

Biologics and chronic obstructive pulmonary disease



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The presence of airway inflammation in patients with chronic obstructive pulmonary disease (COPD) provides a rationale for biological agents targeting specific inflammatory pathways. This approach has been strikingly effective in patients with other chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, and asthma. However, there are important and unresolved challenges in COPD, including our incomplete understanding of heterogeneity of the lower airway inflammatory response and how these contribute to the clinical expression of disease. As a result, progress has been slow, and there have been many failures. One notable exception is the targeting of eosinophilic airway inflammation with anti-IL-5, which has an acknowledged and important role in the treatment of severe eosinophilic asthma. Recent phase III studies have shown a reduction in exacerbations of around 20% in patients with COPD and clear evidence of a blood eosinophil count-dependent beneficial effect. The demonstration of clinical efficacy linked to a clinically accessible biomarker raises the possibility of precision biomarker-directed use of biological agents in patients with COPD. The hope is that this will be an exemplar for the future development of biological agents in patients with COPD. (*J Allergy Clin Immunol* 2018;141:1983-91.)

Key words: *Biologics, chronic obstructive pulmonary diseases*

Chronic obstructive pulmonary disease (COPD) is a common syndrome characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities that usually result from significant exposure to noxious particles or gases.¹ Typical symptoms are nonvariable breathlessness, cough, and sputum production. In some patients day-to-day symptoms are punctuated by periods of acute worsening of symptoms (exacerbations). The most important etiologic factor is cigarette smoking, but other environmental

Abbreviations used

COPD: Chronic obstructive pulmonary disease
FENO: Fraction of exhaled nitric oxide
ICS: Inhaled corticosteroid
METREO: Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level
METREX: Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients

exposures, including biomass fuel exposure and air pollution, contribute in some patients and might be a dominant cause in developing countries. Host factors, such as genetic abnormalities and abnormal lung development, predispose subjects to COPD.

COPD represents an important public health challenge. It is projected to be the third leading cause of death in the coming decades because of continued exposure to COPD risk factors and an aging population.² Health care and societal costs attributable to COPD are significant: in the European Union costs are estimated to be about 6% of the total health care budget and 56% (€38.6 billion) of the cost of respiratory disease, and in the United States there are estimated direct costs of \$32 billion.³ Exacerbations are responsible for the greatest proportion of total COPD burden on the health care system and are a leading cause of the annual winter acute hospital bed squeeze occurring in many countries.

The chronic airflow limitation that is characteristic of COPD is caused by a mixture of small-airway occlusion and fibrosis and loss of parenchymal support provided by alveolar attachments to the small airways. These structural changes result in reduced ability of the airways to remain open during expiration and airflow limitation. Airflow limitation is usually measured by using spirometry; it is by definition not fully bronchodilator responsive, such that the postbronchodilator FEV₁/forced vital capacity ratio is consistently less than 0.7. It is generally held that structural changes are the result of chronic airway inflammation; both tend to increase with increasing disease severity. Airway inflammation is characterized by increased numbers of CD8 T lymphocytes, neutrophils, and macrophages; increased production of proinflammatory cytokines; oxidative stress; and a state of protease/antiprotease imbalance.⁴

An important and poorly understood feature of the inflammatory and structural changes seen in patients with more advanced COPD is that they persist after smoking cessation, possibly as a result of the development of autoantigens and perturbations in the lung microbiome. Systemic inflammation might be present and could play a role in the multiple comorbid conditions found in patients with COPD.

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MANAGEMENT OF COPD

Pharmacologic therapy for COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status. The choice of therapy depends on the availability and cost of medication, the nature of the clinical problem, and the likely side effects of treatment. In general, bronchodilator therapy (ie, long acting β_2 -agonists and long-acting antimuscarinic agents) has proportionate effects on symptoms, airflow limitation, and the risk of future exacerbations, whereas inhaled corticosteroids (ICSs) have a relatively selective effect on the risk of exacerbations. Current treatment guidelines suggest that the treatment regimen is individualized according to the severity of symptoms and the likelihood of exacerbations,¹ with the latter assessed according to prior history of recurrent and/or severe exacerbations.

Preventing the accelerated decrease in lung function characteristic of COPD and reducing mortality are also important treatment goals. To date, there is no consistent evidence that any existing medications for COPD modify either. *Post hoc* evidence of an effect on decrease in lung function with long-acting bronchodilators, ICSs, or both⁵ requires confirmation in specifically designed trials. Moreover, if these established treatments have an effect on these key outcomes, it is likely to be small and needs to be offset against side effects, including a doubling of the risk of pneumonia with ICSs.⁶

This questionable risk benefit reflects a number of problems with new drug discovery in patients with COPD and in those with airways disease in general. There is a high rate of failure, and when efficacy is seen, there is a suspicion that the drug effect has been diluted because of an insufficient account of a number of factors, including the following:

1. There is heterogeneity in patterns of airway inflammation.
2. A significant number of patients have airflow limitation as a result of burnt-out early-life disease,⁷ and we are unable to discriminate this population from those who have disease as a result of active ongoing pathology.
3. There is difficulty in demonstrating modification of the rate of decrease in lung function and the absence of a satisfactory surrogate measure.
4. In a significant number of patients, symptoms and mortality are driven primarily by extrapulmonary factors, such as obesity and cardiac disease. Therefore they are unlikely to be responsive to treatment targeting a pulmonary process.
5. There is heterogeneity in exacerbations. For example, events treated with antibiotics alone are different from those treated with corticosteroids. The latter are more effectively prevented by ICS-containing regimens and are likely to be more eosinophilic, whereas the former are more responsive to long-acting bronchodilators⁸ and are more likely to be neutrophilic.

