potential role of biologics in COPD.

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Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality worldwide. In contrast to other chronic diseases, COPD is increasing in prevalence and is projected to be the third leading cause of death and disability worldwide by 2030. Recent advances in understanding the underlying pathophysiology of COPD has led to the development of novel targeted therapies (biologics and small molecules) that address the underlying pathophysiology of the disease. In severe asthma, biologics targeting type 2 (T2)-mediated immunity have been successful and have changed the treatment paradigm. In contrast, no biologics are currently licensed for the treatment of COPD. Those targeting non-T2 pathways have not demonstrated efficacy and in some cases raised concerns related to safety. With the increasing recognition of the eosinophil and perhaps T2-immunity possibly playing a role in a subgroup of patients with COPD, T2 biologics, specifically anti-IL-5(R), have been tested and demonstrated modest reductions in exacerbation frequency. Potential benefit was related to the baseline blood eosinophil count. These

Abbreviations used

ACOS- Asthma-COPD overlap syndrome
 COPD- Chronic obstructive pulmonary disease
 CXCR2- CXC chemokine receptor 2
 ECLIPSE- Evaluation of COPD Longitudinally to Identify
 Predictive Surrogate End-points
 EGF- Epidermal growth factor
 IL-5R- IL-5 receptor
 T2- Type 2
 TSLP- Thymic stromal lymphopoietin

benefits were small compared with asthma. Thus, whether a subgroup of COPD sufferers might respond to anti-IL-5 or other T2-directed biologics remains to be fully addressed and requires further investigation. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1405-16)

Key words: COPD; ACOS; Biologics; Eosinophil; IL-5; Benralizumab; Mepolizumab; TNF- α ; IL-6; IL-8; IL-1 β ; IL-33; IL-13; IL-17; Anti-IgE antibody; Thymic stromal lymphopoietin (TSLP); Prostaglandin D₂ receptor type 2

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a disease of fixed airflow obstruction driven by airways inflammation and is usually progressive.¹ The etiology of the airways inflammation is triggered through inhalation of noxious external particles, most typically cigarette smoke, though other non-smoking-related causes, such as air pollution and biomass fuel, are being increasingly recognized.²⁻⁴ Although the airflow obstruction is slowly progressive, rapid changes in symptoms and lung function are seen within the natural history of the condition. These rapid inflammatory flare-ups, which are beyond the normal day-to-day variability, are known as exacerbations.

Worldwide, COPD is a major priority and is a common cause of both morbidity and mortality. There are approximately 400 million cases of COPD worldwide,⁵ and it is predicted to become the third leading cause of mortality worldwide by 2030.⁴ The total cost of COPD in the United States is approximately \$50 billion per year.⁶ In the United Kingdom, it is responsible for approximately 30,000 deaths per year and for £1.9 billion per year in direct health care costs.⁷

It is widely accepted that COPD has diverse clinical phenotypes, with a number of different pathophysiologies and various endotypes. This heterogeneity leads to variable responses to therapies.⁸ Current treatment options are primarily aimed at symptomatic relief. This can be in terms of reducing dyspnea, preventing exacerbations, and targeting comorbidities with an overall improvement in quality of life.⁹ However, these are not disease modifying, and have minimal impact on disease progression or mortality. Targeting specific pathophysiological processes in the underlying inflammatory pathways of COPD may lead to more promising therapies. Recently, there have been a number of advances in targeted biologic therapies for specific cytokines or their receptors implicated in airways inflammation in COPD. In this review, we will explore the role of type 1 and

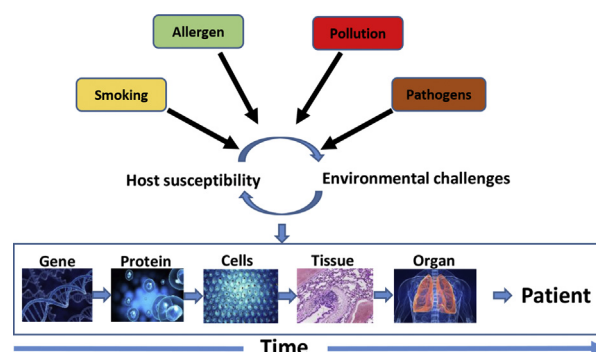


FIGURE 1. COPD is a heterogeneous complex disease as a consequence of complex host-environment interactions across spatial scales within the host over time.

type 2 (T2)-mediated immunity in the underlying airway inflammation and the success and failures of biological therapies to date in COPD.

PATHOPHYSIOLOGY

Patients develop COPD as a consequence of genetic susceptibility for which the persistent airways inflammation is triggered by a complex host-environment interaction over time (Figure 1). Smoking, and other pollutants, pathogens, and allergens insult the lung, promoting airway inflammation and damage in a susceptible host.^{8,10} This in turn leads to irreversible damage, resulting in fixed airflow obstruction and clinical expression of the disease.

