CONCISE CLINICAL REVIEW

Targeting Type 2 Inflammation and Epithelial Alarmins in Chronic Obstructive Pulmonary Disease

A Biologics Outlook

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Abstract

Chronic obstructive pulmonary disease (COPD) is a complex, heterogeneous, progressive inflammatory airway disease associated with a significant impact on patients' lives, including morbidity and mortality, and significant healthcare costs. Current pharmacologic strategies, including first- and second-line therapies such as long-acting β_2-agonists, long-acting muscarinic antagonists, inhaled corticosteroids, phosphodiesterase-4 inhibitors, and macrolides, provide relief to patients with COPD. However, many patients remain symptomatic, with persistent symptoms and/or acute exacerbations and progressive lung function loss. Although neutrophilic inflammation is the most common type of inflammation in COPD, 20–40% of patients with COPD exhibit type 2 inflammation, with roles for $CD4^+$ (cluster of differentiation 4) T-helper cell type 1 cells, type 2 innate lymphoid cells, eosinophils, and alternatively activated macrophages. On the basis of the current limitations of available therapies, a significant unmet need exists in COPD management, including the need for targeted therapies to address the underlying pathophysiology leading to disease progression, such as type 2 inflammation, as well as biomarkers to help select the patients who would most benefit from the new therapies. Significant progress is being made, with evolving understanding of the pathobiology of COPD leading to novel therapeutic targets including epithelial alarmins. In this review, we describe the current therapeutic landscape in COPD, discuss unmet treatment needs, review the current knowledge of type 2 inflammation and epithelial alarmins in COPD, explore potential biomarkers of type 2 inflammation in COPD, and finally provide a rationale for incorporating therapies targeting type 2 inflammation and epithelial alarmins in COPD.

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Triggered by exposure to cigarette smoke and other environmental factors, chronic obstructive pulmonary disease (COPD) is a complex, heterogeneous, chronic inflammatory airway disease characterized by persistent and poorly reversible airflow limitation and significant respiratory symptoms, including cough, shortness of breath, and sputum production (1, 2). The high prevalence of comorbidities, including cardiovascular disease, diabetes, and asthma, suggests the presence of common pathobiological processes, including smoking and underlying systemic inflammation, that can influence a number of related extrapulmonary conditions (3–5). Conceptually, our understanding of the features of COPD comes largely from later stages of the disease, because information regarding early disease is lacking (6). Although animal models have contributed much to our current knowledge, there are considerable gaps in our knowledge regarding the immunopathological mechanisms using samples from patients with COPD, which cannot be fully addressed by animal models.

COPD is a complex condition that involves the activation of multiple inflammatory cells, such as lymphocytes, neutrophils, macrophages, and eosinophils, which contribute to the inflammatory response (7, 8). Inflammation in COPD was originally believed to be driven solely by type 1 immune responses, including $CD4^+$ (cluster of differentiation 4) T-helper cell type 1 cells, $CD8^+$ cytotoxic T cells, macrophages, and neutrophils (7); however, 20–40% of patients with COPD exhibit type 2 inflammation (9–12), a feature more commonly associated with asthma involving $CD4^+$ T-helper cell type 2 (Th2) cells, type 2 innate lymphoid cells (ILC2s), eosinophils, and alternatively activated macrophages (7, 13). The relationship between type 2 inflammation in COPD and disease severity is incompletely understood, but type 2 inflammation has been associated with higher future exacerbation risk in patients with histories of exacerbation (10–14). Furthermore, the type 3 (Th17) inflammatory response has been also identified in patients with COPD.

Although some patients may have both COPD and asthma (e.g., in a person who has had asthma since childhood who smokes and then develops emphysema), type 2 inflammation can occur in patients with COPD without asthma (15, 16). Whether individuals with specific patterns of inflammation represent different phenotypes, stages, or types of COPD is not fully elucidated; however, it is plausible that the presence of type 2 inflammation represents a feature that may be amenable to therapeutic intervention (i.e., a treatable trait) (2).

Current management strategies for patients with COPD include important nonpharmacologic interventions, such as smoking cessation, pulmonary rehabilitation, and management of comorbidities, as well as pharmacologic interventions, typically a combination therapy with long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), sometimes combined with inhaled corticosteroids (ICSs). Additional treatments in more severe cases could include phosphodiesterase-4 inhibitors and intermittent macrolide antibiotics (2, 17). Available treatments lead to bronchodilation and may reduce exacerbation frequency, although a substantial proportion of patients with moderate to very severe COPD continue to have exacerbations despite receiving standard-of-care therapies (18–22).