There is a growing view that we need to deal with these issues by rethinking the way we classify and manage airway diseases.^{9,10} The focus should move from arbitrary disease labels to identifiable pathways (or endotypes) driving disease manifestations (treatable traits). The future is to use a treatable traits-based stratification systems to perform appropriately stratified clinical trials.⁹ It is also important to be clear about the most likely outcome measures associated with effective intervention against a particular trait (Table I).

The presence of airway inflammation provides a rationale for exploring biological agents that selectively block inflammatory pathways. To date, the results of studies reflect the general experience of new drug discovery in patients with COPD and have been disappointing. In many cases this might have been because the treatable trait has not been defined sufficiently clearly. A notable exception is the case of interventions targeting eosinophilic or type 2–high airway inflammation.

EOSINOPHILIC AIRWAY INFLAMMATION AS A TREATABLE TRAIT AND TARGET FOR BIOLOGICAL TREATMENT IN ASTHMATIC PATIENTS AND PATIENTS WITH COPD

Eosinophilic airway inflammation is widely recognized in patients with asthma, and the cellular and cytokine pathways are well understood. Two different pathogenic pathways are thought to be important (Fig 1).¹¹ These pathways differ in their link to allergy, in the master regulator lymphocyte population, and probably also in their responsiveness to treatment with ICSs. The exact mechanisms and clinical implications of involvement of these different pathways remain to be defined, but they could theoretically represent individual distinct treatable components. Importantly, eosinophilic airway inflammation is readily recognizable, and the methods required to identify it are suitable for use in everyday clinical practice (Table II).^{12–15} There is now convincing evidence that asthma and COPD management guided by biomarkers of eosinophilic airway inflammation results in better outcomes and more efficient use of existing treatments.^{16–18}

The ability to identify eosinophilic airway inflammation using clinically accessible biomarkers coupled with an appreciation that this process relates more closely to the risk of exacerbations of asthma than day-to-day symptoms have been key to discovery of the beneficial effects of biological agents in asthmatic patients.¹⁹ Monoclonal antibodies targeting IL-5 (mepolizumab^{20–23} and reslizumab²⁴) or the IL-5 receptor (benralizumab^{25,26}), IL-13 and IL-4 through the IL-4 α receptor (dupilumab^{27,28}), and thymic stromal lymphopoietin (tezepelumab²⁹) have all been shown to be effective in patients with severe eosinophilic asthma.

The clinical efficacy and effect of treatment on biomarkers is summarized in Table III. A number of general principles are apparent. First, the effect of treatment on exacerbations is greater than the effect on measures of lung function and symptoms. Second, efficacy increases with increasing evidence of type 2–high inflammation. Third, although direct comparative studies are lacking, indirect comparisons suggest that clinical efficacy is broader and larger when type 2 immune responses are inhibited more completely. Fourth, the group mean effect of treatment on biomarkers of type 2 inflammation is entirely predictable based on the known effects of the cytokine targeted by the biological agent. Blocking IL-13 and IL-4 (ie, dupilumab) reduces fraction of exhaled nitric oxide (FENO) and IgE levels but increases blood eosinophil counts,²⁸ whereas inhibition of IL-5 has a selective inhibitory effect on blood eosinophils.²¹ Tezepelumab reduces blood eosinophil counts and FENO and IgE levels, presumably reflecting the proximal role of thymic stromal lymphopoietin on type 2 cytokine-producing cells.²⁹

Finally, the biomarker most inhibited by the mAb is also the most predictive of treatment efficacy. The blood eosinophil is a strong predictive biomarker of the response to biological agents

TABLE I. Potentially relevant pulmonary treatable traits in patients with COPD

Trait	Biomarker	Treatments	Likely outcome	Comments
Airflow limitation	FEV ₁ /FVC ratio < 0.7	β ₂ -Agonists, antimuscarinic agents, theophylline	Improved symptoms, lung function, and exercise capacity	Caused by multiple factors, including airway smooth muscle contraction, mucus plugging, airway wall edema, small-airway fibrosis, and loss of airway support; components not readily distinguishable and likely to respond to treatments differently
Eosinophilic airway inflammation	See Table II	ICSs; oral CSs; anti-IL-5, anti-IL-4, and anti-IL-13; anti-TSLP	Reduced exacerbations and variable and smaller improvement in symptoms and lung function	Well-defined, identifiable, and treatable; likely the results of different pathways (Fig 1)
Neutrophilic airway inflammation	Induced sputum neutrophil count; ? CRP	? Macrolides; CXCR2 antagonists	? Reduced exacerbations; ? Reduced rate of decrease in lung function; ? reduced cough and sputum	Not at all well-defined; might be multiple pathways, including infection-associated pathways, caused by exogenous stimuli (ie, smoking) and autoimmune processes (ie, rheumatoid-associated airway disease)
Cough reflex hypersensitivity	24-h Cough counts, Leicester Cough Questionnaire	Gabapentin; ? P2X3 antagonists	Improved cough	Recent progress with new measurement techniques and treatments
Mucus overproduction	CT-based assessment; sputum production	Carbocysteine; no other well-established treatments in patients with COPD	Improved sputum; ? reduced exacerbations	Unclear whether independent of airway inflammation