Airway inflammation

The presence of ongoing inflammation is the hallmark of the pathophysiological appearances of the airways in COPD, both in the stable state and in the exacerbation state. The airway inflammation correlates with severity of airflow obstruction.¹⁰ Typically, increased CD8⁺ T cells and neutrophils are seen within the airway of patients with COPD.^{11,12} Consistent with the heterogeneity of the disease, 10% to 40% of patients with COPD demonstrate increased eosinophilic inflammation.¹³ Analysis of blood samples from the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study showed that 37% of patients had persistent eosinophilia (defined as $\geq 2\%$), 13.6% had persistently low (defined as $< 2\%$) eosinophil count, and 49% of the subjects had variable eosinophilia over a 3-year follow-up period.¹⁴ In patients with the eosinophilic phenotype, there is an increase in blood eosinophil count during acute exacerbation.¹⁵ This group of patients shows good response to corticosteroid treatment, and titrating corticosteroid therapy according to eosinophil count reduces exacerbation rates.¹⁶ Conversely, withdrawal of inhaled corticosteroid therapy in those with blood eosinophil counts of more than 2% leads to increased frequency of acute exacerbation. The etiology of eosinophilic inflammation in COPD is uncertain. A comparison of the possible cytokine networks and triggers involved in neutrophilic- and eosinophilic-predominant COPD is described in Figure 2.

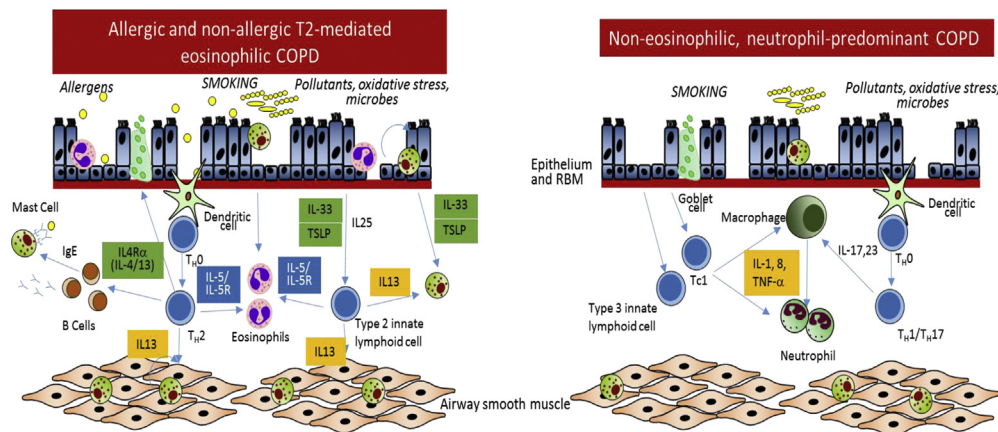


FIGURE 2. Cytokine networks in COPD in those with eosinophilic disease or noneosinophilic predominately neutrophilic disease. Biologics tested in phase 3 are shown in blue boxes (neither met primary outcome), those that are in clinical trials phase 2/3 in green boxes, and those that have been unsuccessful and no longer in development for COPD are in orange boxes. *IL-4Rα*, IL-4 receptor alpha; *RBM*, lamina reticularis and basement membrane. Adapted with permission from Yousuf and Brightling.¹⁷

Airway remodeling

In addition to chronic inflammation changes, airway remodeling is well recognized in COPD. This remodeling is most notably seen in the small airways, with increased smooth muscle associated with a reduced FEV₁.^{18,19} Epidermal growth factor (EGF) receptors are activated by cigarette smoke via tissue damage and increased epithelial permeability.²⁰ Both EGF and EGF receptor expression have been implicated in airways remodeling and are increased in bronchial epithelium in COPD.²¹⁻²⁴ Activation of EGF receptor can lead to mucin synthesis and goblet cell hyperplasia, and EGF is also a stimulator of airway smooth muscle proliferation.²⁵

Lung parenchymal damage

In addition to changes in the airway (chronic bronchitis), destruction of the lung parenchyma has been recognized for more than 150 years. This parenchymal destruction, known as emphysema, leads to a reduction in elastic recoil, premature airways closure, hyperinflation, and reduced gas transfer. Neutrophilic-predominant inflammation destroys the elastin through release of neutrophil elastase, a potent proteinase.²⁶ Emphysema may also be driven through loss of terminal bronchioles.²⁷ In the healthy lung, the neutrophil elastase is neutralized by alpha-1-antitrypsin. A defect in the *SERPINA1* gene leads to alpha-1-antitrypsin deficiency and accelerated emphysematous destruction of the lung. This is currently the only known genetic cause of COPD.²⁸

CURRENT PHARMACOLOGICAL THERAPIES IN STABLE COPD

Despite the significant global burden, pharmacological therapy for COPD is limited. These can be broadly categorized into 2 main approaches. The first is to reduce airflow limitation and hyperinflation through maximizing bronchodilation by targeting the smooth muscle. This is most commonly achieved using β_2 agonists and/or antimuscarinics, though historically methylxanthines have also been used for this purpose. The other mainstay of therapy is to target the airways inflammation. This is commonly achieved by inhaled corticosteroids, but occasionally

