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Review Article

Chronic obstructive pulmonary disease new pharmacological treatments and their relationship with cardiovascular effects

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is considered a progressive inflammatory condition that is often complicated by one or more cardiovascular diseases (CVD). This review explores the cardiovascular impacts of current anti-inflammatory therapies that have shown high relevance in COPD. Phosphodiesterase (PDE) inhibitors may offer anti-inflammatory effects with improved lung function, but may produce cardiac arrhythmias when PDE3 is inhibited, although PDE4 inhibitors reduce cardiovascular events by improving endothelial function and reducing thrombosis. Similarly, p38 mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) inhibitors target COPD-related inflammation and may benefit patients with COPD and CVD. p38 MAPK inhibitors reduce cardiac fibrosis, improve contractility, and reduce arrhythmia risk. PI3K inhibitors target the PI3K/Akt pathway, which drives atherosclerosis and cardiac fibrosis, and thus potentially mitigate both plaque instability and fibrosis. Biologic therapies, including monoclonal antibodies that inhibit IL-5, IL-13/IL-4, thymic stromal lymphopoietin, IL-33, and IL-17A, are promising in reducing exacerbations, but require tight cardiovascular monitoring due to their immunomodulatory effects. Single-target inhibitors of neutrophil elastase or matrix metalloproteinases show limited efficacy in COPD, but may help cardiovascular patients by stabilizing atherosclerotic plaques by promoting vascular smooth muscle cell proliferation. Alpha-1 antitrypsin replacement therapy is promising, potentially reducing COPD exacerbations and providing cardiovascular protection, especially in myocardial injury.

Keywords: COPD, Cardiovascular disease, Inflammation, Cardiac adverse events

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major health problem due to its significant morbidity and mortality and the high social and healthcare costs it entails. According to the world health organization, it will be the fifth most prevalent disease and third cause of mortality worldwide in 2020.[1] The global initiative for the diagnosis, management and prevention of obstructive lung diseases (GOLD) defines it as a preventable and treatable disease with significant extrapulmonary effects, characterized by chronic obstruction to airflow, which is usually progressive and associated with an abnormal inflammatory response to the inhalation of toxic particles or gases.[2]

Despite the significant social and healthcare impact of this disease, research into new treatments for COPD has been relegated to the background until less than decades ago for various reasons, such as the perception of COPD as a fixed obstruction to airflow and therefore "untreatable"; the use of drugs against asthma, despite the fact that it is a disease with a different pathophysiology, where different types of cells and mediators are involved; the fact that in most patients the development of the disease is a consequence of prolonged tobacco consumption, which meant that it

was considered the "fault" of the patient; the conception of COPD as a "dry" disease, which aroused little interest in the molecular and cellular biology of COPD to identify new therapeutic targets, in addition to not having an animal model that reproduces the characteristic changes of the disease after exposure to tobacco smoke. Finally, there are doubts about how to test these new treatments, since long-term studies with a large number of patients are required, and we lack appropriate markers to monitor the response to treatment in the short term.[3]

The inflammatory nature of the disease can be summarized in the following points: a) chronic exposure to the tobacco smoke recruits inflammatory cells to the air spaces of the lung; b) these inflammatory cells release inflammatory mediators with elastolytic capacity that degrade the extracellular matrix, and c) the alveolar repair mechanisms are altered, leading to the destruction of the alveolar spaces characteristic of pulmonary emphysema. The integration of these findings, together with the role of oxidative stress and the imbalance between proteases and antiproteases, is the basis that supports the current knowledge of the etiopathogenesis of COPD (Figure 1).[3] Current treatment of COPD has improved its management, but we need new drugs to reduce the progression of the disease and its mortality.