CRP, C-reactive protein; CS, corticosteroid; CT, computed tomography; FVC, forced vital capacity; TSLP, thymic stromal lymphopoietin.

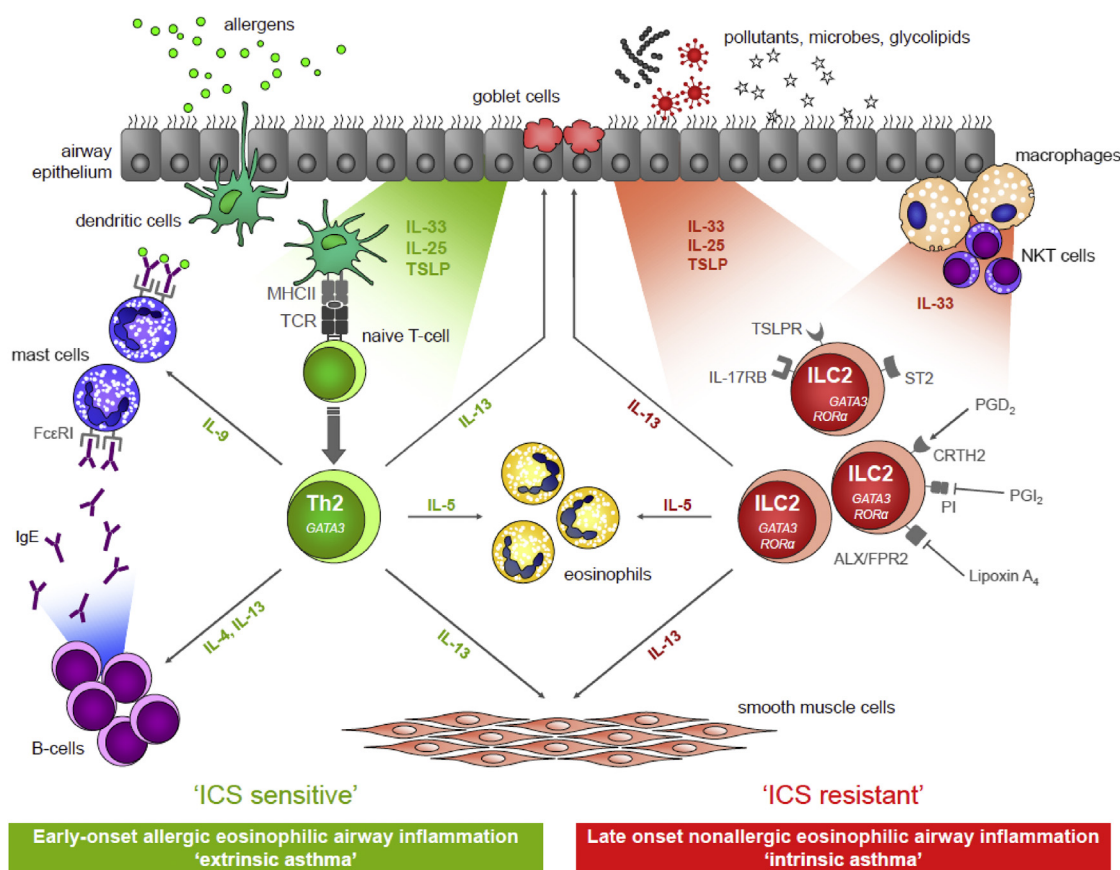


FIG 1. Two pathways leading to abnormal type 2 cytokine production and eosinophilic airway inflammation. The pathway on the right is likely to be more relevant to eosinophilic airway inflammation in patients with COPD. Modified from Brusselle et al.¹¹ ALX/FPR2, G protein-coupled formyl peptide receptor 2; CRTH2, prostaglandin D₂ receptor 2; ILC2, type 2 innate lymphoid cell; MHCII, MHC class II; NK, natural killer; PGD₂, prostaglandin D₂; PGI₂, prostacyclin I₂; PI, phosphoinositide; ST2, IL-1 receptor-like 1; TCR, T-cell receptor; TSLP, thymic stromal lymphopoietin; TSLPR, thymic stromal lymphopoietin receptor.