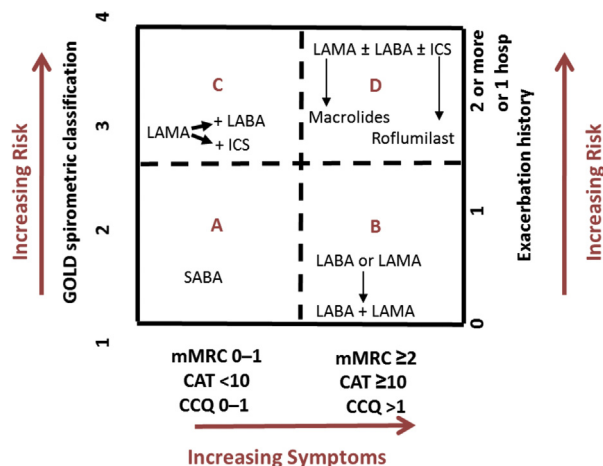


FIGURE 3. Summary of drug treatment based on GOLD disease classification. *CAT*, COPD Assessment Tool; *CCQ*, clinical COPD questionnaire; *hosp*, hospital; *GOLD*, Global Initiative for Chronic Obstructive Lung; *ICS*, inhaled corticosteroid; *LABA*, long-acting β -agonist; *LAMA*, long-acting muscarinic-agonist; *SABA*, short-acting β -agonist. Reprinted with permission.¹

phosphodiesterase 4 inhibitors are also used. The aim of targeting airways inflammation is to reduce exacerbation frequency, which will lead to improved quality of life. Pharmacological treatment for COPD control is aimed at improving symptoms, and reducing future risks (eg, exacerbation frequency and disease severity) (Figure 3).¹ The effect of breathlessness on patients with COPD can be objectively assessed using the Medical Research Council dyspnea score. The 1 to 5 scale is used to grade the degree of disability caused by breathlessness. COPD Assessment Tool is a patient-completed quality-of-life tool that contains 8 questions covering the impact of symptoms in COPD.

As previously discussed, a proportion of patients with COPD have predominantly eosinophilic inflammation. An elevated sputum eosinophil count is associated with a greater response to

TABLE I. Completed phase 2 and 3 trials of biologics in COPD targeting neutrophilic pathways

Agent; Target	Study	Regimen	Primary outcome (if available)	Secondary outcome (if available)
Anti-IL-8; IL-8 ⁴⁷	A multicenter, randomized, double-blind, placebo-controlled trial of anti-IL-8 in COPD N = 109 NCT00035828	800 mg loading dose, 400 mg/mo for 3 mo, 5-mo follow-up	↓ Severity of dyspnea as measured by transition dyspnea index	↔ Health status, lung function, 6-min walk test, rescue use of albuterol
Etanercept ⁵⁰ ; TNF- α	A randomized double-blind double-dummy controlled multicenter trial of etanercept in COPD N = 81 NCT00789997	50 mg, for 90 d	↔ FEV ₁ over 14 d from AECOPD onset	↔ 90-d treatment failure, dyspnea, health status
Infliximab; TNF- α ⁵⁴	Exploratory single-center, double-blind, placebo-controlled, randomized, phase 2 trial in mild-moderate COPD N = 22 NCT00244192	5 mg/kg, for 8 wk	↔ Sputum inflammatory cells	↔ FEV ₁ , SGRQ
Infliximab; TNF- α ⁴⁹	A multicenter, randomized, double-blind, placebo-controlled trial of infliximab in moderate-to-severe COPD N = 157 NCT00056264	3 mg/kg or 5 mg/kg, 44 wk	↔ CRQ	↔ FEV ₁ , 6-min walk test, TDI ↑ Malignancy and pneumonia
MEDI 8968 ⁵⁷ ; IL-1	A multicenter, randomized, placebo-controlled phase II trial of anti-IL-1 antibody (MEDI8968) in COPD N = 160 NCT01448850	300 mg every 4 wk, 52 wk	↔ Moderate-to-severe AECOPD	↔ SGRQ-C
CNTO 6785 ⁶² ; IL-17	A multicenter randomized, placebo-controlled, double-blind, parallel-group phase 2 trial of anti-IL-17 antibody (CNTO 6785) in COPD N = 186 NCT01966549	6 mg/kg every 2 wk for 4 wk, then every 4 wk for remaining 8 wk	↔ pre-BD % predicted FEV ₁	↔ Post-BD % predicted FEV ₁ ↔ SGRQ-C ↔ frequency of AECOPD ↔ weekly usage of rescue medication

AECOPD, Acute exacerbation of COPD; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St George's Respiratory Questionnaire; SGRQ-C, St George's Respiratory Questionnaire-COPD; TDI, transitional dyspnea index.

both inhaled and oral corticosteroids in stable disease in terms of improvement in lung function, health status, and 6-minute walk distance.²⁹⁻³¹ Serum eosinophil count can be used to predict response to corticosteroid response.³² Increased eosinophilic inflammation in peripheral blood and sputum samples in asthma and COPD is associated with favorable response to corticosteroids,^{13,33,34} and is associated with increased risk of exacerbations following corticosteroid withdrawal.³⁵ The latest Global Initiative for Chronic Obstructive Lung report advocates the use of inhaled corticosteroids in patients with eosinophilic inflammation.¹

BIOLOGICS IN COPD

Treatments in other chronic inflammatory diseases have been revolutionized over the past decade with the advent of biological treatments.^{1,36-39} The first trials of biologics in COPD targeted

the neutrophils and proinflammatory cytokines with disappointing results (Table I). In contrast, more recent trials have targeted eosinophilic inflammation, in populations enriched with increased eosinophils. Extending observations in asthma to COPD has led to the hypothesis that biological agents that selectively target and block eosinophilic pathways might reduce the frequency of exacerbation and improve health status.^{47,48} Studies of biologics trialed in COPD are described in Tables I, II, and III; how they map onto the cytokine networks is as shown in Figure 2. Below, we explore the success and the failures of some of these studies.