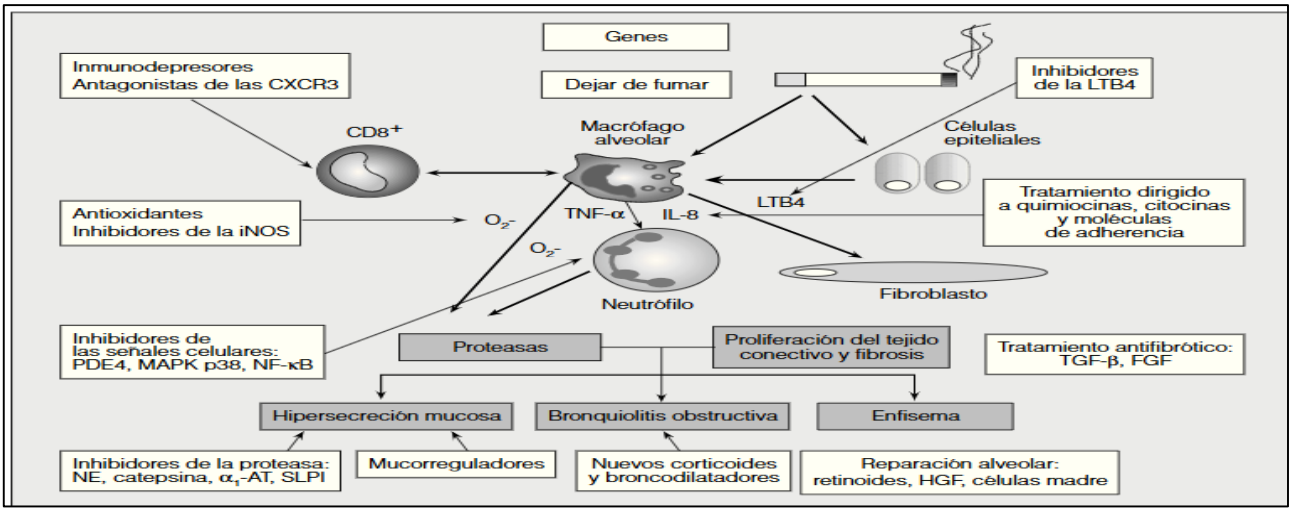

Figure 1: New pharmacological therapeutic perspectives in the management of COPD.

Pharmacological treatment directed at the pathogenesis of COPD. α1-AT: alpha-1-antitrypsin; EGF: epidermal growth factor; FGF: fibroblast growth factor; HGF: hepatocyte growth factor; IL-8: interleukin-8; iNOS: inducible nitric acid synthetase; LTB4: leukotriene B4; MAPK: mitogen-activated protein kinase; NE: neutrophil elastase; NF-κB: nuclear factor-κB; PDE4: phosphodiesterase-4; SLPI: serum leukoprotease inhibitor; TGF-β: transforming growth factor type beta; TNF-α: tumor necrosis factor alpha. (Modified from Hansel TT, Barnes PJ. Atlas of COPD. Pathenon Publishing Group.

LITERATURE SEARCH

It is a descriptive-exploratory study type of bibliographic review. The literature search period is from 2014 to 2024 in electronic databases such as PubMed, Elsevier, and Web of Science. The keywords used in the MesH search were: COPD, cardiovascular disease, inflammation, cardiac adverse events criteria: search terms, level of evidence, summaries and keywords, exclusion criteria: not related to the topic, outside the year limit, not available. They will be classified by year, type of study and level of evidence. For eligibility, a critical reading is carried out, level of evidence, documents available for analysis and according to the topic. A total of 30 sources were obtained for analysis and synthesis.

PDE INHIBITORS

Selective PDE4 inhibitors, an approved treatment for COPD added to the bronchodilator treatment and very frequently replacing the use of theophylline, improve symptoms: cough, dyspnea and expectoration, thus improving quality of life.[4] PDE4 is an enzyme expressed in endothelial cells, vascular cells, airway smooth muscle and immune system cells. The most frequent side effects are diarrhea, dyspepsia, nausea, insomnia, dizziness and joint pain. Different extracellular stimuli such as growth factors and hormones induce PDE activity [5]

In patients with myocardial ischemia and diabetes, PDE inhibitors have antiapoptotic effects, decrease cardiomyocyte fibrosis and decrease nitric oxide.[5] PDE inhibitors are also used as adjuvants in cancer treatment. Multiple studies have shown that they give excellent results in chemotherapy treatment.

In addition, in recent years, their effectiveness as an anti-tumor activity has been demonstrated, being a safe drug with minimal side effects.[6] Figure 2 shows the pathophysiology of PDE inhibitors.