TABLE II. Potential biomarkers of eosinophilic airway inflammation

Biomarker	Association with treatment response	Invasiveness	Comments
FENO	Corticosteroids; anti-IL-13, anti-IL-4 and anti-IL-13; anti-IgE	Noninvasive	Easy, quick, not specific, cheap, generally available; loses specificity in smokers ¹⁴
Serum IgE	Not associated	Minimal	Although recommended to measure, there is no clear association between IgE or allergy as a biomarker of treatment responses or clinical outcome. ¹³ Omalizumab decreases free IgE levels.
Serum periostin	Anti-IL-13, anti-IgE	Minimal	Effect shown with anti-IL-13, limited availability currently; confounded by growth in childhood, pregnancy, and dental disease ¹⁵
Blood eosinophil count	Anti-IL-5, anti-IL-4/IL-13 (?)	Minimal	Generally available, high clinical effect, predicts anti-IL-5 response and ICS response in patients with COPD; associated with increased risk of lung attacks; increases after treatment with anti-IL-13 and anti-IL-13/IL-4
Sputum eosinophil count	Corticosteroids, anti-IL-5, anti-IL-4/IL-13 (?)	Moderate	Specialist centers, tissue specific, time consuming; good therapeutic marker for ICSs, OCSs, and biologics; established evidence of value as a monitoring tool

OCSs, Oral corticosteroids.

TABLE III. Effects of treatment targeting eosinophilic airway inflammation on clinical measures and biomarkers in patients with severe eosinophilic asthma

	Effect on clinical measures					Effect on biomarkers			
	FEV ₁	Symptoms	Exac	PC ₂₀	OCS sparing	Bl eos	Sp eos	FENO	IgE
Oral steroids	+	+	++	++	NA	↓↓	↓↓	↓	↓
Anti-IL-5	+	+	++	0	++	↓↓	↓↓	↔	↔
Anti-IL-13	+	+	+	?	0	↑	↓	↓↓	↓
Anti-IL-4/IL-13	++	++	++	?	?	↑	↓	↓↓	↓↓
Anti-IgE	+	+	+	0	?	↔	↓	↓↓	↓↓
Anti-TSLP	++	++	++	?	?	↓	↓	↓↓	↓

++ and ↓↓, Marked effect; 0, no effect; ?, no information.

OCS, Oral corticosteroid; TSLP, thymic stromal lymphopoietin.

targeting IL-5,¹⁸ whereas FENO value is most closely associated with the response to those targeting IL-13, IL-4, and IgE.^{13,27}

COPD is viewed generally as a disease driven by neutrophilic inflammation.⁴ However, studies have shown that up to 40% of patients have an increased induced sputum eosinophil count,³⁰ and sputum supernatant IL-5 levels are increased to levels similar to those seen in patients with severe asthma.³¹ Although widely assumed to reflect an asthmatic component to airflow limitation, patients with COPD and eosinophilic inflammation are no more likely to have features associated with asthma, including onset of disease before age 40 years, bronchodilator-responsive airflow limitation, allergy, or absent smoking histories.^{30,32} Eosinophilic airway inflammation is also seen in patients presenting with exacerbations of COPD.³³ These episodes are associated with more severe airflow limitation but a quicker recovery with oral corticosteroid treatment.³⁴ Eosinophilic exacerbations tend to occur recurrently in patients with COPD, and it has been shown that patients' inflammatory status when stable is predictive of their inflammatory status at exacerbation.³³

There is now convincing evidence that, as in asthmatic patients, an increased sputum eosinophil count in patients with COPD is associated with a larger response to corticosteroid treatment.^{35,36} Moreover, as in asthmatic patients, a treatment strategy that aims to reduce sputum eosinophil counts in patients with COPD is associated with a significant reduction in severe exacerbations compared with a treatment strategy targeting symptoms in isolation.¹⁸ An important development has been the recognition that

the peripheral blood eosinophil count is a good and more clinically accessible, although less ICS-responsive, biomarker of eosinophilic airway inflammation in patients with COPD whether studied when stable³⁷ or in the setting of an exacerbation.³³ In both cases a differential blood eosinophil count of less than 2% or a total eosinophil count of less than 150 cells/ μ L has a high negative predictive value. Three *post hoc* analyses of studies evaluating the effect of adding ICSs to long-acting β_2 -agonists in patients with COPD and a history of exacerbations have shown no evidence of efficacy of ICSs in patients with a blood eosinophil count of less than this level and a progressive increase in the benefit of treatment with increasing blood eosinophil counts to greater than this level.³⁸⁻⁴⁰

Collectively, this evidence suggests that eosinophilic airway inflammation is a readily identifiable treatable trait in patients with COPD, which raises the possibility of a role for biological treatment. In support of this, a *post hoc* analysis of the Mepolizumab for Severe Eosinophilic Asthma (DREAM) study of mepolizumab in patients with severe eosinophilic asthma showed efficacy in patients with COPD-like disease (ie, adult-onset disease, FEV₁/forced vital capacity ratio, and lack of reversibility).²¹ This evidence provided a strong basis for later-phase clinical trials of biological agents targeting this process.

The first randomized controlled trial investigated benralizumab, an anti-IL-5 receptor α blocker.⁴¹ This small

phase 2a study involved 101 patients with COPD, a history of at least 1 exacerbation in the previous year, and evidence of eosinophilic airway inflammation in the form of an induced sputum eosinophil count of greater than 3% at some point in the previous year. The study result was negative for its primary outcome in reducing exacerbations in patients with eosinophilic COPD. However, a *post hoc* analysis suggested efficacy on lung function and exacerbations in patients with higher blood eosinophil counts (>300 cells/ μL).