Specific proinflammatory and proneutrophilic cytokines and chemokines in COPD

Anti-IL-8 and anti-CXCR. The chemokine C-X-C motif ligand 8 (IL-8) is produced by various cells, including

TABLE II. Completed phase 2 and 3 trials of biologics in COPD targeting eosinophilic pathway

Agent; Target	Study	Biomarker entry criteria	Regimen	Primary outcome (if available)	Secondary outcome (if available)
Benralizumab ⁴⁰ ; IL-5	A randomized, double-blind, placebo-controlled, phase 2a study of benralizumab antibody in moderate-to-severe COPD N = 82	Sputum eosinophil count of $\geq 3.0\%$ in the previous year	100 mg every 4 wk (3 doses), then every 8 wk (5 doses), 56 wk	↔ Moderate-to-severe AECOPD	↑ FEV ₁ in the intervention group ↔ health status ↓ Blood and sputum eosinophils
Mepolizumab; IL-5	A pilot randomized clinical trial of mepolizumab in COPD with eosinophilic bronchitis N = 18 NCT01463644	Sputum eosinophils $>3\%$ at randomization and on at least 1 occasion in the past 2 y	750 mg per month, for 6 mo	↓ Sputum eosinophils	↓ Blood eosinophil ↔ FEV ₁ , CAT, CRQ, exacerbations
Mepolizumab ⁴¹ ; IL-5 (METREX)	A randomized, placebo-controlled, double-blind, parallel group trial of mepolizumab in COPD N = 1070 NCT02105961	Documented ↑ peripheral blood eosinophil count of ≥ 300 cells/ μ L within the past 12 mo or a baseline blood eosinophil count of ≥ 150 cells/ μ L from hematology conducted at visit 1	100 mg or 300 mg every 4 wk, 52 wk	↓ AECOPD in prespecified (n = 462) eosinophilic group	↑ Time to first AECOPD ↔ FEV ₁ , SGRQ, CAT
Mepolizumab ⁴¹ ; IL-5 (METREO)	A randomized, placebo-controlled, double-blind, parallel group trial of mepolizumab in COPD N = 674 NCT02105948	Documented ↑ peripheral blood eosinophil count of ≥ 300 cells/ μ L within the past 12 mo or a peripheral baseline blood eosinophil count of ≥ 150 cells/ μ L from hematology conducted at visit 1	100 mg or 300 mg every 4 wk, 52 wk	↔ AECOPD	↔ Time to first AECOPD ↔ FEV ₁ , SGRQ, CAT

CAT, COPD Assessment Tool; CRQ, Chronic Respiratory Disease Questionnaire; SGRQ, St George's Respiratory Questionnaire.

TABLE III. Ongoing and/or not reported trials of biologics in COPD

Agent; Target	Study	Regimen	Primary outcome (if available)	Secondary outcome (if available)
MSTT1041A; IL-33 receptor (ST2)	A single-center, double-blind, placebo- controlled, parallel- group, randomized controlled trial of MSTT1041A (anti-ST2 antibody) in moderate-to-very severe COPD N = 80 NCT03615040	490 mg S/C or matched placebo dosed every 4 wk for a total of 12 doses	Study is recruiting at present (frequency of moderate- to-severe AECOPD)	Study is recruiting at present (SGRQ-C, CAT, mMRC, post-BD FEV ₁ , sputum biomarkers)
SAR440340; IL-3	A randomized, double-blind, placebo-controlled, parallel-group, proof-of-concept study of SAR440340 (anti-IL-33 antibody), in moderate-to-severe COPD N = 340 NCT03546907	S/C drug or matched placebo	Study is recruiting at present (annualized rate of moderate-to-severe AECOPD over up to 52 wk)	Study is recruiting at present (change in pre-BD FEV ₁ , time to first moderate-to-severe AECOPD, adverse events, change in post-BD FEV ₁)
Benralizumab (TERRANOVA); IL-	A randomized, double-blind, double- dummy, placebo-controlled, multicenter, parallel- group, phase 3 study of benralizumab in patients with moderate-to-very severe COPD N = 2255 (NCT02155660)	Benralizumab or placebo S/C for 48 w	Result not released yet (impact on frequency of exacerbation in moderate-to-severe COPD)	Result not released yet (impact on health status, lung function, respiratory symptoms, frequency and duration of exacerbation, health economics, and safety and tolerability)
Benralizumab (GALATHEA); IL-5	A randomized, double-blind, double- dummy, placebo-controlled, multicenter, parallel- group, phase 3 study of efficacy and safety of 2 doses of benralizumab in patients with moderate-to- very severe COPD with a history of AECOPD N = 1656 (NCT02138916)	Benralizumab or placebo S/C for 48 wk	Result not released yet (impact on frequency of AECOPD in moderate-to-severe COPD)	Result not released yet (impact on health status, lung function, respiratory symptoms, frequency and duration of exacerbation, health economics, and safety and tolerability)

AECOPD, Acute exacerbation of COPD; BD, bronchodilator; CAT, COPD Assessment Tool; mMRC, modified Medical Research Council; S/C, subcutaneous; SGRQ-C, St George's Respiratory Questionnaire-COPD.