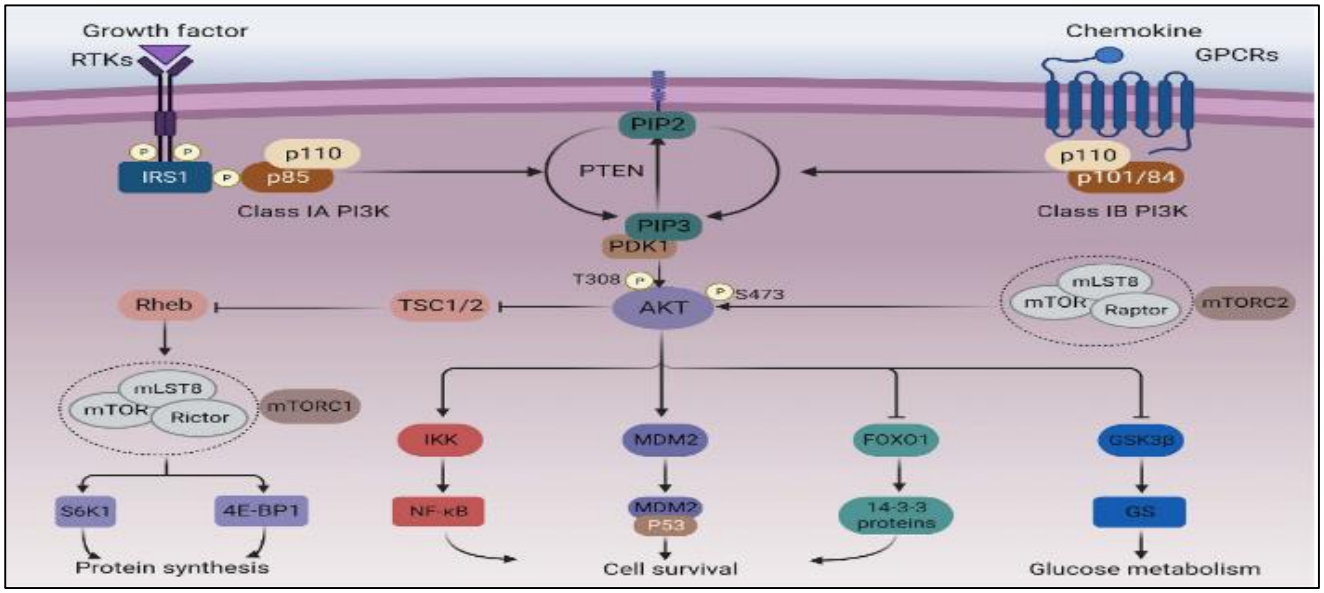

Figure 2: Pathophysiology of PDE inhibitors.

ITEPEKIMAB AND TEZEPELUMAB: THEIR EFFECT ON COPD

Genetic data implicate IL-33 in asthma susceptibility. Itepekimab, a monoclonal antibody targeting IL-33, demonstrated clinical activity in asthma, with potential in COPD.[7] Monoclonal antibodies targeting IgE, interleukin-4 and -13, and interleukin-5 are effective in treating severe type 2 asthma, but new targets are needed. Itepekimab is a novel monoclonal antibody targeting interleukin-33, which is the alarmin.[8]

Compared with placebo, forced expiratory volume in 1 second before bronchodilator use was increased with itepekimab and dupilumab monotherapies, but not with combination therapy. Treatment with itepekimab improved asthma control and quality of life compared with placebo and led to a greater reduction in mean blood eosinophil counts.[8]

Subjects were divided into four groups that received subcutaneous doses of itepekimab, dupilumab, a combination of the two, or placebo every two weeks for 12 weeks. At the end, an event indicating a loss of asthma control occurred in 22% of patients in the itepekimab group versus 41% in the placebo group, 27% in the combination group, and 19% in the dupilumab group. Itepekimab group also significantly improved lung function.[9]

Tezepelumab is a human monoclonal antibody that blocks thymic stromal lymphopoietin, an epithelial cell-derived cytokine implicated in the pathogenesis of asthma. The efficacy and safety of tezepelumab in patients with severe, uncontrolled asthma require further evaluation.[10]

Asthma is a heterogeneous disease that is often driven by allergic or eosinophilic inflammation, which may be present in severe cases. Most biologic drugs approved for severe asthma are indicated for specific phenotypes and target individual type 2 components of the inflammatory cascade. Tezepelumab, a human monoclonal antibody (immunoglobulin G2λ), specifically binds to thymic stromal lymphopoietin (TSLP), an epithelial cytokine that initiates and maintains allergic and eosinophilic inflammation in asthma. By blocking TSLP, tezepelumab has demonstrated efficacy across all known asthma phenotypes and acts upstream of all currently clinically used biomarkers.[11]

The ability of this treatment to address not only eosinophilic inflammation, but also non-eosinophilic allergic inflammation, could significantly improve the quality of life of a broader spectrum of patients.[12] The favorable safety profile of tezepelumab is an aspect that cannot be underestimated. The peace of mind it provides to patients and healthcare professionals is essential for making informed and safe treatment decisions. Tezepelumab not only focuses on symptom control and exacerbation reduction, but also demonstrates improvements in lung function parameters and therefore in patients' quality of life, which is critical. This generates a positive impact on people's ability to lead a full and active life.