Two larger and more definitive studies have been carried out with mepolizumab, the Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients (METREX) and Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level (METREO).⁴² The study target population consists of a population that, despite a history of use of optimal standard-of-care therapy with an ICS and dual bronchodilator, continues to be at risk for future exacerbation, as reflected by a history of 2 or more moderate or 1 or more severe (hospitalized) exacerbations in the previous year. The studies tested the hypothesis that the reduction in circulating eosinophil counts with mepolizumab in patients with COPD would translate into a reduction of COPD exacerbations. In addition, the METREO study explored the dose-related effect of mepolizumab, and the METREX study explored efficacy in patients with low and higher blood eosinophil counts.

The METREO study was a phase III, randomized, placebo-controlled, double-blind, parallel-group trial involving 675 patients. Patients 40 years of age and older with COPD and a history of exacerbations despite ICS-based triple therapy were enrolled; patients were required to have blood eosinophil counts of 150 cells/ μL or greater at screening or 300 cells/ μL or greater in the previous year. These criteria were chosen because efficacy in patients with severe asthma became apparent at blood eosinophil counts of greater than this level.⁴³ Patients received subcutaneous mepolizumab at 100 or 300 mg or placebo in addition to an ICS/long-acting β -agonist/long-acting muscarinic antagonist every 4 weeks for 52 weeks. The primary end point was the annual rate of moderate (treatment with systemic corticosteroids, antibiotics, or both)/severe (hospitalization or death) exacerbations. Secondary end points included time to first moderate/severe exacerbation; the annual rate of exacerbations requiring an emergency department visit, hospitalization, or both; and mean change from baseline at week 52 in St George's Respiratory Questionnaire total score and COPD assessment test score.

The METREX study involved 837 patients meeting the same criteria for COPD and exacerbations as the METREO study but not selected on the basis of blood eosinophil count. A modified intention-to-treat population with a baseline blood eosinophil count of greater than 150 cells/ μL was prespecified ($n = 462$), and the primary outcome was the annual rate of moderate (treatment with systemic corticosteroids, antibiotics, or both)/severe (hospitalization or death) exacerbations in this modified intention-to-treat population. A meta-analysis of the annual rate of moderate/severe exacerbations stratified by screening blood eosinophil count categories was performed with data from METREO and METREX study subjects.

Both studies showed a modest but consistent reduction in the primary outcome measure. This was 18% in the METREX study, 20% with 100 mg of mepolizumab, and 14% with 300 mg of mepolizumab (Fig 2), with the latter 2 results just missing statistical significance after adjustment for multiple comparisons.

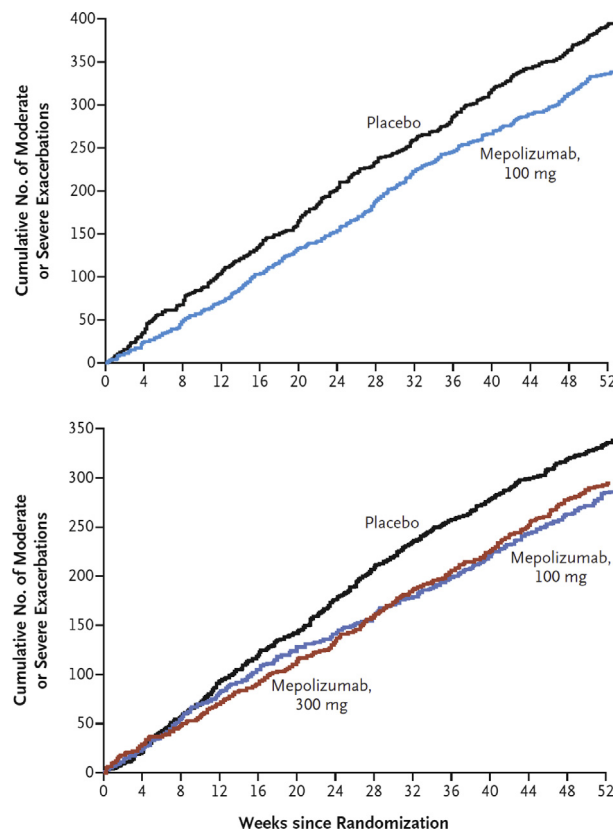


FIG 2. Cumulative incidence of moderate and severe exacerbations in the METREX (top) and METREO (bottom) studies. The METREX population was the modified intention-to-treat population, with a baseline blood eosinophil count of greater than 150 cells/ μL ($n = 462$). The METREO population had a baseline blood eosinophil count of greater than 150 cells/ μL or a history of a blood eosinophil count of greater than 300 cells/ μL in the previous year ($n = 675$). Mepolizumab (100 mg) is shown in blue, and mepolizumab (300 mg) is shown in brown.

Dropout rates were consistently greater with placebo treatment, but there was no effect of mepolizumab on lung function or quality-of-life scores. The combined meta-analysis showed a highly statistically significant 23% reduction in exacerbations in the 25% of patients with a baseline blood eosinophil count of greater than 300 cells/ μL . Interestingly, efficacy was only apparent against the 70% of exacerbations treated with oral corticosteroids, either with or without antibiotics (Fig 3).

