International Journal of Chronic Obstructive Pulmonary Disease Dovepress

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REVIEW

Emerging Anti-Inflammatory COPD Treatments: Potential Cardiovascular Impacts

Mario Cazzola[1], Luigino Calzetta[2], Paola Rogliani[1], Maria Gabriella Matera[3]

[1]Unit of Respiratory Medicine, Department of Experimental Medicine, University of Rome 'tor Vergata', Rome, Italy; [2]Unit of Respiratory Disease and Lung Function, Department of Medicine and Surgery, University of Parma, Parma, Italy; [3]Unit of Pharmacology, Department of Experimental Medicine, University of Campania 'luigi Vanvitelli', Naples, Italy

Correspondence: Mario Cazzola, Department of Experimental Medicine, University of Rome "tor Vergata", Rome, Italy, Email mario.cazzola@uniroma2.it

Abstract: Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory condition often complicated by cardiovascular disease (CVD) due to shared inflammatory pathways. This review explores the cardiovascular impacts of emerging anti-inflammatory therapies in COPD. Phosphodiesterase (PDE) inhibitors may offer anti-inflammatory effects with improved lung function but pose potential risks for 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 COPD patients with CVD. p38 MAPK inhibitors reduce cardiac fibrosis, enhance contractility and lower the risk of arrhythmia. 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, show promise in reducing exacerbations but require close cardiovascular monitoring due to their immunomodulatory effects. Single-target inhibitors of neutrophil elastase or matrix metalloproteinases show limited efficacy in COPD but may aid cardiovascular patients by stabilizing atherosclerotic plaques through promoting vascular smooth muscle cell proliferation. However, their tendency to degrade the extracellular matrix and attract immune cells may heighten plaque rupture risk, contraindicating use in CVD. Alpha-1 antitrypsin replacement therapy holds promise, potentially reducing COPD exacerbations and providing cardiovascular protection, especially in myocardial injury. Understanding the influence of these innovative therapies on CVD is vital, making it imperative to examine these molecules in COPD patients with CVD at an early stage.

Keywords: chronic obstructive pulmonary disease, cardiovascular disease, inflammation, anti-inflammatory treatments, cardiac adverse events

Introduction

It is well documented that chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) frequently co-occur.[1–3] Indeed, studies have estimated that between 28% and 70% of individuals with COPD also have CVD.[4–8] Both diseases are prevalent among older populations and share major risk factors, including smoking, ageing, and a sedentary lifestyle. The link between the two diseases extends beyond shared risk factors, with systemic inflammation appearing to be a fundamental bridge that connects them.[9]

The role of inflammation in the pathophysiology of COPD and CVD is of critical importance.[10] COPD is characterized by chronic inflammation in the airways, lung parenchyma, and pulmonary blood vessels. Neutrophils, eosinophils, macrophages, and $CD4^+$ and $CD8^+$ T lymphocytes are key players in this process, although the extent of their participation varies according to the patient's endotype.[11] This inflammation, which is attributable to irritants such as cigarette smoke, pollution, or other noxious particles, has the potential to overflow from the lungs into the bloodstream.[12] The release of inflammatory mediators into the circulation leads to systemic inflammation, with increased levels of specific proteins that signal inflammation, including C-reactive protein, interleukin (IL)-6, tumor necrosis factor (TNF)-α, and fibrinogen, in the bloodstream.[10] These markers indicate the presence of inflammation throughout the body, rather

Received: 27 September 2024
Accepted: 15 November 2024
Published: 21 November 2024

than in a single location. Systemic inflammation is associated with acute endothelial dysfunction of systemic blood arteries, which lose their ability to expand and contract effectively.[13] This promotes arterial stiffness and increases the likelihood of thrombotic events, contributing to the progression of CVD. Furthermore, hypoxemia in patients with COPD can result in pulmonary vasoconstriction, which may contribute to right ventricular diastolic dysfunction.[13] This dysfunction can elevate pulmonary vascular resistance, leading to a leftward displacement of the interventricular septum and subsequent impact on ventricular filling, stroke volume, and overall cardiac output.

In light of the established association between COPD and CVD, the management of inflammation represents a pivotal strategy in the treatment of patients with both conditions.[9] Therapeutic modalities targeting inflammation may confer a dual benefit, improving both respiratory and cardiovascular outcomes.

Inhaled corticosteroids are the most often utilized anti-inflammatory medications in the treatment of COPD.[14] It is possible that they may also contribute to cardioprotection.[15] However, corticosteroid interventions often prove ineffective in treating inflammation within the lungs of COPD patients.[16,17] This highlights the need for the development of novel pharmacological anti-inflammatory treatments to effectively manage the condition.