In patients with COPD and elevated blood eosinophils, treatments targeting the IL pathway IL-5 have shown inconsistent efficacy (23–25), suggesting that targeting eosinophils alone may be insufficient to address the underlying type 2 inflammation present in these patients. In preclinical studies, IL-4 and IL-13 have been associated with airway remodeling and the destruction of lung parenchyma, common features of COPD (26–28). IL-4 and IL-13 also promote the activation and trafficking of type 2 inflammatory cells, including eosinophils, to further perpetuate inflammatory processes in the lungs (29–31), and are the key drivers of inflammation in other type 2 inflammatory diseases, such as asthma (32).

Unmet needs in COPD management include symptom alleviation and exacerbation prevention, slowing the progression of lung function decline, and improving health-related quality of life (2, 33). A tailored approach to treatment, in which a patient receives an individualized treatment plan according to both clinical and inflammatory characteristics, could maximize efficacy and improve risk–benefit ratios (34). In addition, there is a need to ensure that patients with COPD receive such treatments at the optimal time to slow the progression of disease. There exists a specific need for therapies targeting the underlying type 2 inflammation present in a proportion of patients with COPD, as well as predictive biomarkers to identify individuals most likely to benefit from these treatments.

The objectives of this review are *1*) to describe our current understanding of how the type 2 cytokines IL-4, IL-5, and IL-13 and the epithelial alarmins IL-33 and TSLP (thymic stromal lymphopoietin) contribute to clinical features of COPD, including airway remodeling and parenchymal destruction; *2*) to review the potential pharmacologic biomarkers in COPD; *3*) to discuss the unmet needs for treatment in COPD; and *4*) to review the current and developing therapeutic landscape targeting type 2 inflammation and epithelial alarmins in COPD.

Biology of Type 2 Inflammation in COPD

Type 2 inflammation is a specific pattern of immune response, classically believed to provide protection against parasitic infection but most studied for its role in allergy and allergic diseases, such as asthma, as well as nonallergic conditions, such as inflammatory bowel disease. Type 2 inflammation is characterized by the presence of Th2 cells and ILC2s, which secrete the type 2 inflammatory cytokines IL-4, IL-5, and IL-13 in response to epithelial-derived alarmins, including IL-33 and TSLP, as well as the presence of eosinophils, mast cells, and alternatively activated macrophages (7).

IL-4 and IL-13 are key drivers of type 2 inflammation. They signal through the shared receptor IL-4Rα, expressed by airway epithelial cells as well as innate and adaptive immune cells. IL-4 and IL-13 promote activation and trafficking of type 2 inflammatory cells, including eosinophils, to the lungs via the release of chemoattractants, in particular eotaxin-3 (also known as eosinophil chemotactic protein), from airway epithelial cells (29–31). IL-4 and IL-13 have been shown to impair rhinovirus-induced IFN-γ production via inhibition of Toll-like receptor signaling, leading to increased rhinovirus replication (35), an important finding given that exacerbations in COPD are often mediated by viral infection.

In a mouse model, targeted IL-13 expression in the lung resulted in the production of eotaxin, mononuclear and eosinophilic inflammation, mucus cell

metaplasia, and airway obstruction (36). A related study showed that pulmonary overexpression of IL-13 resulted in a phenotype resembling human COPD, with emphysema, enlarged lungs, mucus metaplasia, and a mixed inflammatory infiltrate that is typical of COPD (26). Preclinical studies demonstrate that, outside of orchestrating type 2 inflammatory responses, IL-4 and IL-13 can also contribute to airway remodeling and lung parenchyma destruction, as well as promoting mucus cell hyperplasia (26–28).

Eosinophilic inflammation can be stimulated directly by epithelial-derived alarmins and indirectly by epithelial-derived alarmin activation of ILC2s, which produce IL-5 and IL-13. Although eosinophilic inflammation may be a hallmark of pulmonary type 2 inflammation, the difficulty in demonstrating the efficacy of treatments targeting eosinophils in patients with COPD and higher blood eosinophil concentrations (24, 25) suggests that not all of this subgroup (with higher eosinophils) respond equally to this treatment strategy. This also suggests a potential role for other components of type 2 inflammation in COPD beyond eosinophils. Of six biomarkers widely cited in the asthma literature, four were significantly greater in patients with COPD with elevated blood eosinophil counts compared with those with low blood eosinophil counts, namely, sputum gene expression of eotaxin-3 (an eosinophil chemoattractant), calcium-activated chloride channel regulator (a regulator of chloride transport and mucus production), cystatin-SN (a type 2 cysteine protease inhibitor with a proposed role in regulating eosinophilic inflammation), and IL-13 (37). These results suggest that the pattern of type 2 inflammation observed in subsets of patients with COPD may include a wider profile of type 2 inflammation, in particular, IL-13–driven pathways that may contribute to airway remodeling and mucus secretion (37).