The findings of the first phase 3 program of anti-IL-5 in patients with COPD are predictable. The large efficacy apparent in patients with severe eosinophilic asthma on exacerbations is diluted in a population selected based on possession of an alternative and dominant treatable trait (ie, fixed airflow limitation). The treated population were 96% Global Initiative for Chronic Obstructive Pulmonary Disease class D, and they had very severe disease with marked airflow limitation, severely impaired quality of life, and multiple comorbidities. It seems likely that these additional factors were the main cause of patient-reported morbidity. However, the ability to clearly define a responsive population in prespecified subgroups and the compelling evidence of a dose-response relationship between baseline blood eosinophil counts and efficacy against exacerbations (particularly those treated with oral corticosteroids) suggest that there will be a role for this treatment in selected patients.

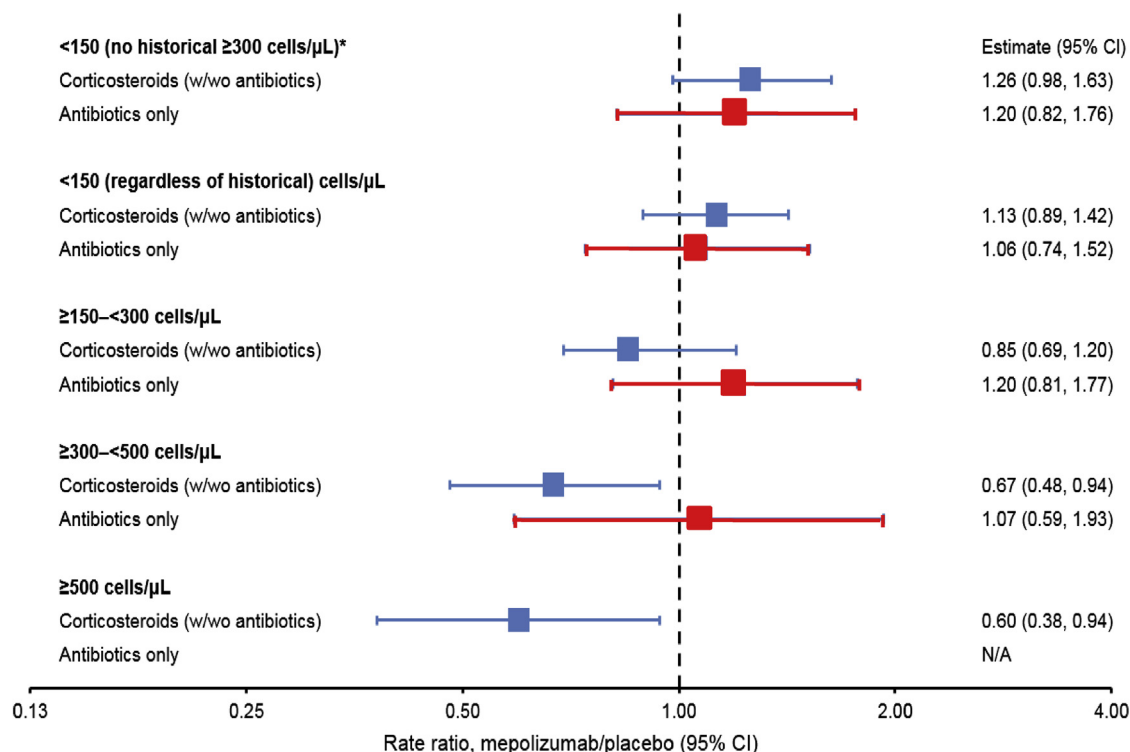


FIG 3. Mepolizumab-related reduction in exacerbations treated with oral corticosteroids with or without antibiotics (black) or with antibiotics alone (red) by baseline blood eosinophil count.

A larger phase 3 program with benralizumab is ongoing, and the findings are awaited with interest. In these studies the treated population has a baseline blood eosinophil count of greater than 300 cells/ μ L and can have less severe disease because not all the recruited patients are receiving triple-inhaled therapy. These factors suggest that more clear evidence of efficacy will be apparent. A phase 3 study of the IL-13 blocker lebrikizumab is also ongoing, although the disappointing efficacy of this agent in patients with severe asthma⁴⁴ suggests that this approach will be less successful.

There remains frustration that our ability to clearly demonstrate the clinical potential of anti-IL-5 biological agents has been compromised by a regulatory requirement to evaluate treatment in populations whose dominant problem has little to do with eosinophilic airway inflammation. What is needed is an entirely different clinical development program in which the focus is on patients in whom eosinophilic airway inflammation is a dominant treatable trait.⁹ Hopefully, the clinical development plan for future biological agents for COPD will adopt this approach.