RELATIONSHIP BETWEEN IL4 AND IL13 WITH COPD

COPD is a disease characterized by neutrophilic inflammation; however, there is an endotype where eosinophilic inflammation exists, and this subgroup faces a higher risk of exacerbations. Approximately 40% of patients present with COPD exacerbations with high blood eosinophil counts. For this COPD phenotype, a combination therapy of inhaled glucocorticoids with bronchodilators is mainly used for those with eosinophil

counts greater than 300 cells/uL. Currently, randomized clinical trials are investigating the possible use of biological drugs against eosinophils and TH2 cytokines, such as IL5 and IL4Ra.[16]

It is considered important to mention two important causes of COPD, exposure to biomass and smoking. According to a study conducted in 2015, factors to which patients with COPD were exposed were analyzed; in case of patients who were exposed to biomass as cause of their disease, they present high concentrations of Th2-type cytokines, such as IL4. On other hand, patients with exposure to tobacco smoke have higher titers of Th17-type cytokines.[15]

Interleukins IL-4 and IL-13 are key signaling molecules in the immune system. Both bind to specific receptors on the cell surface to activate a cascade of signals within the cell. Although each binds to a different main receptor (IL-4 to IL-4Rα and IL-13 to IL-13Rα1). These signaling complexes, in turn, activate a protein called STAT6. IL-13 plays a central role in COPD, both in the inflammatory phase and in the remodeling phase. By recruiting and activating cells such as eosinophils, mast cells, and macrophages, it intensifies inflammatory response in the lungs. Likewise, it induces structural changes in airways, thickening the bronchial walls and increasing mucus production. This cytokine also collaborates with other inflammatory molecules, such as IL-4, potentiating the immune response and contributing to tissue damage, such as apoptosis of epithelial cells and pulmonary fibrosis.[13,14]

BOREAS, a double-blind, randomized phase III clinical trial, evaluated the effect of dupilumab in patients with eosinophilic COPD who were administered dupilumab at a dose of 300 mg and a placebo every 2 weeks. Patients treated with dupilumab showed favorable results by reducing the number of exacerbations by 30%, increasing FEV1 by 160ml in 12 weeks, and decreasing symptoms. Dupilumab is a human monoclonal antibody that targets the interleukin-4 alpha receptor, which is a shared receptor for the cytokines IL4 and IL13, which are cytokines involved in type 2 inflammation. The results shown have suggested that research on the pathology of COPD should be directed to the study of IL4 and IL13 cytokines.

This study was conducted only in patients with a diagnosis of COPD, patients with asthma were completely excluded.[16] However, other researchers express concern about an overlap of asthma-COPD which may justify the favorable results of monoclonal antibodies in patients in addition to the high concentrations of type 2 cytokines. Similarly, there has also been questioning about the underdiagnosis of late-onset intrinsic asthma which can be confused with COPD.[17]

MAPK-P38 INHIBITORS, THEIR EFFECT ON COPD AND CARDIOVASCULAR EFFECTS

P38-MAPK is activated in alveolar macrophages and in different inflammatory cells that are triggered by airborne pollutants, such as cigarette smoke and certain microbial pathogens. When activated, it results in an increase in the production of cytokines and chemokines, specifically IL-1β, IL-8 and TNF-α, which are related to the neutrophilic endotype of COPD. Therefore, the suppression of p38 MAPK is a treatment that gives good results in people who suffer from COPD, reducing the activity of this pathway, decreases the inflammatory responses that are responsible for the evolution of this pathology.

