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Review

A review of current and prospective therapeutic approaches in the treatment of chronic obstructive pulmonary disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a progressive, heterogeneous disease representing a major socioeconomic burden and the fourth leading cause of death worldwide. Its complex pathogenesis, characterized by chronic inflammation and irreversible airway obstruction, justifies the current use of bronchodilators and anti- inflammatory drugs, although these treatments are often insufficiently effective. The aim of this review is to summarize and critically evaluate current and emerging therapeutic strategies for COPD, with a particular focus on biologically targeted treatments and novel pharmacological approaches.
Material and methods: Monoclonal antibodies such as dupilumab and mepolizumab have shown promising clinical efficacy. Dupilumab was recently approved by the U.S. Food and Drug Administration (FDA) for patients with uncontrolled COPD and eosinophilic inflammation. The dual PDE3/4 inhibitor ensifentrine, also FDA-approved, exhibits both bronchodilatory and anti- inflammatory properties. Another potential agent from this group is tanimilast. Additionally, ongoing research explores other compounds targeting various aspects of COPD pathogenesis.
Conclusion: Due to the disease's complex nature, unmet therapeutic needs remain. Continued investigation into biological markers and innovative treatments may enable more effective, personalized management of COPD, improving clinical outcomes and quality of life.

Keywords: biomarkers, chronic obstructive pulmonary disease, inflammation, monoclonal antibodies, phosphodiesterase inhibitors, precision medicine

1. Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, accounting for an estimated 3.5 million deaths in 2021 [according to data from the World Health Organization (WHO)] [1, 2]. Globally, the prevalence of COPD in 2020 was estimated at 10.6% among both men and women, corresponding to approximately 480 million cases. This figure is projected to rise by 112 million by 2050, reaching a total of 592 million cases, which represents a relative increase of 23.3% [3].

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is a complex respiratory condition marked by persistent symptoms such as shortness of breath, coughing, mucus production and exacerbations. These symptoms result from structural changes in the airways (like bronchitis and bronchiolitis) and/or damage to the alveoli (such as emphysema), ultimately resulting in persistent and often advancing obstruction of airflow [4].

For a long time, COPD was regarded as a smoker's disease- a fatal condition primarily diagnosed in older adults, with limited treatment options. However, research demonstrates there is a complex interaction of multiple risk factors, both genetic and external, that can damage the lungs or disrupt their normal development or aging processes [1, 4]. Various factors contribute to the development of COPD, with cigarette

smoking and inhalation of harmful particles and gases from air pollution identified as the main environmental exposure [4]. Occupational exposure to various industrial and agricultural dusts and fumes is also significant [5]. Smoking accounts for over 70% of COPD cases in high-income countries. In low- and middle-income countries, smoking is responsible for approximately 30-40% of cases, with household air pollution being the predominant cause [2]. The most significant (albeit epidemiologically rare) genetic risk factor identified to date is mutation in the SERPINA1 gene, resulting in α1-antitrypsin deficiency (α1-AT). Other genetic variants with smaller individual effects are also associated with reduced lung function and increased risk of developing COPD [4]. In addition, external risk factors may act additively with an individual's underlying genetic predisposition, damage to the respiratory tract caused by prenatal smoke exposure or childhood infection, thereby increasing the incidence of this disease [5]. COPD should therefore be considered a spectrum of lung conditions that require personalized therapeutic approaches [1].

COPD, as a debilitating and progressive disease, significantly impairs patient's quality of life- it is the eighth leading cause of poor health worldwide [(measured in disability- adjusted life years (DALY)] [2]. The disease negatively affects the ability to perform daily activities, physical activity, sleep, coexisting anxiety and depression, especially in the face of the risk of exacerbations and disease progression [6]. Multimorbidity is also characteristic of COPD patients. The pathogenesis of COPD is associated with pathologies of the cardiovascular, endocrine, musculoskeletal, renal and gastrointestinal systems, further reducing the quality of life of patients and complicating treatment. The most frequently reported comorbidities include skeletal muscle wasting, cachexia, lung cancer (small cell or non-small cell), pulmonary hypertension, ischemic heart disease, congestive heart failure, hyperlipidemia, diabetes, metabolic syndrome, osteoporosis, arthritis, obstructive sleep apnea and depression. These complex interactions are based, among other factors, on many common predisposing factors, chronic hypoxia, and low-grade systemic inflammation and are currently the subject of numerous studies [7].

In addition to its clear impact on significantly reducing patients' quality of life, COPD also constitutes a major socioeconomic burden- both in terms of direct costs to healthcare systems and indirect costs to society, particularly in countries with a low sociodemographic index [8, 9]. Pharmacotherapy also remains an important issue. Although treatment regimens are tailored to individual patient needs, they are still primarily based on inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA), and long-acting muscarinic antagonists (LAMA). Despite recent advances in this field and the availability of guideline-recommended therapies, current treatment turns out insufficient for many COPD patients. This, combined with the high prevalence of the disease, indicates a significant clinical and economic burden and highlights the need for continued research into alternative therapeutic strategies [9].

There is therefore still an unmet need for a better understanding of the pathophysiology of the disease and more effective diagnosis and treatment. Innovations in genomics and imaging techniques have provided deeper insight into the pathobiology of COPD, offering a promising starting foundation for improving the effectiveness of the therapy. Although few new treatments for COPD have been approved in recent years, progress has been made in developing more personalized therapeutic options based on novel biomarker-driven strategies [10]. Such possibilities are offered by monoclonal antibodies such as mepolizumab, dupilumab and several other potentially effective biologics, as well as phosphodiesterase (PDE) inhibitors such as ensifentrine and tanimilast. In addition, ongoing research is exploring a variety of other compounds that may prove effective in the treatment of COPD.

Given the growing prevalence, complex pathophysiology, and significant clinical and socioeconomic impact of COPD, there is a clear need to explore and evaluate new therapeutic options beyond standard pharmacotherapy. Despite existing guidelines, many patients remain symptomatic and at risk of progression, indicating treatment gaps and the necessity of more personalized approaches. Recent research highlights the potential of targeted biological therapies and novel pharmacological compounds that act on specific mechanisms of disease development. However, evidence is still emerging, and some approaches remain controversial or insufficiently validated. The aim of this article is to provide a comprehensive narrative review of current and emerging therapeutic strategies for COPD, with particular emphasis on biologically targeted treatments, including monoclonal antibodies and phosphodiesterase inhibitors. By synthesizing available evidence, this review seeks to identify knowledge gaps and highlight promising directions for future research to support more effective and individualized management of COPD.

2. Materials and methods

This review was based on an extensive analysis of the available scientific literature concerning the pathogenesis and modern treatment strategies in COPD. The literature search was conducted between February and April 2025 using electronic databases such as PubMed, Google Scholar, ScienceDirect and ClinicalTrials.gov, along with official websites of key institutions including the World Health Organization

(WHO), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the American Thoracic Society (ATS).

Publications were selected based on their scientific relevance, publication date (with a focus on studies published after 2015) and methodological quality. Preference was given to peer- reviewed original research articles, systematic reviews, meta-analyses, and randomized clinical trials. Additionally, authoritative guidelines, editorials and position papers were included to provide a broader clinical and regulatory context.

In total, over 80 publications were analyzed, covering both basic research on the pathogenesis of COPD and the latest data on innovative treatment methods.

3. Pathogenesis of COPD and potential therapeutic targets and opportunities for personalized therapy

The pathogenesis of COPD is complex, however two primary pathological processes can be distinguished: emphysema and chronic bronchitis. Emphysema involves the destruction of alveoli, leading to decrease surface area available for gas exchange. Chronic bronchitis, in contrast, is characterized by chronic inflammation of the bronchi, causing excessive mucus production and airway obstruction [10, 11]. In reality, this disease is characterized by a complex interplay between molecular mechanisms that drive its development and progression. A thorough understanding of these fundamental processes is essential for identifying potential therapeutic targets and for formulating personalized treatment strategies [11].

3.1 Inflammation

Inflammation is a fundamental driver of COPD development by activating immune reactions throughout the respiratory system [11] and is associated with an abnormal innate response to harmful particles and gases [12]. The predominant form of inflammation in COPD is neutrophilic (neutrophilic endotype), which is strongly dependent on IL- 1α [13, 14]. In addition to the increased influx of neutrophils, impaired clearance of these cells is also observed, which may result from defective phagocytic responses by alveolar macrophages. Cigarette smoke further hinders the elimination of neutrophils by stimulating the release of pro- inflammatory cytokines such as TNF- α, IL- 6 or IL- 8. In this context, neutrophil count may serve as a biomarker correlating with the rate of lung function decline [14]. An important mediator is also IL- 17A- a key cytokine produced by Th17 cells, which induces the release of two crucial molecules by pulmonary macrophages: chemokine ligand CCL20- a chemoattractant for dendritic cells involved in perpetuating this inflammatory loop and matrix metalloproteinase 12 (MMP- 12)- a potent enzyme that degrades the protective lung antiprotease α1- antitrypsin (α1- AT) [15]. However, around 10- 40% of COPD patients exhibit an eosinophilic endotype, associated with type 2 immune responses, in which Th2 lymphocytes as well as type 2 innate lymphoid cells (ILC2s) play a central role. Following exposure to smoke, pollutants or pathogens, epithelial cells release alarmins, such as thymic stromal lymphopoietin (TSLP), IL- 33 and IL- 25, promoting differentiation of naïve T cells into Th2 cells producing IL- 4, IL- 5 and IL- 13 [16]. This immune cascade activates eosinophils, basophils and mast cells, induces immunoglobulin E (IgE) production and enhances epithelial activity, resulting in mucus hypersecretion, airway hyperresponsiveness and remodeling [17]. IL- 4 may contribute to elevated IgE in the eosinophilic COPD subtype, potentially worsening lung function [14]. These cytokines involved in the described pathways represent potential therapeutic targets for biological agents directed against IL- 5, IL- 4, IL- 13 and IL- 17. Taken together, these two inflammatory endotypes capture the major immunological heterogeneity of COPD and provide the biological rationale for endotype- driven therapeutic strategies. A summary of these two types of inflammation predominant in COPD is presented in Figure 1.

3.2 Lung tissue remodelling

COPD by structural remodeling of lung tissue, including alterations in both the airways and alveoli [11]. Chronic exposure to tobacco smoke and airborne pollutants disrupts airway epithelial integrity, impairing innate immune functions and significantly contributing to airflow obstruction [18]. Persistent epithelial repair and regeneration lead to pathological remodeling, most notably squamous, observed in the majority of smokers. This indicates that that although inflammation mediated by immune mechanisms plays a major role in COPD pathogenesis, one of the earliest abnormalities in smokers appears to be structural changes within the small airways (those less than 2 mm in diameter) [10, 18, 19]. Squamous metaplasia is often accompanied by fibrotic changes as well as hypertrophy/ hyperplasia/metaplasia of goblet (mucus-producing) cells [18]. As COPD progresses, airway pathology intensifies, including mucus accumulation, immune cell infiltration and airway wall thickening. In the lung parenchyma, components of the extracellular matrix are degraded (proteolysis), whereas in the bronchi and bronchioles, excessive deposition of these components leads to fibrosis. Thus, tissue remodeling in COPD results from an imbalance between proteolytic and antiproteolytic activity [10, 18]. Myofibroblasts play a critical effector role in airway fibrosis and are therefore considered potential molecular targets for therapeutic intervention in COPD [18]. A graphical overview of these processes is presented in the figure below (Figure 2).

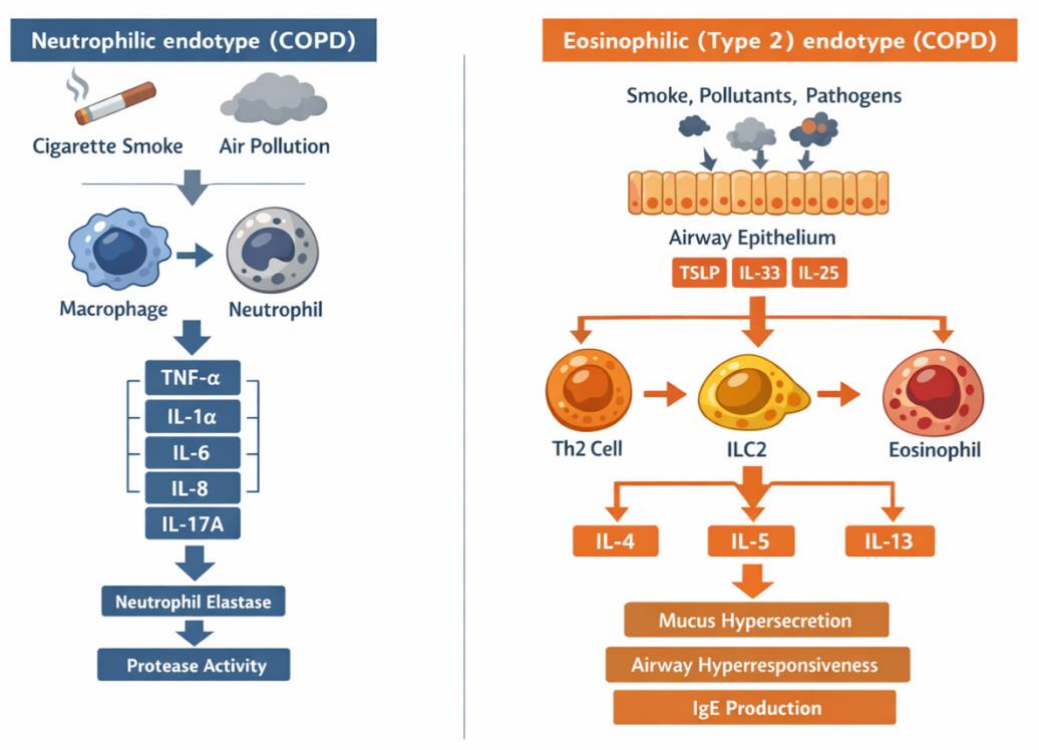

Figure 1. Neutrophilic and eosinophilic inflammation in COPD [own elaboration]**.** Lung tissue remodeling