NEUTROPHILIC AIRWAY INFLAMMATION AS A TARGET FOR BIOLOGICAL AGENTS IN PATIENTS WITH COPD

Neutrophilic airway inflammation is often viewed as the dominant potential treatable trait in patients with COPD.⁴ Induced sputum and bronchoscopy studies have shown increased numbers of activated neutrophils, which correlate with disease severity⁴⁵ and progression.⁴⁶ Neutrophils migrate into the respiratory tract under the direction of various neutrophil chemotactic factors, including leukotriene B₄, CXCL1, CXCL5, and CXCL8 released by epithelial cells, macrophages, and T cells and present in

increased amounts in the airway in patients with COPD (Fig 4).⁴ Neutrophils recruited to the airways secrete granule proteins, such as myeloperoxidase and serine proteases, including neutrophil elastase, which contribute to alveolar destruction.⁴

The clinical value of identifying and modifying neutrophilic airway inflammation in asthmatic patients and patients with COPD is much more uncertain than eosinophilic airway inflammation because subtypes and their likely cause are poorly understood.⁹ Moreover, the clinical benefits and safety of reducing neutrophilic airway inflammation nonspecifically are unclear. Some encouragement is provided by the significant reduction in exacerbations of COPD seen with long-term low dose macrolides⁴⁷ and by preliminary evidence of a marked reduction in sputum neutrophil counts⁴⁸ and clinical efficacy⁴⁹ of CXCR2 antagonists. Macrolides and CXCR2 antagonists have very different effects in smokers and ex-smokers, with the latter effectively reducing exacerbations in smokers⁴⁹ but not ex-smokers and the former having the opposite effect.⁵⁰ These findings need to be confirmed prospectively. However, they do suggest that there are at least 2 types of neutrophilic airway inflammation in patients with COPD, differing in their relationship with smoking and airway infection. The implication is that we might struggle to make progress until we have fully understood different subtypes of neutrophilic COPD and have ways of identifying them.

Several cytokines are associated with neutrophilic airway inflammation and are potential targets for biological treatment (Fig 4).

TNF- α

TNF- α is a pleiotropic cytokine that exerts a wide variety of biological effects and plays a dominant role in a number of

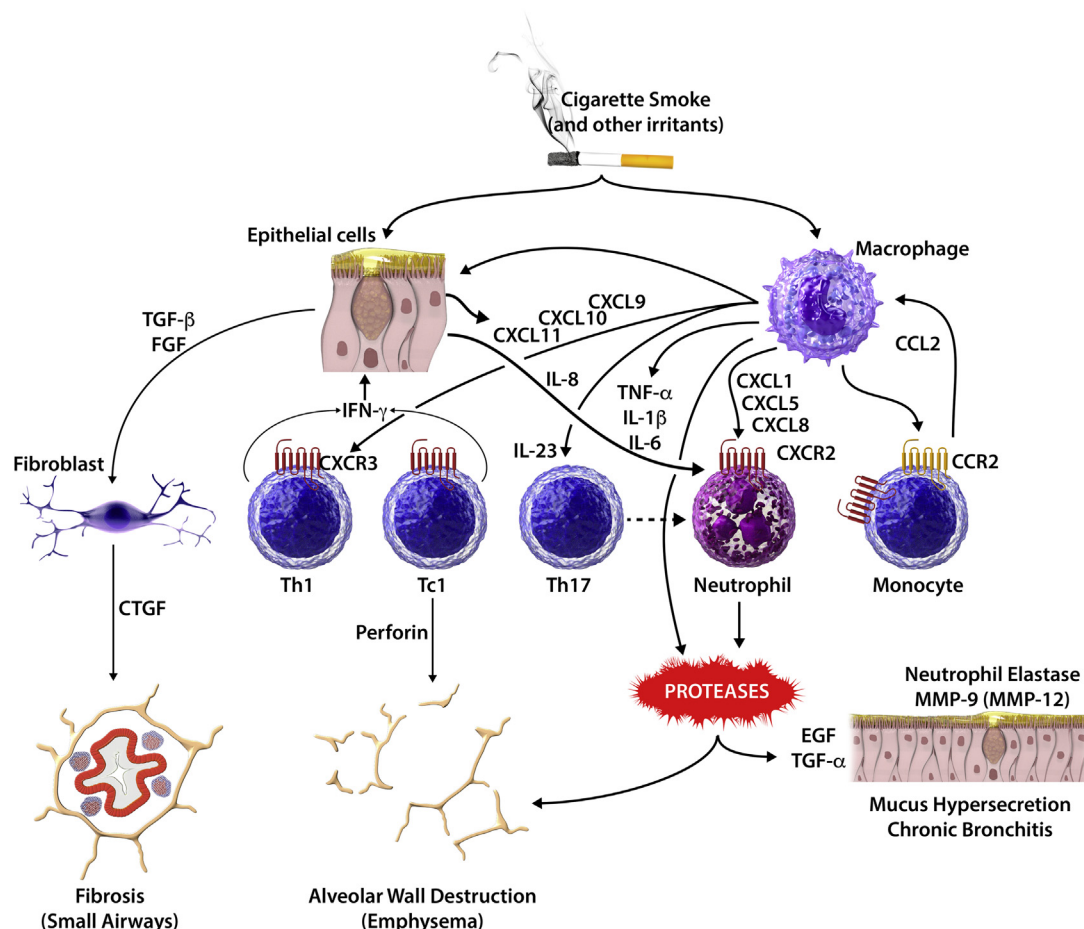


FIG 4. Neutrophilic airway inflammation in patients with COPD.⁴ Inhaled irritants, such as cigarette smoke, activate epithelial cells and macrophages to release chemotactic factors that attract inflammatory cells to the lungs and cytokines (ie, IL-17), which promotes neutrophilic inflammation. These inflammatory cells, together with macrophages and epithelial cells, release proteases, such as matrix metalloprotease (MMP) 9, which cause elastin degradation, emphysema, mucus hypersecretion, and fibrosis around the small airways. CTGF, Connective tissue growth factor; EGF, epidermal growth factor; FGF, fibroblast growth factor.