DISCUSION

P38-MAPK inhibitors, their effect on COPD and cardiovascular effects p38-MAPK is activated in alveolar macrophages and in different inflammatory cells that are triggered by airborne pollutants, such as cigarette smoke and certain microbial pathogens. When activated, it results in an increase in the production of cytokines and chemokines, specifically IL-1β, IL-8 and TNF-α, which are related to the neutrophilic endotype of COPD. Therefore, the suppression of p38 MAPK is a treatment that gives good results in people with COPD, reducing the activity of this pathway, decreases the inflammatory responses that are responsible for the evolution of this pathology.[18]

MAPK-p38 inhibitors are safe in contrast to placebo; however, this intervention can generate a maximum increase in forced vital capacity after the administration of a bronchodilator. CHF6297 exhibits success in treating inflammatory lung disorders. Activation of p38 MAPK promotes heart failure and arrhythmias by promoting fibrosis and disrupting communication between cardiomyocytes.[18]

A safety investigation of p38 MAKI inhibitors was conducted in which 10 studies were evaluated. As a result, no increased risk was observed in the incidence of any serious adverse events, such as COPD exacerbations, neurological, dental and ear or nose effects, respiratory and urinary infections, cardiovascular problems and musculoskeletal pain.[19]

This systematic review and meta-analysis examined the existing evidence and concluded that p38 MAPKI is safe and effective in the COPD population, unlike the placebo group. All p38 MAPKI drugs used were safe in terms of adverse events and in all systems involved, but despite the post-bronchodilator forced vital capacity on lung function, no significant efficacy was observed in improving quality of life, physical resistance or inhibition of inflammation in patients with COPD.[19]

Treatment with p38 MAPK is a key factor in cellular activities such as inflammation, apoptosis and proliferation. The side effects that occurred when using this treatment were of great concern, especially infection, followed by alterations in the neurological system. It was identified that p38 MAPKI produced possible neurological toxicity due to its very high expression in certain brain

areas. Cardiotoxicity was also discovered since at the cardiac level it is an inhibitor of hypertrophy and promotes development in cardiac tissue. At the level of the digestive system, a clear effect is that liver or gastrointestinal toxicity are possible.[19]

This study showed that the use of p38 MAPKI in people with COPD was likely to be safe compared to placebo, with no increase in adverse effects, exacerbations or otherwise.[19]

Different p38 inhibitors have been implemented and used in cellular and animal models of COPD, and clinical trials have also been conducted with patients with COPD. These drugs have strong anti-inflammatory effects identified in in vitro and in vivo studies, stronger than the action of corticosteroids or other kinase inhibitors.[19]

Inhibition of p38 in COPD decreases inflammation and oxidative stress in lung and muscle tissues that are associated with respiratory distress and poor physical tolerance, and has the ability to improve parameters used in lung function and provide relief from dyspnea, which was assessed with forced expiratory volume in 1s, forced vital capacity, and transitional dyspnea index.[20] p38 inhibitors may offer good results compared to steroids, but cause adverse events such as liver toxicity and dermatological reactions that question their use and safety.

In a phase 2 clinical trial, RV-568, a narrow-spectrum inhaled p38 inhibitor, was identified to inhibit proinflammatory cytokines in macrophages and epithelial cells of the respiratory system and smooth muscle cells. The dose of 100 μg/day for seven days was very well tolerated in patients with COPD. Other clinical trials have demonstrated the anti-inflammatory properties and lung function benefits of this drug, which works best in conjunction with corticosteroids.[20]

SB-681323 significantly decreased TNF-α production in COPD, however, the study was discontinued. PH-797804 (6-week therapy) significantly increased lung function and dyspnea in patients with moderate to severe COPD in DBPCRT, however, it was stopped. RV568 (14-day inhaled therapy) significantly increased FEV1 and decreased sputum malondialdehyde and blood myeloperoxidase in COPD patients. However, a recent conference report revealed that 12 weeks of RV568 therapy did not provide any benefit to lung function in over 200 COPD patients.[21]

The requirement for alternative p38 pathway antagonists emerged following the failure of the p38-MAPK clinical trials. Schindler and collaborators have reported several clinical studies with p38-MAPK inhibitors from 2002 to 2007. However, these inhibitors encountered challenges from multiple aspects, such as hepatotoxicity and cardiotoxicity, evidencing the extensive functionality of the p38 pathway but also its ineffectiveness.[22]

Effect of PDE inhibitors on COPD and cardiovascular effects

PDE inhibitors are a heterogeneous group of drugs that have been of interest as potential therapeutic agents in various diseases, especially in COPD and cardiovascular disease. This summary consolidates findings from several studies and reviews of the mechanisms, efficacy, and safety profiles of PDE inhibitors with a focus on PDE4 and PDE5 inhibitors.