Biology of Alarmins in COPD

The epithelial-derived alarmins IL-33 and TSLP can influence both type 1 and type 2 inflammation and have been genetically implicated in COPD (38, 39). IL-33 is a member of the IL-1 family that drives both type 2 and non–type 2 inflammation (40). Epithelial damage signals increase the expression and secretion of IL-33, which acts as an alarmin in the airway epithelium (41), resulting in the recruitment and activation of both innate and adaptive immune cells through its transmembrane receptor, ST2 (suppression of tumorigenicity 2) (40). Specific influences of IL-33 signaling on immune cells include Th2 secretion of IL-4, IL-5, and IL-13 (42); skewing to a type 2 alternatively activated macrophage phenotype (43); and eosinophil degranulation and release of reactive oxygen species (44) (Figure 1).

Animal models suggest a role for IL-33 in COPD pathogenesis. Expression of IL-33 and ST2 is elevated in the lungs of mice exposed to cigarette smoke (45), and exogenous IL-33 treatment in mice results in airway inflammation and mucus secretion, hallmark clinical features of COPD (42). In a mouse model of persistent exacerbating airway disease with a mixed inflammatory phenotype, increased IL-33 concentrations in response to allergen challenge resulted in both inflammation and remodeling in the lung, essentially creating a self-perpetuating amplification of IL-33–mediated inflammation, in which persistent inflammation and remodeled tissue are primed for exacerbation (46). Blockade of the IL-33 pathway was able to normalize inflammation and improve tissue remodeling in this model (46).

Elevated expression of IL-33 and ST2 has been reported in patients with COPD. IL-33 mRNA and protein concentrations are increased in the airway epithelium of patients with COPD compared with control subjects (45, 47). Plasma IL-33 concentrations have also been reported to correlate with eosinophil counts and chronic bronchitis (48). Serum and sputum IL-33 concentrations are higher in patients with COPD with sputum eosinophilia compared with those without (49).

TSLP, another epithelial-derived alarmin, is an IL-7–like cytokine, signaling through the IL-7 receptor α and the TSLP receptor. TSLP is produced upon epithelial injury and responds by acting on $CD4^+$ T-helper cells, $CD8^+$ myotoxic T cells, B cells, mast cells, basophils, eosinophils, and innate lymphoid cells (50, 51). Direct effects of TSLP on eosinophils and ILC2s, as well as on dendritic cell antigen presentation and Th2 cell differentiation, contribute to enhanced type 2 inflammatory cytokine production in COPD (7) (Figure 1). In a genetic risk screening analysis, SNPs resulting in increased TSLP responses were associated with an independent risk of developing severe airflow obstruction in response to heavy smoking (39). TSLP concentrations are elevated in the airways of patients with COPD (52), and viral infection can increase the expression of TSLP in epithelial cells, suggesting a role for TSLP in COPD exacerbations (53). In bronchial biopsies, the number of cells expressing the TSLP receptor was higher in patients with severe COPD compared with healthy control smokers and nonsmokers, as well as in patients with mild or moderate COPD compared with healthy control smokers (54).

Biomarkers to Identify Patient Subgroups within the Heterogeneous COPD Population

Biomarkers play an important role in precision medicine approaches. Predictive biomarkers in clinical trials allow the enrichment of populations more likely to benefit from specific treatments, thus increasing the probability of success and reducing trial costs (14). Here we review the available literature on potential biomarkers of type 2 inflammation on COPD.

Blood eosinophil counts, a commonly used biomarker in asthma, are both a prognostic and a predictive biomarker in COPD (13, 20, 55). Many, although not all, studies have observed a relationship between circulating and lung eosinophil counts, suggesting that blood eosinophil counts can be used as a biomarker of eosinophilic lung inflammation (12, 56–58). Eosinophil counts in sputum are increased in some exacerbations, while bacterial infections may suppress eosinophil counts, complicating the clinical interpretation of this biomarker (11, 12).