monocytes, macrophages, neutrophils, mast cells, and the airway epithelium in response to a number of stimuli including other cytokines (eg, IL-1 and TNF) and endotoxins.⁴⁹⁻⁵² Increased sputum IL-8 is well recognized in COPD, with further increase seen during exacerbations. IL-8 is known to attract and activate neutrophils during an inflammatory response.⁵³ It binds to CXC chemokine receptor 1 and CXC chemokine receptor 2 (CXCR2), members of the G-protein-coupled receptor family. CXCR2 is present on the surface of neutrophils and is involved in their recruitment to the lung.⁵³

In a pilot study of an mAb targeting IL-8 in COPD, Mahler et al⁴¹ showed improved dyspnea measured using the transitional dyspnea index. However, the study was not powered to detect differences in exacerbation rate. There were concerns that blocking IL-8 may lead to clinically significant neutropenia and increase the risk of infection. In a short (4 weeks) study of small molecule CXCR2 antagonist (AZD5069) in 87 subjects with COPD, Kirsten et al⁵³ reported significant neutropenia (defined as $<1 \times 10^9/L$) and acute exacerbations ($n = 4$, $n = 2$, respectively) in the intervention arm. However, there was no increase in infection in those receiving anti-CXCR2 versus placebo.⁵³

In another trial of a CXCR2 antagonist, Stephen Rennard et al⁵⁴ undertook a 6-month dose-ranging proof-of-concept study using MK-7123 in 616 subjects with moderate-to-severe COPD. A small, but statistically significant, improvement in FEV₁ was seen in those receiving the highest dose of anti-CXCR2 (50 mg daily) versus placebo. This difference was most notable in the subgroup of patients who were current smokers. The study was terminated early because not enough patients enrolled into the extension phase of the study (from 6 months to 18 months). There was no difference in rate of infection between the 2 groups at 6 months; however, in patients who continued with treatment beyond 6 months, the frequency of total infection and respiratory infections was higher in the intervention arm than in the placebo arm, 47% versus 35% and 40% versus 28%, respectively. The efficacy of CXCR2 inhibition has been shown to be small, and the potential of increased adverse events has meant that biologics directed at this target have not progressed in COPD.

TNF- α . TNF- α is one of the most well-described proinflammatory mediator in COPD. It is an attractive target because it is a major driver of neutrophilic inflammation in COPD, with significant increase at the time of an exacerbation.^{42,44} It activates nuclear factor-kappa B, increasing upregulation of inflammatory genes, and promotes migration of neutrophils to the inflamed sites.⁵⁵ Proof of concept in other neutrophilic-driven inflammatory conditions makes TNF- α a potentially key target, having transformed treatment of rheumatoid arthritis and inflammatory bowel disease.⁵⁶

In a nested case-control observational study of patients receiving anti-TNF- α biologics for rheumatoid arthritis, who also had COPD, treatment with anti-TNF- α biologics reduced COPD hospitalization (adjusted rate ratio, 0.62). This reduction was noticed in patients treated with etanercept (rate ratio, 0.49) rather than infliximab (rate ratio, 0.95).⁵⁷ The interpretation of this is limited because only 16 of 1205 patients (1.3%) in the study were on etanercept. Participants in this study were identified from an insurance claim database, and therefore, it is uncertain that all the patients had lung function and physician-confirmed COPD.

A pilot study of 22 subjects compared infliximab with placebo for 8 weeks.⁴³ No increase in adverse events in those receiving infliximab was seen. However, no significant benefits in lung function or health status were observed.

An adequately powered trial of infliximab in 234 subjects with COPD showed similar results, with no improvements seen in health status, lung function, symptoms, or exacerbation frequency.⁴⁴ Importantly, increased adverse events were noted in those receiving infliximab, including incidence of cancer (12 vs 3) and pneumonia (10 vs 1). The increased malignancy risk during the study did not persist in the long-term follow-up of patients following treatment cessation. An acute study of anti-TNF- α (etanercept) versus prednisolone at the onset of an exacerbation found no increase in adverse events but neither did it find benefit in favor of etanercept.⁴² The airways of patients with COPD are colonized by pathogenic microbiomes, as opposed to sterile joints in rheumatoid arthritis, and therefore any imbalance in host defense can lead to infection. Failure of the biologics in the neutrophilic phenotype in COPD is unlikely to be due to lack of enrichment for appropriate patients because the eosinophilic phenotype represents only a smaller percentage of patients with COPD compared with the neutrophilic phenotype. The poor efficacy of anti-TNF- α and observations of the increased malignancy and infection rates have stopped progress of this biologic as maintenance therapy in stable COPD. To our knowledge, no further studies of anti-TNF- α in COPD are ongoing.

Anti-IL-1. IL-1 is one of the major proinflammatory cytokines that affect most cells and organs.⁵⁸ It is produced by multiple cell types, including macrophages, monocytes, and fibroblasts.⁵⁹ Unlike many other proinflammatory cytokines, its effects occur at receptor and nucleus levels. IL-1 stimulates the activity of the cells of the innate immune system, including neutrophils, eosinophils, mast cells, and basophils. These widespread effects promote both local and systemic inflammation. Two of the IL-1 cytokine family, IL-1 α and IL-1 β , have marked proinflammatory effects and have been implicated in airways inflammation in COPD and thus represent a potential treatment target.