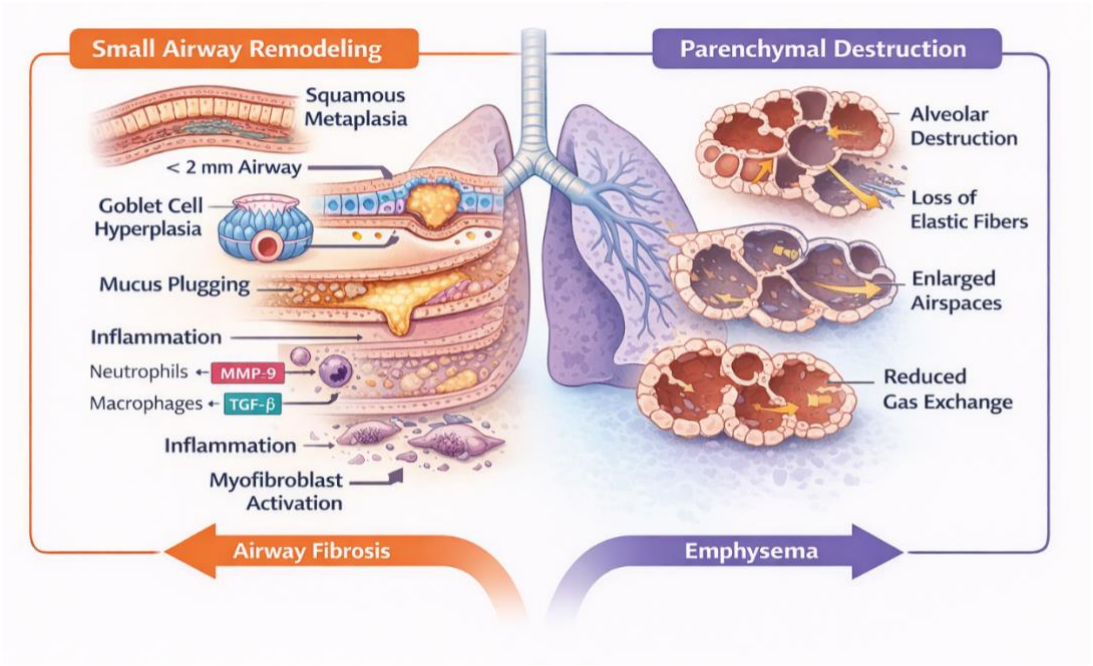

Figure 2. Lung tissue remodeling in COPD [own elaboration]

3.3 Imbalance between proteolytic and antiproteolytic activity

As previously mentioned, a fundamental pathogenic mechanism underlying COPD is the disruption of the protease- antiprotease balance, marked by excessive proteolytic activity coupled with insufficient inhibition of proteases within the pulmonary microenvironment [11, 20]. Serine proteases, such as neutrophil elastase (NE) and proteinase 3 (PR3), are secreted by activated inflammatory cells and contribute to tissue injury by degrading components of the extracellular matrix, ultimately compromising lung architecture. On the other hand, endogenous antiproteases, including α1- antitrypsin (α1- AT), are essential for counteracting protease activity

and preserving tissue integrity. A genetic deficiency or functional impairment of α1- AT is known to predispose individuals to early-onset emphysema, highlighting the critical role of protease- antiprotease balance in COPD susceptibility [11].

3.4 Oxidative stress

In patients with COPD, there is a marked increase in oxidative stress within the lungs, as evidenced by elevated levels of exhaled biomarkers such as 8- isoprostane, ethane, and hydrogen peroxide. Pulmonary tissues are subjected to both exogenous oxidative stress- primarily from cigarette smoke and air pollution- and endogenous oxidative stress, which arises from reactive oxygen species (ROS) released by activated inflammatory cells, particularly neutrophils and macrophages in the lungs. This oxidative environment contributes to disease progression and exacerbations by promoting chronic inflammation, accelerating cellular senescence, impairing autophagy and DNA repair mechanisms, enhancing autoimmune responses, increasing mucus production, and reducing the anti-inflammatory efficacy of corticosteroids. These findings suggest that antioxidant therapies may offer potential as disease- modifying treatments in COPD [21].

3.5 Genetic susceptibility

The most significant genetic risk factor for COPD is mutation in the *SERPINA1* gene, which encodes α1-antitrypsin (α1- AT), a member of the serpin (serine protease inhibitor) family. Deficiency of α1- AT (commonly referred to as α1-antitrypsin deficiency or α1- ATD) significantly increases the risk of developing early- onset COPD and emphysema, particularly in individuals who smoke, though it accounts for only 1- 3% of all COPD cases [22]. Despite its rarity, the genetic contribution to COPD may be relevant in as many as 40% to 70% of patients, although many of the known genetic variants occur only in small subsets of the population. These variants have been identified primarily through genome- wide association studies (GWAS), which have highlighted genes involved in inflammatory pathways (e.g., IL-6, TNF), antioxidant defenses (e.g., glutathione S- transferases) and lung development (e.g., surfactant proteins) [10,11]. Epigenetic modifications- such as impaired microRNA regulation, histone acetylation/deacetylation and abnormal DNA methylation can influence gene expression in response to environmental factors. For instance, cigarette smoke may alter the epigenetic profile of airway epithelial cells and lung macrophages, which in turn affects COPD susceptibility and promotes disease progression [11, 23]. This area of research continues to evolve and represents a promising avenue for future discoveries, particularly in identifying novel therapeutic targets and personalized approaches to COPD management.

An overview of the pathogenic mechanisms involved in COPD, with emphasis on inflammation, is illustrated below (Figure 3).

3.6 Molecular biomarkers in COPD

Biomarkers are defined as objectively measurable indicators used to assess normal biological processes, pathogenic mechanisms or pharmacologic responses to therapeutic interventions. In the context of COPD, they are being increasingly investigated for their potential to support diagnosis, assess disease severity, predict prognosis and treatment response and deepen the understanding of disease pathophysiology. Clinical phenotyping involves categorizing patients based on observable characteristics, whereas endotyping classifies them according to underlying biological mechanisms. Therefore, developing biomarkers capable of identifying distinct endotypes, especially those most likely to respond to targeted pharmacological therapies, is considered a key component of precision medicine in COPD management [25].

3.6.1 Blood- based biomarkers

Blood- based biomarkers provide a minimally invasive approach to assessing inflammation, oxidative stress, and molecular signatures related to COPD pathogenesis [11]. Inflammatory biomarkers such as C- reactive protein (CRP), fibrinogen, and white blood cell count reflect ongoing systemic inflammation and have been associated with disease severity and the risk of exacerbations. Findings regarding IL- 6 and IL- 8 levels have been inconsistent, while TNF- α has not demonstrated a significant link to COPD pathogenesis [11,26]. Oxidative stress biomarkers, including malondialdehyde (MDA) and oxidized DNA/RNA products, may offer insight into the systemic redox imbalance observed in COPD [11]. Several studies report persistently elevated blood MDA levels in COPD patients compared to healthy controls, supporting the critical role of lipid peroxidation and oxidative stress in disease development [26]. Circulating biomarkers indicative of extracellular matrix remodeling-such as matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs)- as well as markers of endothelial dysfunction like endothelin- 1 and von Willebrand factor, may also serve as prognostic indicators of disease progression and cardiovascular comorbidities in COPD patients [11].

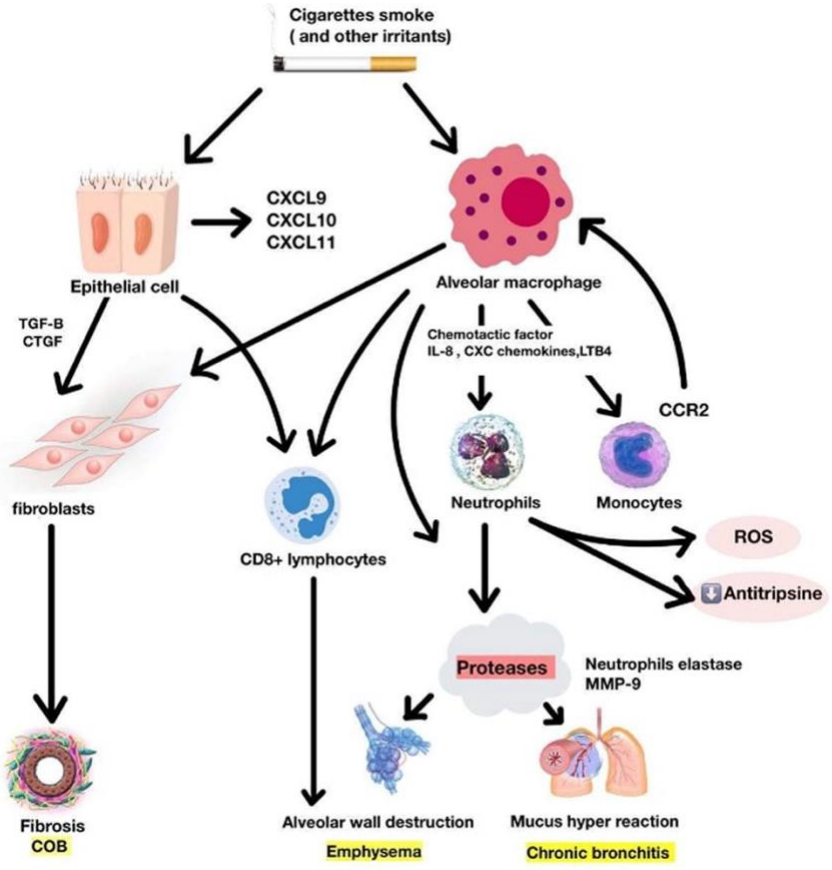

Figure 3. COPD pathogenesis [24]

3.6.2 Sputum- based biomarkers

Sputum- based biomarkers provide a more direct method for assessing inflammation within the airways. They allow for the quantitative measurement of inflammatory cells, such as neutrophils and eosinophils, inflammatory mediators including cytokines or chemokines and protease activity, for example neutrophil elastase, within the airway microenvironment. Furthermore, proteomic and metabolomic profiling of sputum shows potential for identifying novel molecular signatures associated with COPD phenotypes and treatment responses. There is also growing interest in the lung microbiome (evaluated through sputum analysis) as a potential biomarker for COPD or a therapeutic target [27].

3.6.3 Imaging biomarkers

There is an urgent unmet clinical need for non-invasive detection of small airway damage, a key pathological feature of COPD, to enable real-time monitoring of the efficacy of new therapies [28]. Imaging biomarkers offer such an opportunity. Techniques such as computed tomography (CT) imaging allow for quantitative assessment of the severity of pulmonary emphysema, airway wall thickening and pulmonary vascular remodeling- facilitating disease staging and phenotypic characterization. Functional imaging modalities, particularly positron emission tomography (PET) and magnetic resonance imaging (MRI), provide insight into regional lung perfusion, ventilation, and the degree of inflammation, thereby supplying critical information for treatment planning and monitoring therapeutic response [11, 28].

Interest in the use of biomarkers in COPD has been rapidly increasing; however, their clinical utility remains limited at present. This limitation is primarily due to difficulties in interpreting data from various studies, which often show weak associations and a lack of reproducibility across large patient cohorts. According to the GOLD guidelines, blood eosinophil count (≥300 cells/μL) currently serves as a useful indicator for identifying COPD patients at increased risk of exacerbations, as well as those more likely to benefit from prophylactic treatment with ICS [4]. Future research on biomarkers in COPD should be more targeted and

detailed, focusing on specific patient subgroups or phenotypes and integrating the concept of disease endotypes [25].

4. Current treatment strategy

The primary goals of COPD treatment are to improve quality of life, reduce the frequency of exacerbations and decrease mortality. Smoking cessation should be the first- line intervention. Equally important is pulmonary rehabilitation, which enhances lung function, increases patients' sense of control and effectively alleviates disease symptoms [29]. Initial pharmacological therapy depends on the severity of the disease. For patients with mild symptoms, bronchodilator monotherapy is recommended, including long acting β2- agonists (LABA), long acting muscarinic antagonists (LAMA), short acting β2- agonists (SABA) or short acting muscarinic antagonists (SAMA), with a preference for long acting agents. If symptoms remain inadequately controlled with monotherapy, dual therapy combining LAMA and LABA should be initiated. Triple therapy with LAMA/LABA/ICS provides greater symptom relief and lung function improvement than dual therapy but carries an increased risk of pneumonia [4, 29]. PDE- 4 inhibitors, such as roflumilast and prophylactic antibiotics, may improve outcomes in selected patients. Mucolytics, antitussives and methylxanthines show limited efficacy. Long-term oxygen therapy reduces mortality in patients with severe resting hypoxemia or moderate resting hypoxemia accompanied by signs of tissue hypoxia. Lung volume reduction surgery alleviates symptoms and improves survival in patients with severe COPD, whereas lung transplantation improves quality of life but does not significantly impact long- term survival [29].

COPD treatment remains largely dependent on bronchodilators and corticosteroids. Although advances have been made over the years in enhancing the potency, duration of action and delivery devices of existing bronchodilator classes, there remains a need to identify new therapeutic targets that provide benefits beyond those of currently available medications. Moreover, corticosteroid therapy often fails to adequately control persistent pulmonary inflammation in COPD patients. Consequently, alternative, safer and more effective therapeutic strategies are needed to enable more optimized and efficient treatment for COPD [30]. Some of these emerging approaches will be discussed further in this work.

5. Biological therapy in COPD

The use of biological therapies, including monoclonal antibodies, has revolutionized the treatment of many diseases, including those in respiratory medicine, enabling, for example, a transformation in the management of severe asthma. Fortunately, such opportunities are now emerging for patients with COPD as well [31].