An intricate system of inflammatory mediators, encompassing chemokines, growth factors, and lipid mediators, is produced by the structural and inflammatory cells in the lungs and is implicated in the development of COPD.[18,19] The majority of current research has concentrated on the inhibition of the recruitment and activation of inflammatory cells, including macrophages, neutrophils, eosinophils, and T-lymphocytes, within the lungs of COPD patients.[11,14] Furthermore, there have been several attempts to create drugs that specifically target inflammatory mediators believed to be pivotal in the recruitment or activation of these cells, or that are produced by them.[11,14]

These therapies hold promise for improving respiratory symptoms and reducing systemic inflammation, but it is crucial to carefully consider their effects on cardiovascular health. Understanding the balance of benefits and risks associated with these treatments is essential for developing a holistic approach to managing patients with both COPD and CVD.

In this narrative review, we aim to identify innovative anti-inflammatory treatment options for patients with COPD that may also benefit those with coexisting CVD (Table 1). Additionally, we will explain why certain identified targets may not be suitable for treating patients with both conditions.

Table 1 Novel Classes of Anti-Inflammatory Drugs That Have Already Been Tested in Humans as Possible Treatments for Patients with COPD and Their Impact on Heart. The Number Enclosed in Square Brackets Indicates the Relevant Reference

Class	Perspectives in COPD	Influences on CVD
Phosphodiesterase Inhibitors	Oral PDE4 inhibitors associated with multiple AEs,[20] while inhaled PDE inhibitors are safer but less effective due to poor systemic bioavailability.[21] Only tanimilast remains in clinical development.[22,23]	PDE4 modulates vascular and cardiac functions through cAMP pathways, impacting cardiac health, and its inhibition may reduce cardiovascular events by improving endothelial function and lowering prothrombotic activity.[24,25]
	The dual inhaled PDE3/PDE4 inhibitor strategy minimises systemic exposure,[26] with ensifentrine being the only approved inhaled PDE3/PDE4 compound for COPD maintenance due to its efficacy and lack of substantial heart effects[27,28]	PDE3, found in cardiac and vascular tissues, also regulates cAMP signalling, but its inhibition can have harmful effects, including apoptosis and hypertrophy.[29] Combined PDE3 and PDE4 inhibition boosts sinoatrial node activity.[30]
p38 Mitogen-Activated Protein Kinase Inhibitors	Inhibition of p38 MAPK is safe compared to placebo; however, this intervention results in at most a post-bronchodilator increase in forced vital capacity.[31] CHF6297 shows promise in treating pulmonary inflammatory disorders.[32]	p38 MAPK activation contributes to HF and arrhythmias by promoting fibrosis and disrupting cardiomyocyte signalling.[33]

(*Continued*)

Table 1 (Continued).

Class	Perspectives in COPD	Influences on CVD
Phosphoinositide 3-Kinase Inhibitors	Nemiralisib affects neutrophil migration in stable COPD patients but not in AECOPD cases, despite lung function improvement.[34]	PI3K inhibitors may help treat CVD by targeting the PI3K/Akt pathway, important in atherosclerosis and cardiac fibrosis.[35]
Targeting IL-5	Mepolizumab and benralizumab reduce moderate and severe AECOPD in COPD patients with high blood eosinophil levels.[36]	IL-5 may protect against atherosclerosis, as higher levels are linked to reduced carotid plaque.[37] However, there is little evidence that IL-5 inhibition raises CVD risk.[38]
Targeting IL13/IL4	Dupilumab improves outcomes in COPD patients with T2 inflammation.[39,40]	IL4Rα signalling may protect against HF post-MI, while IL-13 signalling aids recovery after MI and could be a potential therapy for ischemic HF.[41,42] Dupilumab, which does not block the interaction of IL-13 with its decoy receptor, may lower cardiac risk from IL-4Rα inhibition,[43] though observational data suggest an increased HF risk after ischemia.[41]
Targeting Thymic Stromal Lymphopoietin	Tezepelumab reduces moderate or severe AECOPD rates by up to 46% in patients with high eosinophil counts.[44]	Higer plasma TSLP levels are found in MI patients compared to those observed in individuals with unstable angina, and lower TSLP levels are linked to a higher incidence of major adverse cardiac events post-MI.[45]
Targeting IL-33	Itepekimab improves lung function and reduces AECOPD in COPD smokers.[46] Astegolimab improves health status and lung function without reducing AECOPD incidence.[47] Tozorakimab significantly reduced serum IL-5, IL-13 and blood eosinophil levels in COPD patients.[48]	IL-33 is crucial for cardioprotection, aiding tissue repair, reducing inflammation, and preventing cardiomyocyte death.[49] In mice, recombinant IL-33 improved survival after aortic constriction surgery, while ST2 receptor deficiency led to more cardiac fibrosis.[49] IL-33 lowers cardiomyocyte apoptosis during ischemia/reperfusion injury, increases anti-inflammatory IL-10 and IL-4, and reduces pro-inflammatory IFN-γ in heart tissues.[49] Lower IL-33 levels in HF patients suggest its role in HF progression.[50] Recombinant IL-33 aids atrial remodelling via ST2 signalling, hinting that blocking the IL-33/ST2 axis may treat atrial arrhythmias.[51]
Targeting IL-17A	CNTO 6785 shows limited benefits, increasing AECOPDs.[52]	Blocking IL-17A may benefit CVD patients by affecting all vascular layers, promoting apoptosis, inflammation, collagen production, and leukocyte recruitment.[53]
Matrix Metalloproteinase Inhibitors and Neutrophil Elastase Inhibitors	Inhibitors targeting NE (alvelestat) or MMPs (AZD1236) have shown limited efficacy.[54,55]	NE may exacerbate myocardial injury.[55] MMPs play both protective and harmful roles in atherosclerosis, influencing plaque stability and rupture risk.[56]
α_1-Antitrypsin Replacement Therapy	Augmentation therapy with AAT is central in the treatment of AAT deficiency despite reaching the lungs in a relatively inactive form.[57] Inhalation AAT therapy shows inconsistent data.[58]	AAT deficiency is linked to increased HF risk.[59] Experimental[59] and clinical studies[60] suggest AAT replacement therapy could reduce ischemic damage and improve systolic function in myocardial injury.