In a phase II randomized controlled trial, Calverley et al⁴⁵ tested a novel anti-IL-1R1 mAb in 324 subjects with a history of multiple exacerbations of COPD.⁴⁵ This biologic inhibits activation of both IL-1 α and IL-1 β . Subjects received monthly dose for 52 weeks following an initial loading dose. The drug did not produce a statistically significant improvement in the primary outcome, moderate or severe exacerbation frequency rate. Secondary outcomes, including lung function and health status, showed no improvement either, and no clear subgroup appeared to respond. There were no differences in adverse events between the groups.

In another study, 147 patients with moderate to very severe COPD were randomized to receive canakinumab, an IL-1-IR1 antagonist, or placebo for 1 year. No statistical analysis was provided at the completion of the study, but changes in lung function that were reported were very similar between the 2 arms.⁶⁰ No further anti-IL-1 studies are currently ongoing.

IL-17. T_H17 CD4⁺ lymphocytes produce IL-17A, which acts on endothelial cells, epithelial cells, and smooth muscle cells to promote production of proinflammatory cytokines, such as IL-6, IL-8, and TNF- α , that recruit neutrophils and promote

inflammation.^{61,62} Therefore, blocking IL-17 activity might lead to reduced neutrophilic airway inflammation.⁶³

In a phase II randomized controlled trial of anti-IL-17A (CNTO 6785), 187 patients with moderate-to-severe COPD were randomized to receive either CNTO 6785 ($n = 93$) or placebo ($n = 94$) intravenously over 12 weeks (twice weekly for 3 weeks then every 4 weeks). They were followed for a total of 24 weeks from randomization.⁴⁶

The primary end point was change from baseline in pre-bronchodilator (pre-BD) percent-predicted FEV₁ at week 16. The main secondary outcomes were change from baseline at week 16 in (1) post-BD percent-predicted FEV₁; (2) average use of rescue medications in a week; (3) St George's Respiratory Questionnaire-COPD total score; and (4) COPD exacerbations, assessed by EXacerbations of Chronic Pulmonary Disease Tool-Patient Reported Outcome questionnaire, through week 24. This study failed to show any statistically or clinically significant differences in primary or secondary end points between the intervention and placebo arms. No deaths were reported in the study. There were more protocol-defined exacerbations in the intervention arm compared with placebo at week 16 (18 vs 11). There were 3 reported cases of pneumonia in the placebo arm, 1 case of septic arthritis in the intervention arm, and 1 case of osteomyelitis in the intervention arm. There were several limitations to this study: (1) The duration of the study was too short to observe any meaningful changes in FEV₁. (2) Quantifying average use of rescue medications in a week is prone to recall bias and not easy to measure. (3) The study did not specify when were most of the patients recruited as the timing of recruitment and follow-up would have impacted the exacerbation frequency.⁶⁴

Summary of antineutrophilic biologic agents in COPD

Although the main inflammatory pathway in COPD is neutrophilic in nature, studies in targeted biologic therapy for neutrophilic inflammation have been disappointing to date. Anti-IL-8 and anti-CXCR2 led to small clinical benefit with evidence of reduced blood neutrophil counts and possibly increased risk of infection. Targeting IL-17, IL-1, and TNF- α has not been associated with efficacy, and inhibiting TNF- α has led to substantial and clinically important adverse events. These findings hindered further the progress of biological therapy targeting proinflammatory cytokines and neutrophilic inflammation in COPD. One possible explanation for the failure of biologics in targeting the neutrophilic pathway could be lack of enrichment for the neutrophilic phenotype. However, this is unlikely because an eosinophilic phenotype represents a minority of COPD population whereas a neutrophilic phenotype is common.

Specific T2 inflammation and proeosinophilic cytokines and chemokines in COPD

Evidence for targeting T2-mediated inflammation using biologics has revolutionized clinical practice in severe asthma.^{48,65-68} Significant eosinophilic inflammation does exist in COPD, albeit in a smaller proportion of patients than in asthma. Unlike asthma, COPD is not associated with increased atopy, and therefore the underlying mechanisms of eosinophilic inflammation in COPD are poorly understood.

Anti-IL-5 and anti-IL-5 receptor. IL-5 is one of the most well-understood cytokines in eosinophilic-predominant inflammation. It is released by CD4⁺ T_H2 lymphocytes, innate lymphoid cells, and eosinophils. IL-5 receptor (IL-5R) is expressed by both eosinophils and basophils. IL-5 stimulates maturation and release of eosinophils from bone marrow and is required for survival of tissue eosinophils.⁶⁹

Brightling et al⁴⁷ undertook a 1-year phase 2a randomized controlled trial of anti-IL-5R (benralizumab) in 101 patients with moderate-to-severe COPD.⁴⁷ Although a reduction in eosinophilic inflammation was observed, the annual rate of acute exacerbations (the primary outcome) was not met. Secondary outcomes showed an improvement in FEV₁ in those receiving benralizumab but no difference was observed in health status. In a prespecified *post hoc* analysis in those with eosinophilic inflammation at screening, defined as either a sputum eosinophil count of more than 2% or a blood eosinophil count of more than 250 cells/ μ L, a greater improvement in lung function and health status and a numerical reduction in exacerbations was seen. No difference in the rate of adverse events was seen. Unsurprisingly, these findings suggested greater efficacy in a more eosinophilic subgroup. However, the phase 3 trial of benralizumab in COPD failed to meet its primary outcome (annual COPD exacerbation rate for patients with baseline blood eosinophil count of ≥ 220 cells/ μ L). The publication of the full results is awaited, and whether a subgroup of subjects with COPD with more marked eosinophilic inflammation respond more favorably will be determined.