5.2 Anti- IL- 4 and anti- IL- 13 antibodies

Type 2 inflammation is present in approximately 20- 40% of patients with COPD and is associated with an increased risk of disease exacerbations. As previously mentioned, this phenotype is typically characterized by elevated numbers of Th2 lymphocytes and ILC2 cells, as well as increased levels of IL- 5, IL- 4 and IL- 13. These cytokine elevations may lead to higher eosinophil counts in sputum, bronchial tissue and peripheral blood, as well as increased levels of fractional exhaled nitric oxide (FeNO). The IL- 5 signaling pathway plays a key role in the maturation and survival of eosinophils, while IL- 4 and IL- 13 pathways are primarily responsible for FeNO elevation and, more broadly, for promoting eosinophilic and type 2 inflammatory cell infiltration within the lungs. These immune cell infiltrates are believed to contribute to COPD pathogenesis, including airway hyperresponsiveness, epithelial barrier dysfunction, airway fibrosis and remodeling, also goblet cell hyperplasia, mucociliary clearance impairment and excessive mucus production- all ultimately leading to deterioration of lung function [32]. These mechanisms provide a strong rationale for the use of monoclonal antibodies specifically targeting this inflammatory axis.

Dupilumab is a fully human monoclonal antibody that inhibits the shared receptor subunit for IL- 4 and IL- 13- key cytokines involved in type 2 inflammation [32]. It is currently approved for the treatment of several chronic inflammatory diseases, including moderate- to- severe atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis and prurigo nodularis. In September 2024, FDA approved dupilumab as the first biological therapy for patients with uncontrolled COPD characterized by eosinophilic inflammation. The European Medicines Agency (EMA) has also authorized its use as an add-on treatment in this patient population [33]. The clinical efficacy of this monoclonal antibody has been demonstrated primarily in two pivotal phase 3 trials- BOREAS (NCT03930732) and NOTUS (NCT04456673) [33, 34].

The BOREAS trial was a randomized, double- blind, placebo- controlled, 52- week study designed to assess the efficacy, safety and tolerability of dupilumab in patients with moderate- to- severe COPD associated with type 2 inflammation, with blood eosinophil counts of approximately 300 cells/μL or higher and at least two moderate exacerbations or at least one severe exacerbation within the year before screening [32, 34]. A total of 939 adult participants were enrolled, all of whom were either current or former smokers [33]. Regarding the primary endpoint, the annual rate of moderate or severe exacerbations was 0.78 in the

dupilumab group compared to 1.10 in the placebo group, representing a relative reduction of approximately 30% (Figure 4). Improvement was also observed in pre- bronchodilator forced expiratory volume in one second (FEV_1), which increased by 160 mL from baseline at week 12 in the dupilumab group, compared to 77 ml in the placebo group (Figure 5). This effect was sustained through week 52 of the trial. Additionally, significant improvements were reported in patient-reported outcomes, including scores on the St. George's Respiratory Questionnaire (SGRQ) (a validated instrument assessing the impact of respiratory disease on overall health status, daily activity and quality of life in patients with obstructive lung disease) [32, 35], as well as on the Evaluating Respiratory Symptoms™ in COPD (E- RS:COPD) diary, a standardized tool for monitoring daily symptom burden in clinical trials [32, 36]. The number of patients who experienced adverse events leading to discontinuation of treatment, serious adverse events or fatal adverse events was comparable between the dupilumab and placebo groups. The most frequently reported side effects included nasopharyngitis, upper respiratory tract infections and headache. Among patients with COPD and evidence of type 2 inflammation, as indicated by elevated blood eosinophil counts, those treated with dupilumab experienced fewer exacerbations, improved lung function, better health- related quality of life and reduced severity of respiratory symptoms compared to those receiving placebo [32].

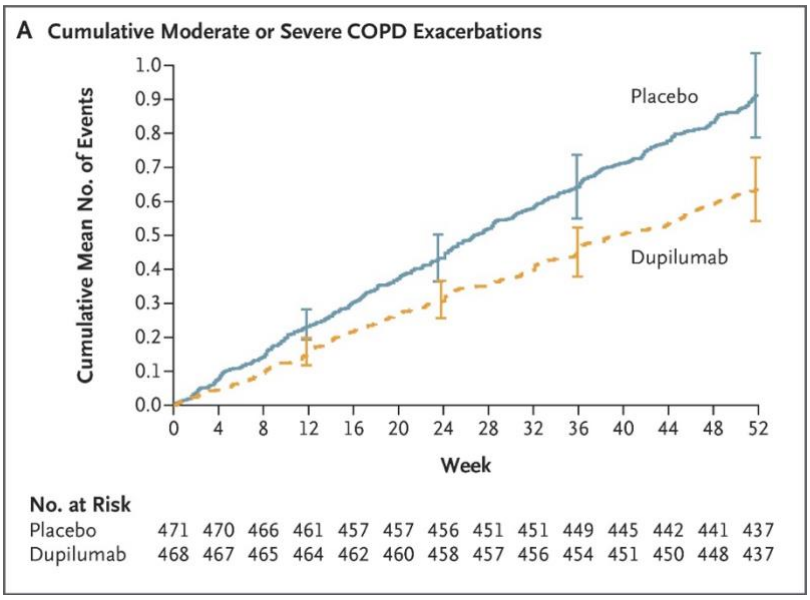

Figure 4. Moderate or severe COPD exacerbations over time [32]

Next in the NOTUS study, which served as a replication of the BOREAS trial, assessed the efficacy and safety of dupilumab in 935 patients aged 40 to 85 years with uncontrolled COPD and evidence of type 2 inflammation (blood eosinophil counts of approximately 300 cells/µL or higher). All participants were receiving a maximal dose of standard inhaled therapy (triple therapy). As in the BOREAS trial, the study population included current and former tobacco smokers [33]. The annual rate of moderate or severe exacerbations was 0.86 in the dupilumab group and 1.30 in the placebo group. The pre- bronchodilator FEV_1 increased from baseline to week 12 by 139 ml in the dupilumab group, compared to 57 ml in the placebo group, resulting in a between- group difference of 82 ml at week 12 and 62 ml at week 52, both statistically significant. No significant difference was observed between the two groups in the change from baseline in SGRQ scores at week 52. The incidence of adverse events was similar in both treatment arms and aligned with the known safety profile of dupilumab [37].

The clinical improvement associated with dupilumab observed in the BOREAS and NOTUS studies confirms the role of IL- 4 and/or IL- 13 in the pathophysiological features of this subgroup of COPD patients with type 2 inflammation. These cytokines are thought to be involved in reducing goblet cell hyperplasia, excessive mucus production and airway remodeling. This, in turn, may lead to reduced airway obstruction and consequently, to an improvement in FEV_1. In addition, dupilumab may lower nitric oxide levels, inhibit the differentiation of eosinophils, mast cells and basophils. These mechanisms may contribute to the observed improvements in exacerbation rates and lung function [32], offering an opportunity to improve treatment effectiveness and enhance the quality of life for patients with COPD.

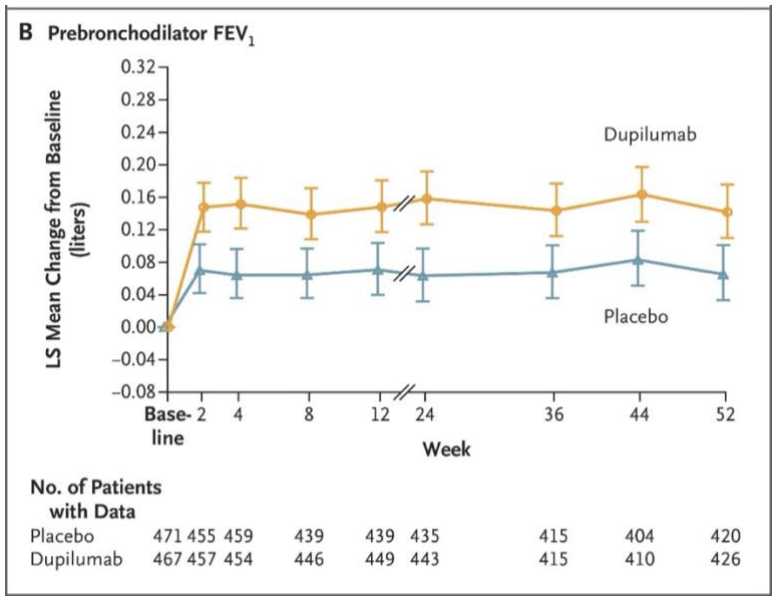

Figure 5. Change in prebronchodilator FEV_1 over time [32]

5.2 Anti- IL- 5 antibodies

As previously mentioned, IL- 5 plays a key role in the pathogenesis of COPD accompanied by Th2- type inflammation. The maturation of eosinophils is significantly influenced by IL- 5, IL- 3 and granulocyte-macrophage colony-stimulating factors, with IL- 5 considered the most critical among them. Additionally, an innate immune response to external stimuli can be triggered by the activation of ILC2 cells, leading to the production of IL- 5 and IL- 13 and resulting in eosinophilic inflammation of the airways. This concept, involving both adaptive and innate immune responses, may help explain the presence of this mechanism in COPD. Numerous studies have demonstrated elevated levels of IL- 5 and IL- 5R in the sputum of patients, supporting the rationale for targeting this pathway with biological therapies [38]. The efficacy of benralizumab and mepolizumab has been evaluated in this context.

Benralizumab is a monoclonal antibody targeting the IL- 5α receptor [39]. Its efficacy in COPD with eosinophilia is currently under investigation in clinical trials. In a phase 2a clinical trial (NCT01227278), the impact of repeated subcutaneous doses of benralizumab was assessed in adult patients with moderate- to- severe COPD, at least one acute exacerbation of COPD and eosinophilia (a sputum eosinophil count of 3.0% or more within the previous year), focusing on the frequency of moderate to severe exacerbations [34, 39]. The study did not meet its primary endpoint, as benralizumab failed to significantly reduce the rate of acute exacerbations, alleviate symptoms or improve health- related quality of life. Nevertheless, a clinically meaningful improvement in lung function (≥100 mL), based on pre- and post-bronchodilator FEV_1 measurements, was observed and maintained up to week 80- 32 weeks after the final dose. Although the differences were not statistically significant, numerical improvements were noted in the rate of acute exacerbations, FEV_1, COPD- specific St. George's Respiratory Questionnaire (SGRQ- C) scores and Chronic Respiratory Questionnaire in Self-Administered Standardised format (CRQ- SAS). These effects were more pronounced in patients with baseline blood eosinophil counts of ≥200 cells/μL or ≥300 cells/μL [39]. Benralizumab's inability to reduce the annual exacerbation rate in patients with moderate to severe COPD was further revealed in two large phase 3 randomized controlled trials- GALATHEA and TERRANOVA. However, ongoing studies (NCT04053634, NCT04098718) are investigating the efficacy and safety of benralizumab with regard to annual exacerbation frequency and overall clinical response [34, 38].

Two randomized, placebo- controlled phase 3 trials evaluated the efficacy of mepolizumab [dose 100 mg in METREX (NCT02105948) and 100 or 300 mg in METREO (NCT02105961)] administered subcutaneously every 4 weeks for a duration of 52 weeks. The study population included patients with COPD who had a documented history of moderate or severe exacerbations while receiving inhaled triple maintenance therapy based on corticosteroids. The primary endpoint in both trials was the annual rate of moderate or severe exacerbations [34, 39]. In the METREX study, among the modified population of patients with COPD and eosinophilic inflammation (stratified according to blood eosinophil count: ≥150 per cubic millimeter at screening or ≥300 per cubic millimeter during the previous year), the mean annual rate of moderate or severe exacerbations was 1.40

in the mepolizumab group versus 1.71 in the placebo group. In the METREO study (all patients with blood eosinophil count ≥150 per cubic millimeter at screening or ≥300 per cubic millimeter during the previous year), the corresponding rates were 1.19 for the 100 mg mepolizumab group, 1.27 for the 300 mg group and 1.49 for placebo. A more pronounced reduction in exacerbation frequency was observed in patients with higher baseline blood eosinophil counts at screening. The safety profile of mepolizumab was comparable to that of placebo [40]. Treatment with the 100 mg dose was associated with a lower annual exacerbation rate compared to placebo in patients with COPD and eosinophilic inflammation, suggesting potential utility of this biologic therapy in this subgroup [40]. Consequently, further investigations into the use of mepolizumab in this clinical context have been undertaken. MATINEE (NCT04133909) was a randomized phase 3 trial that assessed the efficacy and safety of mepolizumab 100 mg as an add- on therapy, administered subcutaneously every 4 weeks for a duration of 52 to 104 weeks, compared with placebo. All patients received background triple inhaled therapy, consisting of dual long- acting bronchodilators and an inhaled corticosteroid. The study enrolled 804 individuals with COPD, a documented history of exacerbations and evidence of type 2 inflammation, characterized by elevated blood eosinophil counts (≥ 300 cells/μL at screening and documented ≥ 150 cells/μL in the previous 12 months, regardless of exacerbation history) [34, 41]. The primary endpoint was met with the addition of Nucala to inhaled maintenance therapy, demonstrating a statistically significant and clinically meaningful reduction in the annual rate of moderate and severe exacerbations compared to placebo, among patients treated over 52 to 104 weeks [41]. Based on these findings, in December 2024, the U.S. FDA accepted a regulatory submission for the potential use of Nucala (mepolizumab) as an add- on maintenance therapy in patients with COPD and eosinophilic inflammation [42]. A similar application was accepted by the Chinese National Medical Products Administration in February 2025 [41]. In March 2025, also the EMA accepted GSK's application for the use of Nucala (mepolizumab) in patients with COPD, initiating its regulatory review in Europe [43] and finally in May 2025 Nucala (mepolizumab) has received FDA approval for the treatment of adults with inadequately controlled COPD and an eosinophilic phenotype as an add- on maintenance treatment [44].

5.3 Anti- IL- 17 antibodies

As previously discussed, IL- 17A plays a significant role in the early inflammatory response to cigarette smoke exposure as well as in the damage to alveolar epithelial cells, both of which are key pathological processes implicated in the development and progression of COPD. There is evidence that serum IL- 17 levels are elevated in patients with stable COPD, with concentrations directly correlating with disease severity and inversely with predicted FEV_1 values [38]. However, early investigations of secukinumab (among healthy volunteers)- a human recombinant monoclonal antibody that targets and neutralizes IL- 17A, have not yielded conclusive or promising results regarding its potential use in this patient population [45].