Inconsistent results have been observed with respect to the association of blood eosinophil counts with COPD exacerbation rates (13, 58–61), as real-world studies are confounded by ICS use and different exacerbation histories. Analysis of data from non-ICS treatment arms from randomized clinical trials showed an association between higher circulating eosinophil counts and future exacerbation risk in subjects with histories of exacerbation (14). It is clear from large clinical studies that blood eosinophil counts are predictive of an enhanced response to both systemic corticosteroids and ICS (9, 11, 13, 14, 20, 55, 62). Blood eosinophil counts are therefore a biomarker

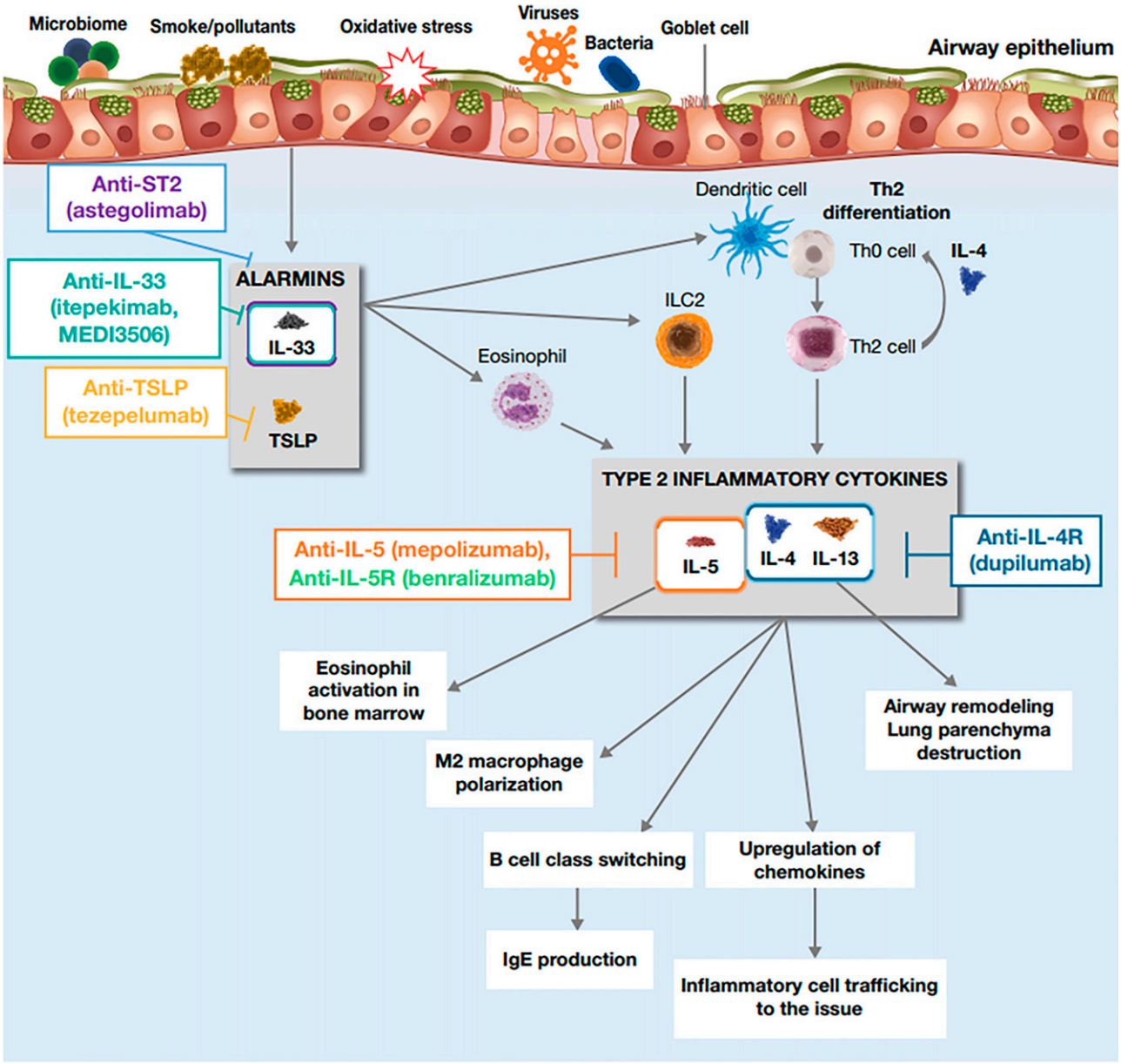

Figure 1. Type 2 inflammatory pathways in COPD. COPD = chronic obstructive pulmonary disease; ILC2 = type 2 innate lymphoid cell; ST2 = suppression of tumorigenicity 2; Th = T-helper cell; TSLP = thymic stromal lymphopoietin.

that can provide clinicians a more targeted approach to the use of ICSs, toward patients most likely to benefit.