In a proof-of-concept pilot study, Dasgupta et al⁷⁰ showed that a different anti-IL-5 (mepolizumab) reduced sputum eosinophil count in 18 subjects with COPD, although no clinically significant benefits were observed in lung function or health status.

In the largest biological trials to date in COPD, Pavord et al⁴⁸ reported on 2 phase 3 trials (METREX and METREO) of mepolizumab in moderate to very severe COPD.⁴⁸ In METREX, subjects were randomized to receive either 100 mg mepolizumab or placebo ($n = 836$), whereas in METREO, subjects received 100 mg mepolizumab, 300 mg mepolizumab, or placebo ($n = 674$) every 4 weeks for 52 weeks. Recruitment by eosinophilic phenotype differed between trials. METREX recruited both eosinophilic (defined as eosinophil count of $\geq 150/\mu$ L on screening or of $\geq 300/\mu$ L in previous year) and noneosinophilic (defined as eosinophil count of $<150/\mu$ L on screening or of $<300/\mu$ L in previous year) patients, whereas METREO included only eosinophilic patients. In METREX, no overall difference in exacerbations between groups was seen (1.49 and 1.52 exacerbations per year). In the eosinophilic subgroup, 18% reduction in moderate or severe exacerbations was observed in the mepolizumab group compared with placebo (1.40 exacerbations per year compared with 1.71 per year; adjusted $P = .04$). In METREO, the mean annual rate of moderate or severe exacerbations was 1.19 per year in the 100-mg mepolizumab group, 1.27 per year in the 300-mg mepolizumab group, and 1.49 per year in the placebo group. A nonsignificant reduction in both doses compared with placebo was seen (100 mg rate ratio, 0.80; adjusted $P = .07$; 300 mg rate ratio, 0.86, adjusted $P = .14$). Higher dose of mepolizumab did not confer any additional benefit. For the secondary end points, time to the first moderate or severe exacerbation was significantly longer with mepolizumab than with placebo in the eosinophilic subgroup in

METREX (192 days vs 141 days; hazard ratio, 0.75; adjusted $P = .04$). In keeping with the smaller pilot study, there were no improvements in lung function and health status in those receiving mepolizumab versus placebo and no differences in adverse events between groups.

Mepolizumab is the first biologic to demonstrate a reduction in the rate of exacerbations in patients with eosinophilic COPD. However, the magnitude and consistency of this benefit was not considered sufficient by the Food and Drug Administration to license mepolizumab for COPD. Importantly, both the mepolizumab and benralizumab studies suggest that the effect size is smaller than that seen in severe asthma and the magnitude of benefit is directly related to the intensity of eosinophilic inflammation.⁴⁸ The subpopulation of patients with COPD most likely to respond to anti-IL-5(R) therapy remains unclear, although it is most likely those with a greater disease burden and higher degree of eosinophilic inflammation. Whether the anti-IL-5 approach or the anti-IL-5R approach increases the risk of exacerbations in subjects with COPD with low eosinophil counts needs to be further explored and the possible mechanisms elucidated.

Anti-IL-13 and anti-IL-4 receptor alpha. IL-13, similar to IL-5, is a T_H2 cytokine produced by T cells, mast cells, and eosinophils. It acts on inflammatory cells, bronchial epithelium, and airway smooth muscle.⁷¹ IL-13 signals through IL-13 receptors I and II, with IL-13 receptor I sharing the IL-4 receptor alpha chain subunit with the IL-4R. A single trial of an anti-IL-13 (lebrikizumab) has been tested in COPD. The full result of the study is yet to be published, but the press release reported that COPD exacerbations were not reduced in those receiving lebrikizumab versus placebo (NCT02546700). In phase 3 studies for asthma, anti-IL-13 (lebrikizumab⁷² and tralokinumab⁷³) failed to meet their primary outcome for reduction in exacerbations, whereas in contrast anti-IL-4 receptor alpha substantially reduced exacerbations.⁷⁴ Whether simultaneously targeting IL-13 and anti-IL-4 receptor alpha (as occurs with dupilumab) has efficacy in COPD needs to be determined.

FUTURE BIOLOGICS IN COPD

With more promising responses seen for biologics targeting T2-mediated inflammation than antineutrophilic inflammation, the immediate landscape has been to explore other cytokines implicated in T2-mediated immunity and/or eosinophilic inflammation.

Thymic stromal lymphopoietin (TSLP) is an IL-7–like cytokine, which signals via IL-7 receptor alpha and thymic stromal lymphopoietin receptor.⁷⁵ It is produced by airway epithelial cells during inflammation, and it stimulates thymocytes and B-cell lymphopoiesis.^{17,76} TSLP orchestrates response to epithelial injury by acting on CD4, CD8 T cells, B cells, mast cells, basophils, eosinophils, and innate lymphoid cells.⁷⁷ Studies have shown increased expression of TSLP in airways disease.^{78,79} Whether targeting TSLP has benefit in an unselected COPD population or in an eosinophilic subgroup is unknown and warrants further investigation.