The efficacy and safety of another anti- IL- 17A monoclonal antibody- CNTO 6785, in patients with symptomatic moderate to severe COPD, was evaluated for the first time in a randomized phase 2 study (NCT01966549). The primary efficacy endpoint was the change from baseline in pre- bronchodilator FEV_1 at week 16. The mean difference between CNTO 6785 and placebo in this endpoint was not statistically significant. Similarly, no other secondary efficacy endpoints showed clinically or statistically meaningful differences between the treatment and placebo groups. These findings suggest that, at present, IL- 17A is unlikely to represent a viable therapeutic target in COPD [34, 46]. However, the development of other anti- IL- 17A and anti- IL- 17RA monoclonal antibodies, aimed at inhibiting the recruitment of inflammatory cells, particularly neutrophils, and thereby reducing inflammation, is ongoing [38]. Other potential candidates targeting IL- 17A include ABT- 122 (bispecific immunoglobulin with dual variable domains targeting IL- 17A and TNF- α, COVA322 (bispecific IL- 17A/TNF- α inhibitor), ALX- 0761 (bispecific anti- IL- 17A/F nanobodies), bimekizumab (bispecific anti- IL- 17A/F monoclonal antibody), NI- 1401 (bispecific anti- IL- 17A/F monoclonal antibody) and SCH 900,117. Some of them have been tested in clinical trials for other conditions, but their use in COPD remains experimental- with no reports demonstrating the efficacy of any of these agents in patients with COPD [30]. The previously mentioned TNF- α inhibitors have also shown limited clinical benefit in COPD. A key limitation in this area is that most research has focused on asthma rather than COPD. Furthermore, considering the critical role of IL- 17 in host defense, particularly in protecting against pulmonary infections, inhibition of this cytokine may carry a risk of immunosuppressive complications, including increased susceptibility to lung infections and exacerbation risk [38].

5.4 Anti- alarmin antibodies

Monoclonal antibodies targeting alarmins, particularly TSLP and IL- 33, have shown potential for the treatment of COPD.

Tezepelumab is a fully human monoclonal antibody that inhibits TSLP, a cytokine found to be overexpressed in patients with COPD compared to healthy individuals. A randomized, placebo- controlled phase 2a trial (NCT04039113, COURSE) was recently completed to assess the efficacy and safety of tezepelumab in patients

with moderate to very severe COPD who were receiving maintenance triple inhaled therapy and had experienced two or more documented exacerbations in the 12 months preceding enrollment [34, 47]. The study enrolled 333 patients stratified by baseline blood eosinophil count. Over the 52-week treatment period, the annual rate of moderate or severe exacerbations was 1.75 in the tezepelumab group and 2.11 in the placebo group. As a result, the study did not meet its primary endpoint. However, in pre- specified subgroup analyses, the following annual exacerbation rates observed over 52 weeks were 2.04 in tezepelumab group vs. 1.71 in patients with baseline eosinophil counts <150 cells/µl, 1.64 vs. 2.47 in those with 150- 300 cells/µl and 1.20 vs. 2.24 in those with ≥300 cells/µl (tezepelumab vs. placebo, respectively). Tezepelumab was generally well tolerated, with no new safety signals identified. The trial included a 52- week treatment phase followed by a 12- week post-treatment observation period. In summary, tezepelumab did not lead to a significant reduction in the overall annual rate of moderate or severe COPD exacerbations. Nevertheless, the subgroup findings suggest a potential benefit in patients with higher baseline eosinophil counts, particularly those ≥150 cells/µl, warranting further investigation into the therapeutic value of tezepelumab in this population [47], with the therapy remaining in clinical development in COPD [47].

As with TSLP, elevated IL- 33 levels have been observed in serum, sputum and bronchial biopsy samples from patients with COPD. Higher concentrations of IL- 33 in serum have also been linked to a history of prior exacerbations. In a phase 2 clinical trial (NCT03546907) involving 653 patients, itepekimab- a monoclonal antibody targeting IL- 33, numerically reduced the annual rate of acute COPD exacerbations (by 19%) and led to an improvement in pre- bronchodilator FEV_1 (of 0.06 l). However, these changes did not reach statistical significance. In a pre-specified subgroup analysis of former and current smokers, all potential benefits related to the reduction in acute exacerbation frequency and improvement in FEV_1 were more pronounced among former smokers, who comprised approximately 55% of the study population (in this subgroup, a 42% reduction in acute exacerbations and a 0.09 l improvement in FEV_1 were observed). In contrast, the remaining 45% of patients, who were current smokers, did not benefit in terms of acute exacerbation rate or FEV_1 [48]. Further studies are currently underway to assess the impact of itepekimab on the annual exacerbation rate in COPD, including AERIFY- 1 (NCT04701983) and AERIFY- 2 (NCT04751487) (both being conducted specifically in former smokers) [38].

IL- 33 belongs to the IL- 1 cytokine family and exerts its effects via its receptor, which is the membrane form/ligand of suppression of tumorigenicity 2 protein (ST2). Similar to IL- 33, elevated levels of the soluble form of this receptor (soluble suppression of tumorigenicity 2, sST2) have also been observed in patients with COPD, prompting an attempt to target the IL- 33- ST2 axis in treatment strategies [50, 51]. Astegolimab is an anti- ST2 monoclonal antibody that has been evaluated for its potential to reduce exacerbation rates in a randomized, placebo- controlled phase 2a trial (NCT03615040, COPD- ST2OP). However, in patients with moderate to very severe COPD and a history of frequent exacerbations, treatment with astegolimab did not significantly reduce exacerbation frequency over a 48- week period compared to placebo. Subgroup analyses based on baseline blood eosinophil count, sputum eosinophil count, serum sST2 concentration and pharmacogenomic response suggested a potentially meaningful, but statistically non- significant effect of the drug on exacerbation frequency in patients with lower eosinophil counts in blood or sputum, higher baseline serum sST2 levels and a genetic haplotype associated with increased IL- 33 signaling. Among the secondary outcomes, improvements in quality of life as measured by the SGRQ- C were observed in the astegolimab group compared to placebo, along with a small, statistically non-significant improvement in lung function [48]. MEDI3506 is another monoclonal antibody targeting IL- 33, whose efficacy and safety were evaluated in adult patients with COPD and moderate to severe chronic bronchitis in a recently completed randomized, placebo- controlled phase 2 trial (NCT04631016, FRONTIER- 4) [34]. Although the outcomes of current studies remain inconclusive, the IL- 33/ST2 axis appears to play a significant role in COPD pathophysiology. This highlights the need for further, well- designed trials to thoroughly assess the therapeutic potential of anti- IL- 33 and anti- ST2 antibodies in this condition and these therapies remain in clinical development for COPD. While IL- 33 is part of the IL- 1 cytokine family, current evidence shows that directly targeting IL- 1 itself (such as with MEDI8968 or canakinumab) does not result in effective COPD treatment, despite previous reports on IL- 33's potential role [50].

5.5 Anti- IL- 8 antibodies and anti- CXCR drugs

IL- 8, also known as CXCL8, is a key cytokine involved in the chemotaxis, degranulation and activation of neutrophils and monocytes through its interaction with CXCR1 and CXCR2 receptors during the inflammatory response [38]. Elevated levels of CXCL8 and its receptors have been detected in the sputum and bronchoalveolar lavage (BAL) fluid of patients with COPD, supporting their pivotal role in the disease's pathogenesis and highlighting them as potential therapeutic targets [38, 51]. However, available data in this area remain limited. A phase 2 pilot study in patients with COPD demonstrated that ABX- IL- 8- a fully human monoclonal antibody, led to a reduction in reported dyspnea, but showed no significant improvement in lung function or

overall health status. It is hypothesized that the lack of clinical efficacy may be related to the binding of the active form of CXCL8 to proteoglycans on the endothelial surface, which may hinder antibody accessibility [51]. Blocking the ligand- receptor interaction using biologics or small- molecule inhibitors designed to prevent chemokine-induced leukocyte recruitment and activation could potentially address this limitation [30]. However, no further development of IL- 8- targeted therapies has been pursued to date and no new data have emerged on this topic.

Another therapeutic target in COPD could be the neutrophil receptor CXCR2. Several CXCR2 antagonists, such as SCH- 527123, SB- 656933, QBM076, AZD5069 and navarixin, have been studied as possible COPD treatments. However, despite some promising outcomes, phase 2 trials had to be halted due to observed adverse events [30]. Danirixin, another agent, in its first clinical trial (NCT02130193) yielded improvements in respiratory symptoms and health status compared to placebo. Yet there was no difference in exacerbation count between the groups, though data suggest a possible reduction in exacerbation duration [52]. In a later phase 2b trial, danirixin did not show any clinically meaningful improvements in COPD symptoms (evaluated by the Evaluating Respiratory Symptoms™: COPD instrument) [35, 53] nor in quality of life (measured by SGRQ). Subgroup explorations failed to identify any patient population that clearly benefits from danirixin, in contrast to one earlier study which had suggested that current smokers might derive more benefit. Additionally, treatment was linked to a higher number of exacerbations and increased incidence of pneumonia- related adverse events, suggesting an unfavorable benefit- risk profile for this therapy in COPD patients [53]. Further trials of danirixin (NCT03170232, NCT03250689) have therefore been discontinued. The path toward finding a CXCR2- targeted drug that is both effective and safe remains open.

5.6 Anti- IL- 6 antibodies

IL- 6 is another pro- inflammatory cytokine implicated in the pathogenesis of COPD, playing a role in the activation, proliferation, differentiation and survival of T cells, as well as in antibody production by B cells. Moreover, several studies have reported elevated levels of IL- 6 in BALF, induced sputum, exhaled breath, and plasma in COPD patients, particularly during exacerbations. These findings highlight IL- 6 as a promising therapeutic target for COPD management. Although several monoclonal antibodies targeting IL- 6, such as tocilizumab, sirukumab, siltuximab, olokizumab and clazakizumab, have been developed, none have yet been evaluated in clinical trials involving COPD patients [38]. The main characteristics of biological therapies in COPD are summarized in Table 1.

Table 1. Key clinical trials of biological therapies in COPD [own elaboration]

Drug	Target	Study / Phase	Key outcomes	Patient phenotype	Regulatory status
Dupilumab	IL- 4Rα (IL- 4/IL- 13)	BOREAS, NOTUS (phase 3)	↓ exacerbations, ↑ FEV_1	type 2 / eosinophilic COPD	FDA, EMA approved
Mepolizumab	IL- 5	METREX, METREO, MATINEE (phase 3)	↓ exacerbations (eosinophilic pts)	eosinophilic COPD	FDA approved
Benralizumab	IL- 5Rα	GALATHEA, TERRANOVA (phase 3)	no significant benefit	Eosinophilic COPD	not approved
Tezepelumab	TSLP	COURSE (phase 2a)	subgroup benefit	high eosinophils	investigational
Itepekimab	IL- 33	phase 2	numerical improvement	former smokers	investigational

6. Phosphodiesterase inhibitors- ensifentrine, tanimilast

Phosphodiesterase (PDE) inhibitors, particularly those targeting PDE3 and PDE4, modulate various respiratory functions. PDE3 regulates intracellular cAMP and cGMP concentrations in airway smooth muscle, thereby influencing airway caliber. PDE4, by altering intracellular cAMP levels in inflammatory cells, contributes to their activation and migration and also stimulates the cystic fibrosis transmembrane conductance regulator

(CFTR). Dual inhibition of PDE3 and PDE4 has demonstrated enhanced or synergistic effects compared to inhibiting either enzyme alone, both in terms of relaxing airway smooth muscle and suppressing inflammation, making this combined approach (schematically illustrated in the figure below) a promising therapeutic strategy for obstructive and inflammatory airway diseases such as COPD, cystic fibrosis and asthma [54].

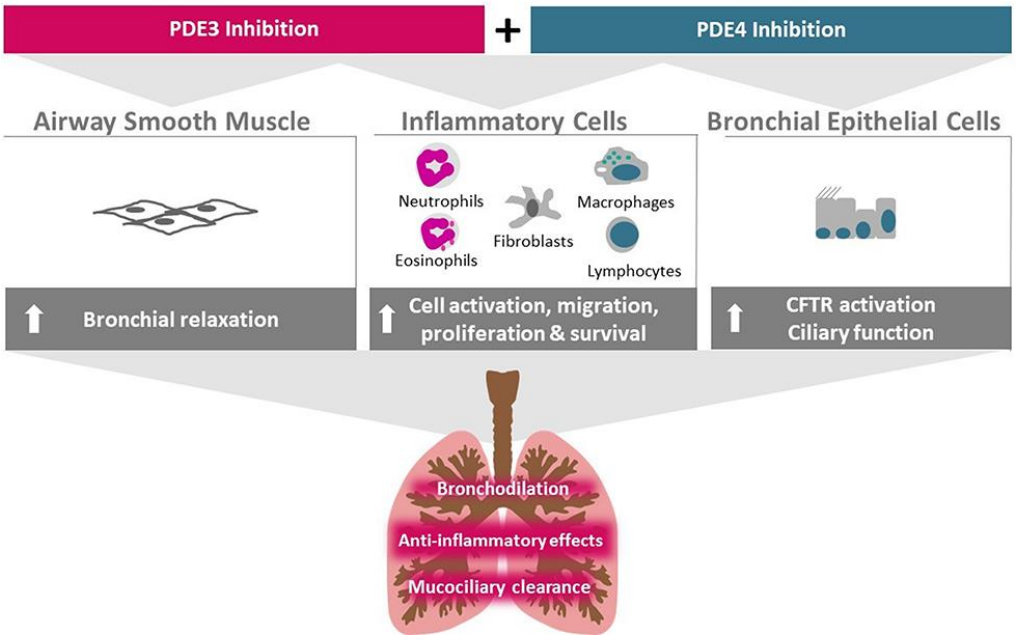

Figure 6. Ensifentrine mechanism of action [54]

Ensifentrine is a new, selective dual inhibitor of PDE3 and PDE4 with simultaneous bronchodilator and anti-inflammatory effects [54], which distinguishes this molecule from other drugs used for this indication, which are usually targeted at only one of these parameters [56]. The chemical structure of ensifentrine, with the molecular formula $C_{26}H_{31}N_5O_4$, is shown in the figure below (Figure 7).