Fractional exhaled nitric oxide (Fe_{NO}) is a biomarker of type 2 inflammation in asthma, indicating eosinophilic inflammation of the airways, driven by mediators including IL-13 (63). Among those with COPD, former smokers had higher Fe_{NO} than current smokers (64). A 2018 meta-analysis demonstrated mildly elevated Fe_{NO} in patients with COPD compared with healthy control subjects (64). A positive correlation was observed between sputum/blood eosinophils and Fe_{NO} in COPD (65–70). This correlation was observed in both stable patients with COPD, particularly those in Global Initiative for Chronic Obstructive Lung Disease category D and those with frequent exacerbations (65). Evidence exists for Fe_{NO} as a clinical biomarker of type 2 inflammation in COPD (71–76), and low Fe_{NO} has been associated with poorer lung function and quality of life (73). To date, data on the association between Fe_{NO} and COPD exacerbations have been inconsistent (70, 71, 73). Several studies have identified Fe_{NO} as a biomarker of ICS responsiveness in COPD (74, 75), with baseline Fe_{NO} values significantly correlating with improvements in lung function and quality of life after treatment with ICS (74). Perhaps, then, Fe_{NO} is a potential biomarker for identifying subgroups prone to exacerbation and could be a useful biomarker for predicting ICS responsiveness; however, to date, pivotal trials have not established Fe_{NO} as a predictive biomarker in COPD. In addition, smoking has been found

to reduce F_{ENO}, making smoking status a confounder in populations that combine both current and former smokers (77).

Serum periostin concentrations are associated with type 2 inflammation and ICS responsiveness in asthma; however, data on the role of periostin as a biomarker of type 2 inflammation in COPD are limited. One small study showed that periostin concentrations are elevated in current and former smokers with COPD compared with healthy smoking control subjects but did not correlate with measures of type 2 inflammation, airway remodeling, or ICS responsiveness in this patient population (78). A separate study revealed that high blood eosinophil counts and high concentrations of plasma periostin were associated with positive improvement in FEV_1 in patients with stable COPD in response to ICS/LABA treatment (79). Further studies are needed to better understand the potential predictive power of periostin in COPD.

Clinical Evidence for Targeting Type 2 Inflammation in COPD

Current Pharmacologic Management Strategies

Current pharmacologic strategies in COPD typically include a combination therapy with bronchodilators (LABAs and LAMAs) with the addition of ICSs in those at risk of exacerbations (1, 2, 17). A proportion of patients with moderate to very severe airflow limitation continue to have exacerbations despite receiving optimized therapy (20–22), suggesting that there are underlying features of COPD disease pathology that are not addressed by existing therapies. Indeed, some patients with COPD and high eosinophil counts continue to have COPD exacerbations, despite receiving triple therapy with LABAs/LAMAs/ICSs (19, 80, 81). Current maintenance therapies do not specifically target key type 2 inflammatory mediators. Additional therapeutic options include roflumilast, an oral phosphodiesterase-4 inhibitor, and macrolide antibiotic therapy (2). Roflumilast reduces eosinophil counts in tissue and sputum, but not circulating eosinophils, and has been shown to be most effective in those with elevated blood eosinophil counts at baseline (82, 83).

Despite the currently available management strategies, disease burden remains high for many patients with COPD. Particular subgroups of patients with COPD can be especially difficult to treat. One study reported that approximately half of patients with COPD have one or two comorbidities, the most common being cardiovascular disease, diabetes, asthma, and anemia (3). These comorbidities are believed to have shared underlying pathobiological mechanisms, including smoking and systemic inflammation (4, 84). The presence of these comorbidities significantly influences healthcare costs and use and independently increases the risk of death (5). Patients with COPD with concomitant asthma had the highest COPD- or asthma-related healthcare costs compared with any other comorbidities (3). The high prevalence of these comorbidities of COPD, associated with high healthcare costs and increased disease burden, indicates additional unmet need in optimizing treatment.

Novel Candidates Targeting Type 2 Inflammation and Alarmins in COPD

A number of novel candidate therapies targeting type 2 inflammation and alarmin cytokines are currently in development for the treatment of COPD (Table 1). Novel candidates for COPD therapeutics include those targeting eosinophils via the IL-5 pathway (mepolizumab and benralizumab), IL-4 and IL-13 signaling (dupilumab), the IL-33 pathway (itepekimab, tozorakimab, and astegolimab), and TSLP (tezepelumab) (Figure 1). Although overlap exists between these novel therapies for asthma and COPD, it is important not to simply apply the findings in asthma to COPD but rather to understand the efficacy of these drugs in targeted COPD subgroups.