IL-6

IL6 is a pleiotropic cytokine that has proinflammatory and immunomodulatory effects.⁸⁰ It is secreted by airway epithelial

cells, alveolar macrophages, and T cells.^{81,82} Studies have shown that high levels of serum or sputum IL-6 in COPD are associated with impaired lung function, pulmonary infections, and exacerbations.^{81,83} A longitudinal study over 3 years showed that raised serum IL-6 levels are predictive of increased mortality in COPD.⁸² Several studies have shown that patients with COPD have higher serum concentration of IL-6 than do patients without COPD.^{84–86} Therefore, targeting IL-6 might slow lung function decline and reduce the frequency of acute exacerbations in COPD. There has not been any trial of anti-IL-6 antibody in COPD to date. Although trials of anti-IL-6 antibody (tocilizumab) in rheumatoid arthritis have been promising, the report from a postmarketing surveillance (4 cases of tuberculosis, 15 cases of malignancy, 3 interstitial pneumonia, 12 serious hepatobiliary disorders, and 7 gastrointestinal perforations) might make anti-IL-6 antibody trials in COPD less attractive.⁸⁷

IL-33

In parallel with asthma, there is also increasing interest in IL-33 as a target. IL-33 is an alarmin released from the epithelium following damage.⁸⁸ It is part of the IL-1 alarmin cytokine family expressed on epithelial barrier surfaces where it is rapidly released from cells during tissue injury. IL-33 signals through a receptor complex of IL-1 receptor-like 1 (known as ST2) and IL-1 receptor accessory protein. This leads to initiation of MyD88-dependent inflammatory pathways.⁸⁹ Eosinophil recruitment to the airway has been shown to be IL-33 dependent, in addition to IL-33 driving eosinophil maturation, via innate lymphoid cells, largely in the bone marrow.⁹⁰ In a rhinovirus-induced viral challenge, IL-33 increased in asthma and therefore might play a role in the consequent inflammatory response and potential susceptibility to secondary bacterial infection.⁹¹ However, the role of the IL-33/ST2 axis in COPD is uncertain. Correlations between blood eosinophil, smoking status, and IL-33 in COPD have been reported, and increased IL-33 levels in both peripheral blood and airways are seen in patients with COPD.⁹² Given that both eosinophilic inflammation and viral infection drive COPD exacerbations, targeting the IL-33/ST2 axis is a plausible mechanism to reduce COPD exacerbations. Trials of anti-IL-33 or anti-ST2 biologics in COPD are ongoing (NCT03546907, NCT03615040).

Small molecules targeting the prostaglandin D2 type 2 receptor are in late-stage development in moderate-to-severe asthma (NCT02563067, NCT02555683), following success in small mechanistic studies demonstrating beneficial effects on eosinophilic inflammation, lung function, and asthma control.⁹³ The prostaglandin D2 type 2 receptor antagonist tested in COPD reduced the intensity of eosinophilic inflammation.⁹⁴ Whether prostaglandin D2 type 2 receptor antagonism is beneficial in a subgroup of patients with COPD with underlying eosinophilic inflammation requires future studies.

Anti-IgE

IgE plays an important role in allergic asthma. Blocking the activities of IgE with anti-IgE antibody (omalizumab) in asthma improves symptoms and quality of life and reduces asthma exacerbations and the need for corticosteroid use.^{95,96} There have not been any major studies of anti-IgE antibody in patients with COPD. In a small observational study, patients with diagnosis of COPD and elevated IgE were given omalizumab for 3 months.⁹⁷ At the end of the treatment period, participants were asked to fill

symptoms score and satisfaction score questionnaires. The authors presented their findings as a conference proceedings and reported improvements in satisfaction and symptoms score with omalizumab. The total number of participants, frequency of treatment, side effects of treatment, definition of elevated IgE, and the type of questionnaires used to assess symptoms score and satisfaction score were not mentioned in the abstract. Another exploratory study of omalizumab in patients with COPD with elevated IgE level was terminated because the researchers were unable to find eligible patients (NCT00851370).

There have been several studies of anti-IgE (omalizumab) in patients with a label of "asthma-COPD overlap syndrome" (ACOS).⁹⁷⁻⁹⁹ These studies have shown that omalizumab improves health-related quality of life in patients with ACOS. However, most of these studies have used tools that are validated for use in asthma only (eg, Asthma Control Questionnaire and Asthma Quality of Life Questionnaire).

The main obstacle in applying the findings of these studies to patients with COPD is that the concept of ACOS is controversial with no overarching definition. Until we better understand the biology and pathophysiology of ACOS, it may not be useful to consider it as a single disease.

CONCLUSIONS

In contrast to asthma, no biological therapies are licensed for COPD. There is increasing evidence that eosinophilic inflammation is present in a subgroup of patients with COPD. To date response to anti-IL-5 has been poor in comparison to asthma, with a small reduction in exacerbation frequency. Benefit was associated with baseline blood eosinophil count. Details of the phase 3 anti-IL-5 receptor trial are awaited. If these findings suggest that there is a responder group of patients with COPD with higher blood eosinophil counts, this might present a group for potential future anti-IL-5 or anti-IL-5 receptor trials. Whether other T2-directed biologics and small molecules that have either demonstrated success in asthma or are in early phase trials will be successful in COPD remain to be determined. The enormous unmet need in COPD means that biological therapy is an attractive option, but the potential promise of this approach getting into the clinic is still to be realized.

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