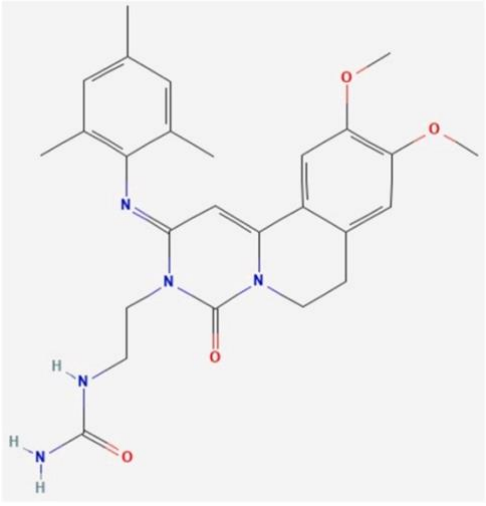

Figure 7. Chemical structure of ensifentrine [55]

In 2024, this drug, delivered directly into the airways via a standard jet nebulizer (PARI), was approved by the FDA for maintenance therapy in adult COPD patients [57]. Significant evidence supporting the efficacy of ensifentrine (formerly RPL554) has already emerged from randomized phase 2 trials [56]. In the first such trial (NCT04027439), the drug was tested using a dry powder inhaler (DPI) in patients with moderate to severe COPD. When given twice daily over 7 days via DPI, ensifentrine produced clinically meaningful, statistically significant,

dose- dependent bronchodilation. Both primary (peak FEV_1) and secondary lung function endpoints were met. The drug was well tolerated and showed a safety profile comparable to earlier studies of nebulized ensifentrine [34, 58]. In a subsequent trial (NCT04091360) using a pressurized metered dose inhaler (pMDI), similar clinically and statistically significant improvements in symptom control and lung function were observed in COPD patients [34, 59]. The decisive evidence came from the phase 3 ENHANCE trials (NCT04535986), which comprised two repeated, randomized, multicenter studies: ENHANCE- 1 (NCT04542057) and ENHANCE- 2 (NCT04778397). These trials evaluated the efficacy of ensifentrine administered via PARI over a 24- week period [34, 57]. Eligible participants were between 40 and 80 years old (760 and 789 patients enrolled in ENHANCE- 1 and ENHANCE- 2, respectively) with a confirmed diagnosis of COPD. Inclusion criteria included a post-bronchodilator FEV_1 ranging from 30% to 70% of predicted values, a Tiffeneau index (forced expiratory volume in one second % of forced vital capacity FEV_1%/FVC below 0.7, a score of 2 or higher on the modified Medical Research Council dyspnea scale and a smoking history of at least 10 pack- years. Patients were either not on long- acting maintenance therapy or were receiving LABA/LAMA with or without inhaled corticosteroids. Changes to maintenance COPD treatment during the trial were prohibited unless medically necessary. Treatment with ensifentrine led to a statistically significant improvement in FEV_1, measured as the area under the curve over 12 hours (AUC_{0-12h}) compared to placebo (87 ml in ENHANCE- 1; 94 ml in ENHANCE- 2), which was the primary endpoint. Secondary outcomes showed a significant increase in peak FEV_1 at week 12 compared to baseline and placebo (147 ml in ENHANCE- 1; 146 ml in ENHANCE- 2). This improvement in peak FEV_1 was consistent and statistically significant from day 1 through weeks 6, 12, and 24, indicating sustained efficacy [54]. Data on patient- reported symptoms and quality of life showed some variability. Participants treated with ensifentrine reported a significant reduction in breathlessness, as measured by the Transition Dyspnea Index (TDI), compared to placebo at week 24 in both studies (reaching the minimum clinically important difference) [60]. Regarding the mean total scores for E- RS and SGRQ, the ENHANCE- 1 trial demonstrated a statistically significant improvement compared to placebo. In contrast, the ENHANCE- 2 trial showed a numerical improvement at week 24 that did not reach statistical significance [54, 60]. At week 24, the average daily use of rescue medication was reduced (-0.45 puffs per day) in the ENHANCE- 1 study compared to placebo, while in ENHANCE- 2 a smaller numerical decrease (-0.14 puffs per day) was observed. Additionally, lower rescue medication use was consistently noted in the ensifentrine groups at weeks 6, 12 and 24 in both trials. Both studies reported similar reductions in the rate of moderate or severe exacerbations, as well as a delay in time to the first moderate or severe exacerbation over 24 and 48 weeks of treatment. In ENHANCE- 1, ensifentrine reduced the annual rate of moderate or severe exacerbations by 36% at 24 weeks and by 44% at 48 weeks, along with a longer time to the first exacerbation compared to placebo. Similarly, in ENHANCE- 2, patients receiving ensifentrine experienced a 43% reduction in the annual rate of moderate or severe COPD exacerbations, with a prolonged time to the first exacerbation relative to placebo [54]. These results are illustrated in the graphs below (Figure 8).

The medication was well tolerated in both trials, with a similar proportion of serious adverse events reported in the ensifentrine and placebo groups. The rates of treatment discontinuation due to adverse events were also comparable between the two groups. While gastrointestinal side effects are frequently observed with oral PDE4 inhibitors, they were rare with this inhaled therapy. Additionally, no increased incidence of pneumonia, often linked to ICS treatments, was noted [60]. Overall, the ENHANCE program provided robust evidence supporting the efficacy and safety of ensifentrine in symptomatic patients with moderate to severe COPD, classified as GOLD group B. These included patients receiving standard background therapies such as LAMA, LABA or LABA/ICS. The studies demonstrated significant bronchodilation, symptom relief and improved quality of life. These findings suggest that ensifentrine, through its novel dual inhibition of PDE3 and PDE4, could represent a valuable and complementary treatment option within the currently limited COPD therapeutic landscape [54].

Another potential PDE inhibitor drug may be tanimilast. Tanimilast (CHF6001) is an inhaled PDE4 inhibitor, non- steroidal anti- inflammatory agent currently in phase 3 clinical trials [NCT04636801 (PILASTER), NCT04636814 (PILLAR)]. This novel compound aims to reduce the risk of exacerbations in patients with COPD and chronic bronchitis when added to triple maintenance therapy. Additionally, its potential use in asthma treatment is being investigated in an ongoing phase 2 trial (NCT06029595, TANGO). Early- phase studies on tanimilast's development have demonstrated promising pharmacodynamic effects and efficacy, alongside a favorable safety profile [34, 61]. Tanimilast remains investigational in COPD, with ongoing phase 3 trials evaluating its efficacy and safety as an add-on to triple maintenance therapy.

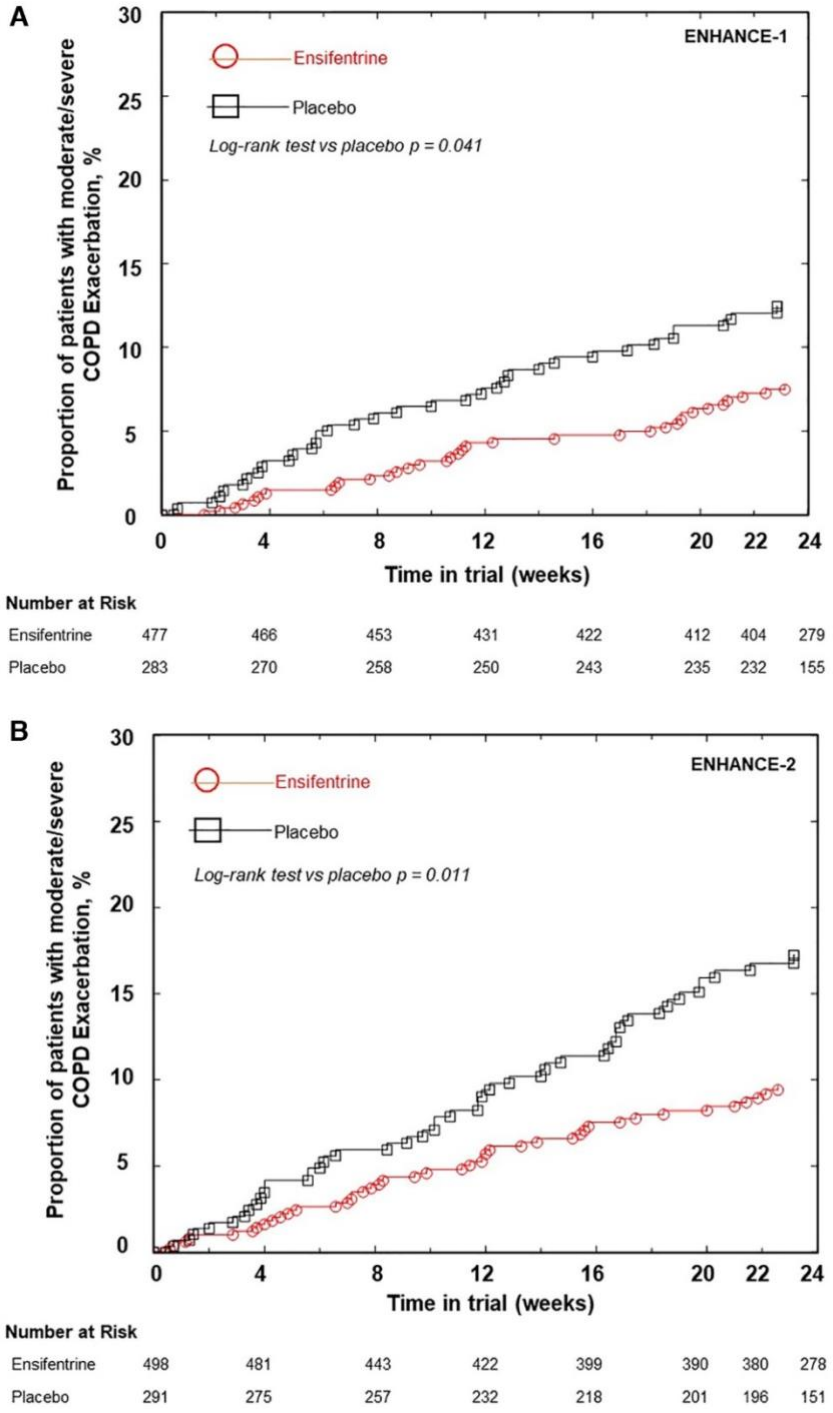

Figure 8. Plot of time to first moderate or severe COPD exacerbation over 24 weeks in the ENHANCE- 1 and ENHANCE- 2 trial [54]

The cystic fibrosis transmembrane conductance regulator (CFTR), mentioned earlier, may represent a potential therapeutic target in COPD treatment. CFTR modulators, originally developed for cystic fibrosis, could also be beneficial in COPD, as CFTR dysfunction caused by smoking- related oxidative stress has been linked to impaired lung function and worsening respiratory symptoms. Two candidate drugs, ivacaftor (VX- 770) and icenticaftor (QBW251), have been studied in COPD populations. In a phase 1 pilot randomized controlled trial, ivacaftor did not lead to an improvement in FEV_1 compared with placebo, but it was associated with a reduction in symptom burden, decreased sweat chloride levels and approximately a 20% increase in CFTR activity, all while maintaining a favorable safety profile [30]. A recently completed phase 2 study (NCT03085485) assessed the

safety and efficacy of ivacaftor in patients with COPD, chronic bronchitis and acquired CFTR dysfunction confirmed by elevated sweat chloride concentrations. Primary endpoints were focused on safety and pharmacokinetics, while secondary endpoints included CFTR activity and clinical outcomes. Ivacaftor was found to be safe and well tolerated, with a similar incidence of adverse events in both the treatment and placebo groups. However, the therapy did not lead to improvements in sweat chloride levels, total mucociliary clearance, pulmonary function or respiratory symptoms. Notably, the serum drug concentrations achieved in this population were lower than those observed in cystic fibrosis patients receiving the same dosage. This suggests that further investigation is required to determine the optimal dosing strategy and to better understand the potential role of CFTR modulation in COPD [34, 62]. The efficacy and safety of various doses of QBW251 (icenticaftor) were evaluated in a clinical trial (NCT04072887) involving patients with COPD, chronic bronchitis and a history of exacerbations, in whom the drug was added to triple inhaled therapy with LABA, LAMA and ICS. Although the primary endpoint- an improvement in FEV_1 after 12 weeks was not achieved, the study demonstrated benefits across several secondary endpoints, including lung function, symptom burden, quality of life and fibrinogen levels. The drug was well tolerated. Moreover, the consistency of the results supports the potential of a 300 mg twice- daily dose of icenticaftor to offer therapeutic benefit in this patient population. These findings further confirm CFTR as a promising therapeutic target for addressing symptoms and exacerbations in COPD [34, 63]. Another study (NCT04268823) aimed to determine whether CFTR modulation with QBW251 in COPD patients could help reduce pulmonary and systemic inflammation, as well as bacterial colonization- factors believed to contribute to airway obstruction, tissue damage, remodeling and exacerbations. Additionally, the study provided supporting data to explore the relationship between COPD phenotype and responses in small airway structure and function, mucus burden, spirometry measures and improvements in overall symptoms and quality of life [34]. Despite some inconclusive findings, this therapeutic approach remains scientifically justified. First, CFTR mutations are relatively common, suggesting that a significant number of COPD patients may be heterozygous carriers of CFTR gene variants. Second, inflammation and other oxidative stressors can lead to acquired CFTR dysfunction. Lastly, because CFTR activity can be modulated in various ways, even in individuals with normal CFTR function, these therapies may still offer clinical benefit in patients with COPD [64]. Described CFTR modulators are still under clinical investigation in COPD and their therapeutic potential has yet to be established. The main characteristics of these drugs are summarized in Table 2.