Several clinical trials of antibodies targeting eosinophils via the IL-5 pathway have been completed in patients with COPD and elevated blood eosinophil counts, with inconsistent efficacy on exacerbation reduction (23–25). Mepolizumab, an anti–IL-5 antibody, demonstrated some degree of exacerbation reduction, but only in patients with the highest blood eosinophil counts, particularly in those experiencing systemic corticosteroid-treated exacerbations (24). Studies of benralizumab, an antibody targeting the IL-5 receptor, did not demonstrate a reduction in COPD exacerbation rates (23, 25). A *post hoc* analysis of the phase 3 benralizumab trials found that the subgroup of patients receiving triple therapy, with elevated baseline blood eosinophil counts and three or more exacerbations in the prior year, were most likely to benefit from treatment (85). Follow-up phase 3 studies of both mepolizumab and benralizumab are ongoing, with both trials including a requirement for baseline blood eosinophil counts $\geqslant$300 cells/μl at screening and documented historical $\geqslant$150 cells/μl within 52 weeks of enrollment, as well as a history of prior exacerbations treated with systemic corticosteroids (NCT04133909 and NCT04053634), respectively.

Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation, thus inhibiting their signaling (35). In the recently completed phase 3 BOREAS (Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-Severe COPD with Type 2 Inflammation) trial, dupilumab was investigated in patients with COPD with moderate or severe exacerbations while on ICSs, LAMAs, and LABAs (or LAMAs and LABAs, if ICSs were contradicted) and baseline blood eosinophil counts $\geqslant$300 cells/μl. Dupilumab demonstrated a 30% reduction in moderate to severe COPD exacerbations over 52 weeks versus placebo and significantly improved lung function from baseline by 160 ml compared with 77 ml for placebo by Week 12 (86). Dupilumab also significantly improved measures of health-related quality of life and alleviated respiratory symptoms. The observed reduction in exacerbations and improvements in lung function support an important role of IL-4 and/or IL-13 in this COPD subpopulation and of these cytokines in type 2 inflammation. Through inhibition of IL-4/IL-13, dupilumab may play a role in mucus hypersecretion, airway remodeling, and reducing goblet cell hyperplasia. One possibility is that dupilumab may have improved airway obstruction through reduced mucus hypersecretion and hence improved lung function that may reflect an improvement in air trapping. These mechanisms of action could all theoretically contribute to improvements in exacerbations, lung function, and bronchitis symptoms (87, 88).

Epithelium-derived alarmin cytokines such as IL-33 and TSLP can regulate both type 1 and type 2 immune responses and are therefore attractive targets for biologic therapy in patients with COPD. In a phase 2a

Table 1. Clinical Trials of Agents Targeting Type 2 Inflammation in COPD and Associated Evidence

Target	Inhibitor	Study	Asthma Exclusions	Blood Eosinophils	Results
IL-5	Mepolizumab, 100 mg Q4W	Ph3 METREX	Excluded patients with current asthma in current/former smokers and history of asthma in nonsmokers	No cutoff; stratification by blood eosinophil	Completed Primary endpoint: annual rate of moderate or severe exacerbations Results: reduced exacerbations in those with highest baseline blood eosinophils (23)
	Mepolizumab, 100 mg Q4W, 300 mg Q4W	Ph3 METREO	Excluded patients with current asthma in current/former smokers and history of asthma in nonsmokers	⩾150 cells/μl at screening or ⩾300 cells/μl in past year	Completed Primary endpoint: annual rate of moderate or severe exacerbations Results: primary and secondary endpoint results were not significant (23)
	Mepolizumab, 100 mg Q4W	Ph3 MATINEE	Excluded patients with current diagnosis or history of asthma	⩾300 cells/μl at screening and documented historical ⩾150/μl within 12 mo to 1 mo before screening or visit 1	Estimated primary completion: July 2023 Primary endpoint: annualized rate of moderate* or severe† exacerbations https://clinicaltrials.gov/ct2/show/NCT04133909
IL-5Rα	Benralizumab, 30 mg Q4W/Q8W, 100 mg Q4W/Q8W	Ph3 GALATHEA	Excluded patients with asthma as a primary or main diagnosis according to GINA guidelines or other	Stratification by blood eosinophils; cap for blood eosinophil counts	Completed Primary endpoint: annualized COPD exacerbation Rate ratio in patients with baseline blood eosinophil counts >220 cells/μl Results: no reduction in annualized exacerbation rate ratios vs. placebo (24)
	Benralizumab, 10 mg Q4W/Q8W, 30 mg Q4W/Q8W, 100 mg Q4W/Q8W	Ph3 TERRANOVA	Excluded patients with asthma as a primary diagnosis according to GINA guidelines or other	Stratification by blood eosinophils; cap for blood eosinophil counts	Completed Primary endpoint: annualized COPD exacerbation Rate ratio in patients with baseline blood eosinophil counts >220 cells/μl Results: no reduction in annualized exacerbation rate ratios vs. placebo (24)
	Benralizumab, 100 mg Q4W (first three doses) and Q8W	Ph3 RESOLUTE	Excluded patients with current diagnosis or history of asthma or asthma/COPD overlap, excluding resolved childhood asthma	⩾300 cells/μl at screening and documented historical ⩾150/μl within 52 wk of enrollment	Estimated primary completion: March 2024 Primary endpoint: annualized rate of moderate* or severe† exacerbations https://clinicaltrials.gov/ct2/show/NCT04053634
IL-4Rα	Dupilumab, Q2W	Ph3 BOREAS	Excluded patients with current diagnosis or history of asthma	⩾300 cells/μl at visit 1	Completed Primary endpoint: annualized rate of moderate* or severe† exacerbations https://clinicaltrials.gov/ct2/show/NCT03930732