PDE inhibitors function by blocking the breakdown of cyclic nucleotides (cAMP and cGMP), raising their levels and producing a variety of physiological effects, including vasodilation and anti-inflammatory characteristics. This process contributes to their therapeutic effectiveness in conditions such as asthma, Alzheimer's disease, schizophrenia, and inflammatory disorders.[22]

PDE4 inhibitors, most notably roflumilast, are used to treat COPD, a progressive lung disease marked by chronic inflammation and restricted airflow. Roflumilast has been shown to reduce exacerbations and improve lung function in patients with severe COPD; however, its use is limited due to gastrointestinal side effects and weight loss.[23] Clinical trials have shown that roflumilast is successful in reducing inflammation and exacerbations, making it a viable therapy option for patients who have not responded well to conventional medications.[24]

PDE4 inhibitors can be used with other medications, such as PDE3 inhibitors, to maximize therapeutic efficacy while limiting side effects. Although PDE3 inhibitors can relax airway smooth muscle, their presence in cardiac tissue increases cardiovascular safety concerns when used with PDE4 inhibitors.[25] Therefore, careful patient selection and supervision are required when contemplating such combinations.

PDE5 inhibitors like sildenafil and tadalafil have been extensively studied for their cardiovascular effects, particularly in the treatment of pulmonary hypertension and heart failure. These inhibitors raise cGMP levels, which cause vasodilation and increased blood flow. Clinical studies have found that PDE5 inhibitors increase exercise capacity and quality of life in patients with heart failure and pulmonary arterial hypertension.[1] Furthermore, they may have cardioprotective properties that promote ischemia recovery and reduce the incidence of cardiovascular events.[26]

Despite their therapeutic benefits, PDE inhibitors can have a number of adverse effects. PDE4 inhibitors may cause gastrointestinal problems and weight loss, while PDE3 inhibitors may increase the risk of arrhythmias.[4] The safety profiles of these medications must be extensively studied, particularly in patients with concurrent respiratory and cardiovascular problems. Ongoing research is aimed at determining the safety and effectiveness of these inhibitors in a diverse range of patient groups, including those with

overlapping illnesses such as COPD and cardiovascular disease.[23]

Recent studies have demonstrated that new PDE inhibitors and combination medicines have the potential to enhance outcomes in COPD and cardiovascular disease. Ensifentrine, a dual inhibitor of enzymes that degrade inflammatory mediators, has shown promise in reducing COPD exacerbations.[3] Furthermore, ongoing clinical trials are examining the effects of PDE5 inhibitors on right heart failure and exercise tolerance in various scenarios, indicating rising interest in expanding their use in clinical settings.[26]

PDE inhibitors are effective in treating both COPD and heart failure. PDE4 inhibitors, such as roflumilast, have the potential to treat COPD, but their side effects render them unsuitable. PDE5 inhibitors have shown promising results in cardiovascular applications, suggesting that they may be more appropriate for those with COPD and heart disease. The clinical use of PDE inhibitors will be impacted by the development of safer compounds and combination therapies that optimize therapeutic benefits while minimizing risks. As research progresses, a greater understanding of these inhibitors' mechanisms of action will be necessary to improve their use in patients with complex medical histories.

CONCLUSION

The chronic inflammation, which characterises COPD and affects its natural course, also impacts on symptoms. This is the reason why there is a real, ongoing interest in finding therapies that can reduce COPD-related inflammation and prevent COPD worsening. The identification of new targets associated with the pulmonary inflammatory process has facilitated the development of novel molecules targeting various potential mediators of inflammation. Nevertheless, it is anticipated that a considerable number of these molecules, many of which are still undergoing pre-clinical evaluation, will not be incorporated into the

COPD therapeutic armamentarium likely because the absence of compelling clinical outcomes. Indeed, the multifaceted actions of the numerous mediators involved in the intricate inflammatory response associated with COPD ultimately constrains the capacity of molecules targeting a singular entity to effectively address the inflammatory process. Furthermore, it seems reasonable to speculate that, should these emerging molecules gain approval, they may prove to be unhelpful for the significant proportion of COPD patients who also experience coexisting CVD.

The development of innovative anti-inflammatory drugs, particularly when led by pulmonologists, tends to focus on COPD as an isolated condition or, at most, on select endophenotypes of COPD. This perspective frequently fails to consider the common occurrence of comorbidities, which often emerge in the later stages of clinical drug development, or even in the post-marketing phase, when therapies are administered to the general population rather than to a specifically selected cohort.

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