Table 2. Key clinical trials of PDE4 inhibitors and CFTR modulators in COPD [own elaboration]

Drug	Mechanism	Phase	Main effects	Status
Ensifentrine	PDE3/4 inhibitor	ENHANCE- 1, ENHANCE- 2 (phase 3)	↑ FEV_1, ↓ exacerbations	FDA approved
Tanimilast	PDE4 inhibitor	PILASTER, PILLAR (phase 3)	↓ exacerbations	ongoing
Ivacaftor	CFTR modulator	phase 2	symptom improvement only	not approved

7. Other potential drugs

7.1 Inhibitors of matrix metalloproteinases and neutrophil elastase

The previously mentioned MMPs, especially MMP- 9 and MMP- 12, as well as NE, produced by neutrophils and macrophages, are deeply involved in the inflammatory processes characteristic of COPD. They affect not only proteolytic activity but also the persistence and regulation of inflammation. As such, they are regarded as promising therapeutic targets in this condition [30]. Currently, few studies have investigated the use of MMP inhibitors in COPD. V85546- a selective MMP- 12 inhibitor, has completed phase 1 clinical trials, while AZD1236- a dual MMP- 9/12 inhibitor, failed to demonstrate efficacy in patients with moderate to severe COPD. Phase 1 trials of andecaliximab (GS- 5745)- a recombinant chimeric monoclonal antibody, have also been completed and the compound is now being evaluated in COPD patients. FP- 025- an MMP- 12 inhibitor, has been tested in asthma (NCT03858686), but to date, no trials in COPD have been reported [34, 63]. In patients with COPD who show excessive NE expression, blocking this enzyme and restoring the balance between NE and endogenous antiproteases may offer a therapeutic strategy [65]. Currently, sivelestat (ONO- 5046) is available in Japan and South Korea for the treatment of acute lung injury and acute respiratory distress syndrome, in patients experiencing a systemic inflammatory response. Several other NE inhibitors are in various stages of clinical

development and could potentially be applied in COPD treatment, although they are not specifically targeted at this disease. These include BAY 85- 8501, CHF6333 and lonodestat [30, 65]. Alvelestat has undergone clinical evaluation for its ability to reduce lung tissue damage and slow disease progression in patients with α1- ATD (NCT03636347, ASTRAEUS). However, it did not show clinical benefits or effects on inflammation- related biomarkers when added to tiotropium in COPD patients. Furthermore, when combined with maintenance treatment using budesonide/formoterol, it failed to improve lung function, respiratory symptoms or SGRQ- C outcomes [30, 34]. BAY 85- 8501 demonstrated a favorable safety and tolerability profile after 28 days of administration in patients with non-cystic fibrosis bronchiectasis [66]. The inhaled NE inhibitor CHF6333 has been investigated for its impact on NE activity in airway secretions in individuals with cystic fibrosis and in non- CF bronchiectasis [67]. Another molecule from this group, POL6014, is currently under development as a treatment for cystic fibrosis [68].

Although most existing studies on NE inhibitors have not directly focused on COPD, there is a potential for their future application in this disease, provided that broader and more comprehensive studies are conducted. Focusing exclusively on NE activity appears insufficient to meaningfully alter persistent airway inflammation in a way that would translate into improved clinical outcomes. Therefore, it has been proposed that a more effective strategy might involve the use of combination therapies and/or multifunctional agents with both anti-protease and anti- inflammatory effects. Another possible approach is the development of targeted inhalation delivery systems that could act not only on free NE but also on the enzyme bound to extracellular vesicles present in BALF [65].

Another promising strategy under investigation to control protease activity and restore the protease-antiprotease balance involves indirectly modulating NE function by inhibiting peptidases responsible for its activation during neutrophil development in the bone marrow. One such enzyme is dipeptidyl peptidase 1 (DPP1), also referred to as cathepsin C, a lysosomal cysteine protease that plays a crucial role in activating pro-inflammatory neutrophil serine proteases- including NE, PR3 and cathepsin G (CG) by cleaving the N- terminal dipeptide during neutrophil maturation. Inhibiting DPP1 may result in the production of neutrophils lacking these active proteases, thereby reducing their local release and limiting associated tissue damage. This area of research remains active, with several NE- targeting agents currently progressing through various stages of clinical development [69].

Granzyme B is a multifunctional serine protease that, upon release from the cytoplasmic granules of CD8+ T lymphocytes, can trigger a cascade of DNA damage leading to apoptotic death of target cells, such as bronchial epithelial cells, ultimately contributing to tissue injury and structural remodeling. In addition to its cytotoxic effects, it also amplifies inflammation by enhancing cytokine activity or promoting the release of sequestered growth factors. Given these roles, the use of selective granzyme B inhibitors may represent a promising therapeutic strategy in COPD [65].

7.2 α1- antitrypsin replacement therapy

Patients with α1-antitrypsin deficiency (α1- ATD) are at increased risk of developing COPD and pulmonary emphysema, which makes them potential candidates for α1-AT therapy. The inhaled route of administration appears particularly promising, as it enables direct delivery of the drug to the affected areas in the lungs. Available data indicate that this method achieves considerably higher local concentrations of α1- AT in the airway epithelial lining fluid compared to the occasionally used intravenous route [70]. A phase 2/3 randomized trial (NCT01217671) was conducted to evaluate the safety and efficacy of inhaled human α1-antitrypsin (α1- AT) in patients with α1- ATD and emphysema, including individuals with severe COPD and a predominant emphysematous phenotype who are at increased risk of exacerbations and whose episodes cannot be adequately controlled with other inhaled medications. Treatment over a 50- week period was found to have no effect on the time to first exacerbation, however, it appeared to alter the nature of such events- showing a reduction in symptom severity and a tendency toward improved FEV_1 values. This suggests that α1- AT may primarily influence the frequency or intensity of dyspnea, which is a key feature of exacerbations in this patient group [34, 65, 71]. A phase 3 trial (NCT04204252, InnovAATe) is currently underway, investigating the same inhaled formulation in patients with α1- ATD and moderate to severe airflow limitation but a low number of exacerbations in the previous year. The aim is to assess whether the treatment can help slow or prevent disease progression, particularly the decline in lung function in individuals whose condition is driven by this genetic deficiency [34, 65]. Gene therapy strategies aimed at increasing α1- AT expression using various vector systems, as well as transdermal administration of α1- AT, represent intriguing alternative approaches that are currently under investigation [65]. One ongoing study is evaluating the safety, tolerability and pharmacokinetics of subcutaneous α1- AT administration in individuals with α1- ATD (NCT04722887) [34, 65].

The most common disease- related mutation is the Z form- the Z mutation of the AAT gene (ZAAT), which leads to improper folding and accumulation of α1- AT in hepatocytes, where the majority of this protein is normally produced. The sequestration of α1- AT in the liver results in reduced circulating levels, which may

contribute to uncontrolled inflammation and subsequent lung damage [72]. In light of this, efforts have been made to develop therapies targeting the underlying protein misfolding defect. A phase 2 clinical trial (NCT04474197) evaluated the efficacy, safety and pharmacokinetics of VX- 864- a folding corrector, in patients with the ZZ protease inhibitor genotype (PiZZ) [34]. The study demonstrated a statistically significant increase in plasma levels of functional α1- AT compared to placebo and the treatment was generally well tolerated. These findings support the therapeutic concept, although it remains uncertain whether the observed improvements will result in meaningful clinical outcomes. Nevertheless, the results may inform the development of future therapeutic approaches aimed at addressing conformational abnormalities in α1- ATD, including the exploration of other "small molecule correctors" [73]. More recently, another study (NCT05643495) evaluating the efficacy and safety of VX- 864 in individuals with the PiZZ genotype over a 48- week period has also been completed [34].

7.3 Antioxidant therapy

Since oxidative stress plays a key role in the pathophysiology of COPD, antioxidant therapies could offer substantial therapeutic benefits. However, antioxidants are not routinely incorporated into current COPD treatment regimens, suggesting that the agents presently available are insufficiently effective. Different strategies to reduce oxidative stress in COPD have been explored using animal models and in vitro models of COPD cells [including antioxidant mimetics, such as superoxide dismutase (SOD) mimetics- AEOL- 10150, glutathione peroxidase (GPx) mimetics- ebselen), myeloperoxidase inhibitors- AZD 5904, inducible nitric oxide synthase (iNOS) inhibitors- N(6)- (1-iminoethyl)- L- lysine (L- NIL), aminoguanidine- which has also been tested in humans]. Nevertheless, clinical trial data remain limited [21].

Thiol- based antioxidants, including N- acetylcysteine, carbocysteine and erdosteine, exert only a moderate effect on reducing COPD exacerbations and show no significant impact on lung function or quality of life. Their main limitation is rapid inactivation due to the high oxidative stress levels in COPD lungs, prompting the ongoing search for more stable antioxidant compounds [21].

New antioxidants currently in development include, among others, inhibitors of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX) [21]. NOX is a membrane- associated molecular complex that, through the generation of superoxide anions, is likely the main source of ROS in COPD. It exists in several isoforms. Several NOX inhibitors have been identified, however, finding ones that act selectively has proven challenging [21]. Apocynin, a reversible, non- selective NOX inhibitor, has been shown in some studies to reduce certain concentrations of ROS in exhaled breath condensate in asthmatic patients, individuals with COPD and healthy subjects. Its effect on the expression of IL- 6, IL- 8 and TNF- α was also examined in vitro, revealing an increase in the expression of each of these cytokines in incubated samples [74]. A recent study in mice exposed to cigarette smoke showed that eight weeks of apocynin treatment reduced airway neutrophil infiltration by 42%, fully preserved endothelial function and eNOS availability. It also reduced airway inflammation, attenuated lung function decline and prevented collagen deposition, suggesting that NOX inhibition may slow COPD progression and reduce cardiovascular risk [75]. Selective NOX inhibitors already approved for clinical use (though not yet for COPD), such as setanaxib (GKT137831) and isuzinaxib, indicate that NOX inhibition is a promising therapeutic strategy in COPD, but further clinical validation is needed [76].

Mitochondria, the primary source of ROS, exhibit structural and functional impairment in COPD, which leads to reduced oxidative capacity and excessive ROS generation. Potential mitochondria- targeted antioxidants (MTAs), such as mitoQ, mitoTEMPO, mitoTEMPOL, SkQ1 and SkQR1 (classified as lipophilic cation-conjugated MTAs) have shown efficacy in vitro, however, no clinical trials in COPD patients have been conducted to date (existing studies focus on other disease contexts). Other theoretically promising MTA candidates include peptide-based antioxidants, Mn (III) porphyrin- derived MTAs and liposome- encapsulated formulations [77].

Nuclear factor erythroid 2- related factor 2 (Nrf2) is a key transcription factor in the antioxidant response that protect cells from oxidative stress by "upregulating" various antioxidant enzymes and related defense mechanisms. Its activation can reduce oxidative stress, suppress inflammatory responses and prevent cellular aging, making Nrf2 activators potential therapeutic agents in COPD. However, studies on their effects on bronchial epithelial cell aging and COPD progression are limited and primarily preclinical [78].

Current compounds such as sulforaphane, bardoxolone methyl and dimethyl fumarate (BG- 12) show either limited efficacy or lack supporting clinical data, are not specific to Nrf2 and may have several adverse effects [21]. Bach1 protein is a transcription factor that antagonizes the activity of Nrf2. Therefore, reducing Bach1 gene expression (or silencing the Bach1 gene) may be a potential therapeutic strategy to enhance the expression of antioxidant genes regulated by Nrf2, thereby protecting against both intermediate inflammatory phenotypes and oxidative stress in various chronic diseases, including potentially in COPD [21, 79]. As these findings are based largely on preclinical models, further studies are needed to clarify their relevance and therapeutic potential in COPD.

7.4 Protein kinase inhibitors and selectin antagonists

Another therapeutic approach, less extensively documented than monoclonal antibodies targeting specific cytokines, involves inhibiting the activity of protein kinases involved in the pathophysiology of COPD. Additionally, selectin antagonists are also considered to play a potential role.

The first group of candidate drugs are inhibitors of p38 mitogen- activated protein kinase (MAPK). MAPKs play a key role in chronic inflammation. The p38 MAPK subgroup consists of four isoforms (α, β, γ, and δ), with p38α MAPK thought to be particularly relevant in COPD. Its expression is increased in bronchial epithelial cells, macrophages and CD20+ and CD8+ lymphocytes in the lungs of patients with COPD. A variety of extracellular stimuli activate the p38 MAPK pathway, which in turn induces the transcription of inflammatory genes, resulting in increased production of cytokines and chemokines, especially IL- 1β, CXCL8 (IL- 8) and TNF- α. Therefore, inhibiting the p38 MAPK pathway may offer a promising therapeutic strategy for COPD [65]. Over the years, multiple inhibitors from this class have been studied, including losmapimod, AZD7624, RV568, acumapimod, CHF629SB681323 and PH797804. While some of these agents have shown improvements in specific outcomes, such as a reduction in exacerbation frequency, variable effects on FEV_1 or decreased expression of certain cytokines- these findings suggest a potential therapeutic benefit. However, their use in clinical practice would require confirmation through robust evidence obtained from further high-quality studies [65, 80]. A phase 1b trial of PUR1800 has been recently completed. This is a novel dry powder inhalation formulation (iSPERSE® RV1162) of a narrow- spectrum kinase inhibitor targeting p38 MAPK, Src and Syk, currently in development for the treatment of COPD exacerbations. The study assessed the safety, tolerability and pharmacokinetics of PUR1800 administered for 14 days in patients with stable, long-standing (≥1 year) stage 2 or 3 COPD (NCT04759807). The results showed that inhaled PUR1800 was safe and well tolerated in this patient population. However, additional studies in patients experiencing acute exacerbations are needed to validate the therapeutic potential of this approach [81].

Therapeutic potential is also being considered for inhibitors of phosphoinositide 3- kinase (PI3K). PI3K catalyzes the production of phosphatidylinositol- 3,4,5- trisphosphate (PIP3) and plays a key role in the activation of macrophages and neutrophils. Since PI3K function may be altered in COPD, inhibition of its δ isoform, which is known to regulate neutrophil trafficking and directional migration, and which also induces hyperphosphorylation and ubiquitination of histone deacetylase 2, leading to decreased activity and consequently reduced glucocorticoid sensitivity, has been proposed as a potential therapeutic strategy for this disease [30]. Several PI3K inhibitors, including CHF6523, AZD8154, RV1729, GSK045 and ZSTK474, have undergone preliminary evaluation in COPD [65]. Nemiralisib is a potent and highly selective PI3Kδ inhibitor, however, data on its efficacy are mixed. Some studies suggest that nemiralisib may reduce the need for oral corticosteroids (OCS) in patients experiencing COPD exacerbations, though the absence of clear criteria for OCS discontinuation limits the validity of this finding. Conversely, its impact on exacerbation frequency and lung function, assessed by spirometry and functional respiratory imaging, remains inconclusive. Therefore, further research is necessary to clarify the therapeutic role of nemiralisib in patients with COPD exacerbations [82].