(*Continued*)

Table 1. (*Continued*)

Target	Inhibitor	Study	Asthma Exclusions	Blood Eosinophils	Results
	Dupilumab, Q2W	Ph3 NOTUS	Excluded patients with current diagnosis or history of asthma	⩾300 cells/μl at visit 1	Estimated primary completion: April 2024 Primary endpoint: annualized rate of moderate* or severe† exacerbations https://clinicaltrials.gov/ct2/show/NCT04456673
IL-33	Itepekimab, Q2W	Ph2	Excluded patients with asthma	No cutoff	Completed Primary endpoint: annualized rate of moderate to severe acute exacerbations of chronic obstructive pulmonary disease Results: reduced exacerbations and improved lung function in subgroup of former smokers (37)
	Itepekimab, Q2W, Q4W in former smokers	Ph3 AERIFY-1	Excluded patients with current diagnosis or history of asthma	No cutoff	Estimated primary completion: December 2023 Primary endpoint: annualized rate of acute moderate* or severe† exacerbations https://clinicaltrials.gov/ct2/show/NCT04701983
	Itepekimab, Q2W in current and former smokers, Q4W in former smokers	Ph3 AERIFY-2	Excluded patients with current diagnosis or history of asthma	No cutoff	Estimated primary completion: February 2024 Primary endpoint: annualized rate of acute moderate* or severe† exacerbations in former smokers https://clinicaltrials.gov/ct2/show/NCT04751487
	MEDI3506, NR	Ph2 FRONTIER-4	Excluded patients with asthma	No cutoff	Estimated primary completion: March 2023 Primary endpoint: change from baseline to Week 12 in prebronchodilator FEV_1 https://clinicaltrials.gov/ct2/show/NCT04631016
ST-2 (IL-33R)	Astegolimab, 490 mg Q4W	Ph2a COPD-ST2OP	Excluded patients with known respiratory disorders other than COPD	No cutoff	Completed Primary endpoint: frequency of moderate to severe exacerbations Results: no reduction in exacerbation rates in the ITT population (86)
	Astegolimab, Q2W or Q4W, dose NR	Ph2b	Excluded patients with asthma	No cutoff	Estimated primary completion: May 2024 Primary endpoint: annualized rate of moderate and severe COPD exacerbations https://clinicaltrials.gov/ct2/show/NCT05037929

(*Continued*)

Table 1. (*Continued*)

Target	Inhibitor	Study	Asthma Exclusions	Blood Eosinophils	Results
TSLP	Tezepelumab, Q4W, dose NR	Ph2 COURSE	Excluded patients with asthma	No cutoff	Estimated primary completion: February 2023 Primary endpoint: moderate or severe COPD exacerbation rate ratio (tezepelumab vs. placebo) https://clinicaltrials.gov/ct2/show/NCT04039113