inflammatory conditions, including rheumatoid arthritis. It is produced mainly by activated macrophages as a monomeric type 2 transmembrane protein. This is cleaved by TNF- α -converting enzyme to a soluble circulating trimer, which is also biologically active.⁵¹

TNF- α is produced by relevant cells in response to cigarette smoke and has been shown in animal models to induce pathologic features associated with COPD. TNF- α levels are increased in peripheral blood, induced sputum, and bronchoalveolar lavage fluid of patients with stable COPD.^{51,52} Furthermore, a pathogenic role is suggested by the finding that polymorphism of the promoter region of the TNF- α gene has been implicated in the occurrence of COPD.⁵³

These cross-sectional studies provide a strong basis for clinical trials of biological agents targeting TNF- α . In general, these have been disappointing and have also identified a worrying safety signal. In a dose-finding placebo-controlled study of patients with moderate-to-severe COPD, 3 or 5 mg/kg infliximab for 24 weeks had no effect on health status, lung function, or severe exacerbation frequency.⁵⁴ Adverse events included pneumonia and a trend toward more cases of cancer. It is possible that a

more responsive population of patients with COPD in whom the safety signal is attenuated is present; biomarkers, such as C-reactive protein, might be useful for this purpose. For example, a health claims database observational study suggested that TNF- α antagonists given to treat rheumatoid arthritis prevented exacerbations, resulting in hospitalization in patients with both rheumatoid arthritis and COPD.⁵⁵ However, this effect was exclusively due to a reduction of 50% in the rate of COPD-related hospitalization with etanercept. The other TNF- α inhibitor under study, namely infliximab, did not reduce the risk of COPD-related hospitalization. Biomarker-directed therapy might also be effective because Berry et al⁵⁶ showed that membrane TNF- α levels were associated with the beneficial effect of etanercept in patients with severe asthma.

A recent small study population of cachectic patients with COPD revealed no change in levels of inflammatory markers in exhaled breath condensate and minor effects on systemic inflammatory markers after treatment with infliximab.⁵⁷ Etanercept has been evaluated in patients presenting with an exacerbation of COPD. Aaron et al⁵⁸ randomized 81 patients to prednisolone or a subcutaneous injection of etanercept in addition

to open-label treatment with levofloxacin. There was no treatment effect on the primary outcome, change in FEV₁, at 14 days or on treatment failure rates.

IL-1 β

Canakinumab neutralizes IL-1 β and has an established role in the treatment of familial cold autoinflammatory syndrome and Muckle-Well syndrome. A placebo-controlled phase 2 study showed no effect on various measures of lung function.⁵⁹ Med18968 inhibits the effect of IL-1 β and IL-1 α by blocking their common receptor (IL-1R1). This biological agent had no effect against exacerbations in a placebo-controlled study of 324 subjects with moderate-to-severe COPD.⁶⁰

IL-8

ABX-IL-8 is an mAb blocking IL-8, a key cytokine involved in neutrophil recruitment. In a placebo-controlled study of 109 patients with COPD and evidence of chronic bronchitis, treatment had a modest beneficial effect on the translational dyspnea index, which was only statistically significant at 2 weeks.⁶¹ No other beneficial effects were seen. The effects of IL-8 can be blocked by low-molecular-weight inhibitors of CXCR2. These agents have a strong biological effect, reducing induced sputum neutrophil counts in asthmatic patients,⁴⁸ but as discussed above, the clinical effects have been less impressive.⁴⁹

Other potential targets

IL-6 amplified neutrophilic airway inflammation and is present in increased concentrations in sputum from patients with COPD. An effective mAb, tocilizumab, has an established role in patients with rheumatoid arthritis but has not been evaluated in patients with COPD. IL-17 is also present in increased amounts in sputum from patients with COPD,⁶² and a range of biological agents inhibiting the T_H17 pathway are available, all showing impressive evidence of efficacy in psoriasis. No studies have yet been carried out in patients with COPD, although experience in patients with severe asthma has been disappointing.⁶³

CONCLUSIONS

The effects of biological agents in patients with COPD have thus far been mixed. This likely reflects the presence of multiple different inflammatory phenotypes of the disease and our inability to discriminate these or understand fully how they relate to disease-associated morbidity. Most progress has been made against eosinophilic airway inflammation. This process is measureable in routine clinical practice and has an acknowledged and well-understood role in the pathogenesis of exacerbations. Hopefully the progress can be an exemplar for progress with biological treatments more widely.

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