Selectins form a group of three cell adhesion molecules: E- selectin, P- selectin, and L- selectin. These molecules are involved in the early steps of leukocyte activation and their attachment to the vascular endothelium, allowing immune cells to exit the bloodstream and move into surrounding tissues. It is believed that selectins may also be involved in the inflammatory mechanisms underlying COPD. Increased expression of selectins has been observed in the lung tissue of individuals with this disease, along with elevated levels of P-selectin ligand- 1 on leukocytes. Additionally, higher concentrations of soluble E- and P- selectins in the blood, often regarded as indicators of endothelial inflammation, have been shown to correlate with pulmonary function. Bimosiamose is a synthetic agent that blocks all three types of selectins, making it a pan- selectin antagonist. In a phase 2a clinical trial involving COPD patients, it showed encouraging outcomes. When administered for four weeks alongside standard bronchodilator therapy, bimosiamose led to a reduction in airway inflammation and a modest improvement in lung function. Despite these early findings, there are currently no ongoing clinical studies investigating this compound [30, 83]. Other selectin- targeting agents, such as uproleselan (a specific E- selectin blocker) and rivipansel (GMI- 1070, another pan- selectin antagonist), have also been studied in human subjects, though not yet in the context of COPD [30, 65]. Developing effective inhibitors that interfere with selectin- ligand binding in a living organism remains challenging. Agents with very strong inhibitory activity may unintentionally hinder wound healing processes, while those with lower potency may fail to sufficiently modulate disease- related inflammation. Some experts suggest that for a selectin inhibitor to be clinically effective, it should be capable of targeting at least two members of the selectin family [65]. Table 3 summarizes emerging and potential therapies in COPD, listing drug classes and their clinical development status.

Table 3. Emerging and potential pharmacological therapies in COPD [own elaboration]

Drug	Class/mechanism	Clinical status, main effects
MMP inhibitors (V85546, AZD1236, andecaliximab, FP-025)	protease inhibition	phase 1- 2; mixed efficacy
NE inhibitors (sivelestat, BAY 85-8501, CHF6333, lonodestat, alvelestat, POL6014)	protease inhibition	preclinical /early clinical; some approved outside COPD
DPP1 inhibitors	indirect NE modulation	potential therapy; preclinical /early clinical
Granzyme B inhibitors	serine protease inhibition	potential therapy; preclinical
α1- AT therapy (inhaled, VX-864)	protein replacement/folding corrector	phase 2-3; improves symptoms
Antioxidants	oxidative stress reduction	preclinical/limited clinical efficiacy
Protein kinase inhibitors (p38 MAPK, PI3K)	inflammation modulation	early clinical; mixed results
Selectin antagonists (bimosiamose, uproleselan, rivipansel)	leukocyte adhesion inhibition	phase 2a/preclinical

8. New classes of currently used drugs in COPD therapy

Bronchodilator therapy remains the cornerstone of symptom management in COPD, despite the limited reversibility of airway obstruction. Over time, advancements have led to improvements in both the pharmacodynamic properties of these medications, such as greater efficacy and prolonged action and in the technologies used for their inhaled delivery. Moreover, significant advances have been made in the development of fixed- dose inhalers combining agents from different therapeutic classes, such as LABA with LAMA or bronchodilators with ICS [30].

So- called “triple inhalers,” which deliver fixed-dose combinations of both major bronchodilator classes along with an ICS, have been introduced in recent years [30, 84]. Such triple therapies have demonstrated their effectiveness in relieving symptoms and reducing serious disease outcomes, including exacerbations and mortality in COPD patients, across numerous clinical trials (ETHOS, IMPACT, KRONOS, TRILOGY and TRIBUTE). Some of these studies also demonstrated an marked reduction in exacerbation frequency compared to dual therapies (LAMA/LABA or ICS/LABA). The addition of ICS has proven particularly advantageous for COPD patients experiencing one or more exacerbations annually (frequent exacerbations) and it currently represents the primary indication for triple therapy in this group of patients. Moreover, delivering three distinct medications via a single inhaler has been found to enhance patient compliance and adherence, which constitutes another benefit of this technological progress. Nonetheless, formulating multiple drugs into one device poses significant challenges due to the differing characteristics and profiles of the three active agents involved. To address the need for reducing the internal technological complexity associated with triple and dual therapies, researchers have introduced the concept of a single heterobifunctional molecule featuring two distinct pharmacokinetic profiles within its structure. This led to the attempt to create MABA- a dual muscarinic receptor antagonist and β2- adrenergic receptor agonist- in which the LABA and LAMA pharmacophores are linked by covalent bonds. Three such dual-pharmacology single molecules from the MABA class: batefenterol (GSK961081), nawafenterol (AZD8871) and CHF- 6366, have progressed to phase 2 clinical trials [85]. They constitute a significant advancement in bronchodilator therapy. Considering their pivotal role in COPD management, ongoing efforts focus on identifying novel drug targets that could promote bronchodilation surpassing the effects of currently available medication classes [30].

9. "Omic" technologies in COPD research

The traditional perception of COPD as a condition primarily caused by smoking in genetically predisposed individuals has been questioned by recent studies. Instead, COPD may be better understood as the cumulative outcome of lifelong gene- environment interactions experienced by an individual. The biological responses and clinical manifestations resulting from various exposures can differ depending on the age at which these gene-environment interactions occur, as well as on the cumulative history of prior interactions. Future research should focus on elucidating the impacts of these dynamic gene- environment interactions by integrating data from foundational "omics" disciplines (such as genomics, epigenomics and proteomics) alongside clinical "omics" approaches (including phenomics, physiomics and radiomics) with exposure data (the exposome) over time, using frameworks like GETomic. Accordingly, COPD should be regarded not as a single disease entity but as a clinical syndrome marked by a distinct pattern of chronic symptoms and structural and functional impairments driven by gene-environment interplay throughout life, influencing normal lung development and aging processes [86].

The development of "omic" technologies has profoundly reshaped our understanding of complex diseases like COPD, by enabling comprehensive molecular profiling of biological systems across multiple layers, including DNA, RNA, proteins and metabolites. Advanced "omic" methods, especially genomics, transcriptomics and metabolomics, broaden the possibilities for uncovering molecular mechanisms that drive COPD pathogenesis and heterogeneity, which in turn affect treatment outcomes and disease progression. Integrating multi- omic datasets supports the identification of novel therapeutic targets and the construction of predictive models to tailor treatment strategies according to individual patient characteristics and distinct paths of disease progression, facilitating personalized interventions and precision medicine. Furthermore, approaches based on systems biology and bioinformatics assist in the consolidation and interpretation of diverse "omic" data, exposing intricate regulatory networks and interactions that underlie COPD biology. By synthesizing information from genomics, transcriptomics, proteomics and metabolomics, researchers are positioned to discover innovative biomarkers, therapeutic targets and diagnostic tools that can enhance COPD management and foster the advancement of personalized healthcare.

10. Results

The greatest potential currently lies in drugs targeting specific inflammatory pathways within a personalized treatment approach. Among the currently available biologic therapies for COPD, dupilumab stands out as one of the most promising options for patients with type 2 inflammation and is the first biologic therapy approved by the FDA for use in COPD as an add- on treatment. Its consistent benefits in two large phase III trials- showing a reduction in exacerbation rates, improvement in FEV_1 and favorable patient- reported outcomes- place it ahead of many other novel biologics, particularly those targeting IL- 5 or alarmins, whose efficacy in COPD remains more variable. The main limitation of dupilumab is that its efficacy is restricted to a specific endotype, meaning that patients without eosinophilic or type 2 inflammation are unlikely to benefit from its use. Nevertheless, dupilumab currently represents the greatest advance in evidence- based personalized treatment of COPD, offering clinically meaningful improvement with a well- established safety profile.

Among anti- IL- 5 therapies, mepolizumab shows the greatest potential in patients with COPD characterized by eosinophilic or type 2 inflammation, demonstrating a consistent reduction in exacerbation rates, particularly in patients with higher baseline eosinophil counts, while maintaining a favorable safety profile. On the other hand, benralizumab shows more variable efficacy, with limited impact on exacerbation rates, despite moderate improvement in lung function in selected subgroups. The main limitation of both therapies is their use exclusively in patients with type 2 inflammation, which means that individuals without eosinophilic phenotypes are unlikely to benefit from their use.

Another promising group of drugs are PDE inhibitors, particularly those targeting both PDE3 and PDE4, which offer a novel therapeutic approach in COPD. Ensifentrine, a selective dual PDE3/4 inhibitor, has demonstrated consistent improvements in FEV_1, symptom relief and quality of life in phase 2 and 3 trials, with a favorable safety profile and minimal systemic side effects. Importantly, it reduces the rate of moderate- to- severe exacerbations, even in patients already receiving standard inhaled therapies such as LAMA, LABA or ICS. Compared to oral PDE4 inhibitors, ensifentrine shows lower gastrointestinal adverse events and does not increase the risk of pneumonia. Tanimilast, an inhaled PDE4 inhibitor, is still under investigation in phase 3 trials for COPD with chronic bronchitis and has shown promising anti- inflammatory effects alongside a favorable safety profile. The main advantages of PDE inhibitors lie in their dual mechanism, which simultaneously targets airway smooth muscle and inflammatory pathways, producing clinically meaningful bronchodilation and symptom improvement. They also provide an alternative or complementary strategy for patients not fully controlled by standard inhaled therapies. However, their limitations include the fact that long- term real- world efficacy and cost- effectiveness of ensifentrine are still under evaluation and tanimilast is not yet approved and restricted to clinical trials.

Furthermore, PDE inhibitors do not specifically target type 2 inflammation, meaning they may be less effective in patients who would benefit most from biologics such as dupilumab or anti-IL-5 antibodies.

Despite the clear involvement of IL- 17A in COPD pathophysiology, targeting this cytokine with monoclonal antibodies such as secukinumab or CNTO 6785 has so far shown no meaningful clinical benefit. Phase 2 trials failed to demonstrate improvements in lung function or exacerbation rates, suggesting that IL- 17A is currently not a viable therapeutic target. The ongoing development of other anti- IL- 17A/F or anti- IL- 17RA agents remains experimental, but concerns about potential immunosuppressive effects, including increased infection risk, limit enthusiasm for this approach. Monoclonal antibodies targeting alarmins, including tezepelumab (anti- TSLP), itepekimab (anti- IL- 33), astegolimab (anti- ST2) and MEDI3506 (anti- IL- 33), have shown some promise in reducing exacerbations in COPD subgroups with higher eosinophil counts or in former smokers. However, overall results are modest, often not reaching statistical significance and broader efficacy remains unproven. While generally well tolerated, these therapies are still in early clinical stages and require further investigation to confirm clinical utility.

Targeting neutrophil recruitment via IL- 8 or CXCR2 has been challenging. Monoclonal antibodies like ABX-IL- 8 and small- molecule CXCR2 antagonists (e.g. danirixin) showed limited symptom benefit, inconsistent impact on exacerbations and in some cases- increased infection risk. Safety concerns and a lack of clear clinical efficacy have halted further development, making this class less promising compared to established or emerging therapies. Although IL- 6 is elevated in COPD and represents a plausible target, monoclonal antibodies such as tocilizumab or sirukumab have not yet been evaluated in COPD patients. Their clinical relevance in this context remains theoretical. Originally developed for cystic fibrosis- CFTR modulators, aim to correct acquired or genetic dysfunction contributing to mucus retention and airway inflammation in COPD. Early- phase trials show some improvements in secondary outcomes such as symptom burden, quality of life and biomarkers, but primary endpoints like FEV_1 have largely not been met. These agents are still experimental in COPD and require optimization of dosing and patient selection.

MMP and NE inhibitors have been evaluated as strategies to modulate airway inflammation and tissue destruction. While phase 1 trials of selective MMP- 12 inhibitors (e.g. V85546) demonstrated safety, dual inhibitors like AZD1236 failed to show efficacy in patients with moderate- to- severe COPD. Similarly, NE inhibitors such as sivelestat, are approved for acute lung injury but have not yet demonstrated clear clinical benefit in COPD. Studies with alvelestat and BAY 85- 8501 indicate safety and tolerability, but improvements in lung function or inflammation- related outcomes remain minimal. These findings suggest that targeting a single protease may be insufficient, supporting the notion that combination therapies or multifunctional agents, potentially delivered via inhalation to reach both free and extracellular vesicle- bound enzymes, may be necessary to achieve clinically meaningful effects.

α1- AT replacement therapy continues to show promise in patients with α1- ATD. Inhaled formulations achieve higher local airway concentrations and appear to reduce the severity of exacerbations, although they have limited effect on the frequency of events or long- term lung function decline. Gene therapy approaches and small- molecule correctors, such as VX- 864, have successfully increased plasma α1- AT levels in PiZZ patients, yet whether these biochemical improvements translate into clinical benefit is still unclear. These findings indicate that addressing the underlying protein misfolding defect may be feasible, but further research is needed to determine meaningful outcomes.

Antioxidant strategies remain largely exploratory. Traditional thiol- based antioxidants (e.g. N-acetylcysteine) demonstrate moderate reductions in exacerbations, but little impact on lung function or quality of life. Novel approaches, including NOX inhibitors, mitochondria- targeted antioxidants and Nrf2 activators, show encouraging preclinical results in reducing oxidative stress, inflammation and tissue damage. However, clinical evidence is limited and challenges remain regarding compound stability, specificity and adverse effects.

Protein kinase and selectin inhibitors represent additional anti- inflammatory avenues. p38 MAPK inhibitors, including PUR1800, have shown reductions in cytokine production and potential benefits in exacerbation prevention, though outcomes vary between compounds and studies. PI3Kδ inhibition with nemiralisib may reduce oral corticosteroid use in exacerbations, but its effect on lung function and exacerbation frequency remains inconclusive. Selectin antagonists such as bimosiamose demonstrated modest reductions in airway inflammation over four weeks, suggesting short-term potential; however, long- term efficacy and clinical relevance remain uncertain. These findings collectively suggest that targeted inhibition of specific inflammatory pathways may benefit selected patient subgroups, but broad applicability is limited.