Definition of abbreviations: AERIFY-1 = Study to Assess the Efficacy, Safety, and Tolerability of SAR440340/REGN3500/Itepekimab in Chronic Obstructive Pulmonary Disease; AERIFY-2 = Study to Assess the Efficacy, Safety, and Tolerability of SAR440340/REGN3500/Itepekimab in Chronic Obstructive Pulmonary Disease; BOREAS = Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients With Moderate-to-Severe COPD with Type 2 Inflammation; COPD = chronic obstructive pulmonary disease; COPD-ST2OP = Anti-ST2 (MSTT1041A) in COPD; COURSE = Tezepelumab COPD Exacerbation Study; FRONTIER-4 = A Phase II, Randomized, Double-Blind, Placebo-controlled Study to Assess MEDI3506 in Participants with COPD and Chronic Bronchitis; GALATHEA = Benralizumab Efficacy in Moderate to Very Severe Chronic Obstructive Pulmonary Disease with Exacerbation History; GINA = Global Initiative for Asthma; ITT = intention-to-treat; MATINEE = Mepolizumab as Add-On Treatment in Participants with COPD Characterized by Frequent Exacerbations and Eosinophil Level; METREO = Efficacy and Safety of Mepolizumab as an Add-On Treatment in Chronic Obstructive Pulmonary Disease; METREX = Study to Evaluate Efficacy and Safety of Mepolizumab for Frequently Exacerbating Chronic Obstructive Pulmonary Disease Patients; NOTUS = Pivotal Study to Assess the Efficacy, Safety and Tolerability of Dupilumab in Patients with Moderate to Severe COPD with Type 2 Inflammation; NR = not reported; Ph = phase; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; RESOLUTE = Efficacy and Safety of Benralizumab in Moderate to Very Severe Chronic Obstructive Pulmonary Disease With a History of Frequent Exacerbations; TERRANOVA = Efficacy and Safety of Benralizumab in Moderate to Very Severe Chronic Obstructive Pulmonary Disease with Exacerbation History; TSLP = thymic stromal lymphopoietin.
*Acute worsening of respiratory symptoms that requires systemic corticosteroids and/or antibiotics.
†Acute exacerbations of COPD that require hospitalization or observation for ⩾24 hours.

study with 343 participants, itepekimab, an anti–IL-33 antibody, did not significantly reduce acute exacerbations despite decreasing blood eosinophil counts in the intention-to-treat (ITT) population but significantly reduced exacerbations and improved lung function in the subgroup of former smokers (38). The mechanisms involved in the differential efficacy of itepekimab in former versus current smokers are still being elucidated, but smoking is known to have broad proinflammatory effects and has been associated with decreased circulating IL-33 concentrations (38, 48). Two ongoing phase 3 studies are designed to further elucidate the efficacy of itepekimab in former smokers with COPD (NCT04701983 and NCT04751487).

In a phase 2a study of the ST2 (an IL-33 receptor) inhibitor astegolimab in 81 participants, no significant reduction in exacerbation rates was observed in the ITT population, but there was a reduction in exacerbations with astegolimab versus placebo in the subgroup with baseline blood eosinophil counts $<$300 cells/μl (86). In the ITT population, astegolimab provided a significant improvement in quality of life compared with placebo and also reduced circulating eosinophil counts. An intriguing observation from this study comes from a subgroup analysis demonstrating a relationship between higher baseline eosinophil counts and greater effects of astegolimab on lung function and quality of life, but lesser effects on COPD exacerbations, compared with those with lower baseline eosinophil counts. The differential effects of astegolimab on exacerbations compared with lung function and quality of life suggest the presence of different pathways contributing to different aspects of disease pathology (89). A phase 2b study of astegolimab is currently ongoing (NCT05037929). Phase 2 studies of the IL-33 inhibitor tozorakimab (NCT04631016) and the anti-TSLP antibody tezepelumab (NCT04039113) are also ongoing.

The results of these phase 2 studies targeting the IL-33 pathway illustrate the heterogeneity of COPD, as well as the potential ability of precision medicine to target treatments to specific groups of patients most likely to benefit (87). Both itepekimab and astegolimab reduced blood eosinophil counts and increased FEV_1; whereas itepekimab reduced exacerbations only in the subgroup of former smokers, astegolimab had the greatest effect on

exacerbation reduction in the subgroup with lower baseline eosinophil counts (38, 89). The differing effects of these two therapies may potentially be explained by differences in targeting the cytokine compared with the receptor. If confirmed in larger studies, the efficacy in particular subpopulations of COPD may describe clinical characteristics and treatable traits to inform treatment decisions and deliver precision medicine approaches to patients with COPD.

Conclusions

It is clear that COPD pathophysiology is complex and yet to be fully elucidated. Our expanding understanding of COPD pathophysiology, combined with advances in predictive biomarkers in COPD, holds the promise for a more precise medicine approach to COPD management. Ultimately, the goals are to identify certain homogeneous patient subgroups within the heterogeneous COPD population that may respond to biologics, to provide patient-tailored disease management, to stall or prevent progressive disease, and to preserve quality of life. The clinical trial evidence so far indicates a high potential for the targeting of type 2 cytokines and epithelial-derived alarmins to achieve these goals. ■

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