Triple inhalers provide well- established benefits, including improved symptoms, better lung function and reduced exacerbations, largely due to synergistic bronchodilation and good adherence. Their limitations relate mainly to ICS-associated risks and the fact that they do not modify disease progression. New MABA molecules offer a simpler, single- compound alternative that may overcome formulation challenges and provide strong dual bronchodilation. However, unlike triple therapy, their clinical impact remains unproven, with evidence limited to early-phase studies. Overall, triple therapy is effective but imperfect, while MABAs are promising yet still

experimental- highlighting the need for future treatments that combine streamlined bronchodilation with true disease- modifying potential.

In summary, the most convincing clinical benefits currently come from therapies targeting type 2 inflammation, especially dupilumab and, to a lesser degree, mepolizumab, as well as from dual PDE inhibitors such as ensifentrine, which consistently improve lung function, symptoms and exacerbation rates. In contrast, agents aimed at IL- 17, alarmins, IL- 8/CXCR2, IL- 6, proteases, CFTR dysfunction or oxidative stress show limited or early- stage efficacy. While triple inhalers remain effective symptomatic treatments and MABA compounds offer a promising simplification of bronchodilation, emerging targeted therapies continue to expand the potential for more personalized and effective COPD management.

11. Limitations and future directions

Despite significant advances in understanding COPD pathogenesis and the development of novel therapeutic strategies, several important limitations remain that constrain both current treatment options and the interpretation of emerging research.

First, most novel therapies, particularly biologics and targeted anti- inflammatory agents, demonstrate meaningful efficacy only in selected COPD endotypes, such as type 2 inflammation or eosinophilic phenotypes. This restricts their applicability to a relatively small subset of patients, leaving the majority with neutrophilic or mixed- pattern inflammation without effective targeted options. Moreover, many promising agents, including alarmin inhibitors, CFTR modulators, MMP/NE inhibitors and protein- kinase inhibitors, have shown inconsistent or modest results in clinical trials, often failing to meet primary endpoints such as improvements in FEV_1 or reductions in exacerbation rates. This discrepancy between robust preclinical data and limited clinical translation highlights the complexity of COPD biology and the difficulty of targeting single pathways in a highly heterogeneous disease.

Another limitation lies in the predominance of short- term, highly controlled clinical trials, which may not adequately reflect real- world patient populations who often have multiple comorbidities, polypharmacy and suboptimal inhaler adherence. Long- term safety and cost- effectiveness data for many emerging therapies, particularly ensifentrine, tanimilast and biologics, remain limited, creating uncertainty about their long- term role in everyday clinical practice. Additionally, the absence of validated biomarkers for predicting treatment response significantly limits personalized therapy, as current stratification relies heavily on blood eosinophils, which may not fully capture underlying endotypes.

The availability and pricing of these emerging therapies may pose significant barriers to patient access, potentially limiting their real- world use despite demonstrated clinical efficacy. In September 2024, dupilumab was approved by the FDA for use in patients with uncontrolled COPD and eosinophilic inflammation; the EMA has also accepted it for adjunctive treatment in this patient group [33]. According to the official manufacturer's website, the list price of Dupixent (active substance: dupilumab; two pre- filled syringes/pens; dose 200/300 mg) is USD 3,993.36 per carton, but it can vary depending on healthcare coverage and local pricing policies [87]. In Poland dupilumab is available as a prescription- only medicine for restricted use and mains reimbursed for the treatment of three other indications under the relevant drug programs: severe bronchial asthma (drug program B.44), chronic sinusitis with nasal polyps (drug program B.124) and atopic dermatitis (drug program B.156) [88]. The retail cost of Dupixent in Poland, based on publicly available pharmacy price lists, is approximately PLN 5,000 per package (two pre- filled syringes/pens; dose 200/300 mg) [89-91]. Given the typical dosing schedule- 300 mg every two weeks [92], the monthly cost of therapy is high, making dupilumab largely inaccessible to most patients under standard conditions. Thus, despite its proven efficacy in patients with type 2 inflammatory subtypes, limited availability and high cost remain major barriers to its wider use in Poland. Among anti- IL- 5 therapies, mepolizumab (Nucala) received FDA approval in May 2025 as add- on maintenance therapy for adults with eosinophilic COPD [44]. In March 2025 EMA accepted GSK's application for the use of Nucala (mepolizumab) in this group of patients, initiating its regulatory review in Europe [43]. The official NUCALA website indicates a list price of approximately USD 3,837.48 per dose, while noting that actual patient costs may vary depending on insurance coverage and available savings programs [93]. Nevertheless, mepolizumab is not yet formally approved for COPD treatment in Poland or most European countries, which means it is currently unavailable under standard reimbursement schemes. Reliable data on its price for COPD use in Poland are not yet accessible; based on the cost of mepolizumab in other indications (about 4500 PLN per package) [94], it is likely to be substantial and limited access should be expected in the near term. For non- biologic emerging therapies, such as the dual PDE3/4 inhibitor ensifentrine (Ohtuvayre), although it was approved by the FDA in 2024 for maintenance therapy in adult COPD patients [57], the previously submitted application for marketing authorization in other regions was withdrawn by the manufacturer in October 2025 [95]. In the United States, the drug's estimated cost is approximately USD 2,950 per month (around USD 35,400 per year) [57], whereas information on approval status, reimbursement coverage and pricing in Poland and other countries remains undefined. While clinical trials report promising efficacy and safety, access for patients outside of study settings is likely to remain limited until national

regulatory and reimbursement decisions are made and commercial availability in most regions appears restricted. Other classes of potential COPD therapies, including inhibitors of IL- 17, alarmin- targeted antibodies (e.g. anti- TSLP, anti- IL- 33), IL- 8/CXCR2 inhibitors, protease (MMP/NE) inhibitors, CFTR modulators, antioxidant agents, protein kinase or selectin inhibitors, are still in early- phase development or have failed to demonstrate consistent clinical benefit. Consequently, none of them are currently approved for COPD treatment and reliable information regarding cost or market availability is not available. Their use remains limited to clinical trials or research contexts. In summary, while several novel therapies exhibit strong mechanistic rationale and promising early data, the majority are not yet accessible to patients. Only a small subset, dupilumab, and potentially mepolizumab and ensifentrine in future if approved, may become available outside trial settings. This gap between therapeutic innovation and real- world availability underscores the necessity for regulatory approval, inclusion in reimbursement programmes and transparent pricing strategies to ensure equitable access.

Future therapeutic development in COPD should focus on strategies that overcome the limitations of current treatments and address the disease's heterogeneity. Priorities include the identification and validation of robust biomarkers and molecular endotypes to enable precise patient stratification, allowing therapies to be tailored to individuals most likely to benefit. Omics- based approaches, such as genomics, transcriptomics, proteomics, and metabolomics, hold particular promise for uncovering novel disease subtypes, elucidating underlying mechanisms and identifying new therapeutic targets. Combination approaches are likely to play an important role, including dual- or multi- pathway inhibition, inhaled delivery of protease inhibitors and therapies designed to target multiple inflammatory or structural pathways simultaneously. Advances in drug delivery systems, including inhaled formulations for targeted airway delivery and the development of multifunctional molecules such as MABAs or dual PDE inhibitors, may further improve efficacy and reduce systemic adverse effects. Finally, long- term pragmatic trials in diverse, real- world populations are essential to evaluate not only efficacy but also safety, adherence and cost- effectiveness. By combining precise patient stratification, innovative therapeutic mechanisms and real- world evidence, future research aims to bridge the gap between mechanistic promise and meaningful clinical benefit, ultimately expanding effective and personalized treatment options for all COPD patients.

12. Discussion

COPD is a heterogeneous condition characterized by complex pathophysiology that leads to progressive respiratory decline and a marked deterioration in patients' quality of life. Currently available therapies, including bronchodilators and corticosteroids, provide only partial relief from symptoms and do not effectively halt disease progression or significantly reduce the frequency of exacerbations. COPD also presents a considerable challenge for healthcare systems. Individuals affected by the disease often face daily functional limitations, loss of work capacity and a need for frequent medical consultations, hospital admissions or outpatient care. These demands result in increased public healthcare expenditures and a substantial socioeconomic burden.

The greatest drawback of current COPD treatment lies in its pharmacological intervention being largely uniform, relying mainly on disease severity and symptom assessment rather than the individual's specific disease pathogenesis. To curb the worrying rise in COPD burden, therapeutic strategies must evolve, especially by emphasizing personalized therapy. That's why novel and emerging pharmacological agents, some of which have been discussed in this work, are critical in the fight against this disease. The advancement of numerous novel therapies has been largely facilitated by molecular research, which has provided deeper insights into the pathogenesis, progression, and variability of COPD, also leading to the introduction of the disease- endotype paradigm [13]. Key insights, such as delineating inflammatory pathways, elucidating oxidative stress mechanisms, emphasizing protease- antiprotease imbalance and identifying genetic susceptibilities, have not only enriched our comprehension of COPD biology, but also paved the way toward breakthrough targeted therapies tailored to individual patient profiles. Precision medicine relies on recognizing discrete COPD subtypes or endotypes based on molecular drivers, clinical phenotypes, and biomarker signatures, thereby opening the door to personalized treatment strategies. It is also worth highlighting the potential further development of biomarkers for disease severity, progression and treatment response, which could substantially improve patient stratification, identifying those most likely to benefit from specific therapies- and thus support the individualization of treatment regimens and optimization of therapeutic outcomes [11]. These objectives can largely be realized through the advancement of "omic" technologies, particularly genomics, transcriptomics and metabolomics. Investigating the molecular mechanisms underlying COPD and its heterogeneity enables the identification of novel biomarkers, precise disease subtype classification, discovery of new therapeutic targets and the prediction of disease trajectory, progression and treatment response, all aligned with the goals of personalized medicine.

One of the first significant groups of drugs facilitating personalized treatment are monoclonal antibodies targeting specific components of the inflammatory pathways in COPD. Dupilumab, an inhibitor of IL- 4 and IL- 13,

has demonstrated considerable efficacy in improving lung function, alleviating symptoms and reducing exacerbations by primarily targeting cells involved in type 2 inflammation, which led to its approval as an adjunct therapy in patients with eosinophilic inflammation. Similarly, therapies such as mepolizumab and benralizumab, which target IL- 5 and its receptor, show greater benefits in this patient subgroup. The expansion of biologic therapies for these patients thus represents a promising opportunity to enhance treatment outcomes and improve quality of life. Research into other treatments, including antibodies against alarmins, is ongoing and while initial results are encouraging, further studies are required to fully assess their efficacy. Currently, the development of biological drugs targeting the recruitment and activation of Th1 and Th17 lymphocytes, as well as the cytokines they secrete, including IL- 1, IL- 6, IL- 8 and IL- 17, faces significant challenges. Nevertheless, such therapies could offer effective treatment options for a substantial group of patients with distinct disease endotypes who are unlikely to respond to therapies aimed at neutrophilic inflammation. These investigations represent important progress toward a deeper understanding of the inflammatory pathways involved in COPD and provide hope for more effective treatments. Another promising therapeutic avenue for COPD patients involves dual PDE inhibitors, specifically PDE3 and PDE4 inhibitors. This approach combines the bronchodilatory effects typical of traditional agents with anti-inflammatory properties, while maintaining a favorable safety profile and reduced incidence of serious adverse effects. Enzifentrine has demonstrated significant improvements in lung function and reductions in exacerbation rates in clinical studies, resulting in its approval as an add-on treatment for COPD. Tanimilast also shows potential as a therapeutic agent in this class. Additionally, the continued development of existing bronchodilators and corticosteroids, including “triple inhalers” that combine LABA, LAMA, and ICS, as well as heterobifunctional compounds that integrate the effects of LABA and LAMA (MABA), remains a critical area of advancement.

In addition, there are several other compounds that may prove effective in the future treatment of COPD. Research has indicated that CFTR modulators, such as ivacaftor and icenticaftor, hold potential, although the results have been somewhat inconsistent. Ivacaftor improved CFTR function, reduced symptom severity and lowered sweat chloride levels, yet it did not have a significant impact on lung function. Conversely, icenticaftor, despite not improving primary spirometric outcomes, demonstrated benefits in enhancing quality of life and reducing symptom burden. Drugs from the MMP and NE inhibitor classes are also under investigation for their potential efficacy in COPD management. Given the crucial role of oxidative stress in COPD pathophysiology, the development of effective antioxidant therapies would represent a significant advancement in the future, although current investigations remain at the preclinical stage. For patients with α1- ATD, who are particularly susceptible to COPD development, inhaled α1- AT may offer benefits in alleviating exacerbation symptoms and improving quality of life. However, its effect on disease progression remains to be fully elucidated. Considering the detailed pathophysiological mechanisms underlying COPD, there are also theoretical rationales supporting the potential effectiveness of p38 MAPK inhibitors, PI3K inhibitors and selectin antagonists as therapeutic options.

13. Conclusion

Although the number of therapeutic options available to COPD patients has been limited over the past decade, advances in various research fields have begun to shift this paradigm. A significant milestone is the recent FDA approval of two important drugs for COPD treatment: dupilumab and ensifentrine. Additionally, ongoing studies on other monoclonal antibodies, particularly mepolizumab and the inhaled PDE4 inhibitor- tanimilast offer promising prospects for expanding the therapeutic arsenal for COPD patients. Furthermore, rapid progress is being made in the development of other drugs, both biologics and those targeting different aspects of the disease’s pathogenesis. Although many of these therapeutic approaches demonstrate therapeutic potential, there is still a need for further research to fully determine their applicability in the treatment of COPD in the future. Undoubtedly, considering the heterogeneity of the disease and the possibility of stratifying patients into specific subgroups based on distinct COPD endotypes, this paves the way for the development of effective personalized therapies that will enable better symptom control, influence disease progression, and ultimately improve patients’ quality of life.

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