Abbreviations: AAT, α1-antitrypsin; AE, adverse effect; AECOPD, acute exacerbation of COPD; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV_1, forced expiratory volume in the first second; HF, heart failure; IFN, interferon; IL, interleukin; IL-4Rα, IL-4 receptor subunit α; IL-13R, IL-13 receptor; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MMP, matrix metalloprotease; mTOR; mammalian target of rapamycin; NE, neutrophil elastase; PDE, phosphodiesterase; PI3K, phosphoinositide 3-kinase; ST2, tumor suppressor protein 2; TSLP, thymic stromal lymphopoietin.

Search Strategy

An extensive literature review was conducted, encompassing publications up to October 2024, utilizing the PubMed, Scopus, Web of Science, and Google Scholar databases to identify clinical trials, reviews, and updates relevant to our aim of reviewing innovative drugs in development for the treatment of COPD and their potential impact on CVD. The combination of the following keywords was used as search terms: 'chronic obstructive pulmonary disease', 'cardiovascular diseases', 'cardiovascular diseases in COPD, 'inflammation in COPD', 'inflammation and cardiovascular diseases', 'anti-inflammatory treatments', 'phosphodiesterase inhibitors', 'p38 mitogen-activated protein kinase inhibitors', 'phosphoinositide 3-kinase inhibitors', 'biologic therapies', 'anti-IL-5 monoclonal antibodies', 'anti-IL13/anti-IL4 monoclonal antibodies', 'anti-thymic stromal lymphopoietin monoclonal antibodies', 'anti-IL-33 monoclonal antibodies", 'anti-IL -17A monoclonal antibodies', 'matrix metalloproteinase inhibitors', 'neutrophil elastase inhibitors', 'α_1-antitrypsin replacement therapy', 'treatment of cardiovascular diseases in COPD' and 'cardiovascular adverse effects'. In addition, the reference lists of the retrieved articles were further searched to identify their relevance to the concept of this review.

The data obtained were synthesized narratively to present a comprehensive overview of principal novel anti-inflammatory approaches to COPD that are under investigation or recently approved, and their documented or potential impact on CVD.

Novel Anti-Inflammatory Approaches to COPD

In this article we focus on novel classes of anti-inflammatory drugs that have already been tested in humans and are possible treatments for patients with COPD. As in our two previous articles,[11,14] which we recommend for further reading, we proceed to examine these classes through a classification comprising two distinct categories. The first category encompasses classes that impede the recruitment and activation of the cellular components of inflammation. The second category comprises classes that antagonize the products of these cellular components.

Inhibition of Recruitment and Activation of the Inflammatory Cells

Several small molecule inhibitors and biologic therapies have demonstrated the potential to prevent, at least in experimental models, the recruitment and activation of the cellular components that contribute to inflammation.[11,14] Some of these therapies have recently been evaluated in patients with COPD.

The principal categories of small-molecule inhibitors that are under investigation for the treatment of COPD encompass phosphodiesterase (PDE) inhibitors, p38 mitogen-activated protein kinase (MAPK) inhibitors, and phosphoinositide 3-kinase (PI3K) inhibitors.[11] Biological therapies with potential applications in the treatment of COPD include anti-IL-5 monoclonal antibodies (mAbs) that target interleukin (IL)-5, IL-13/IL-4, thymic stromal lymphopoietin (TSLP), IL-33, and IL-17A, respectively.[11]

Macrolides need to be discussed separately because, although there is considerable evidence that they produce immunomodulatory effects by suppressing neutrophilic inflammation and activating macrophages,[61] there are signs that, beyond the considerable heterogeneity observed in various studies and the immunological markers examined, their continued use may not be beneficial.[62] A plausible explanation for the decreased effectiveness of azithromycin following a year of treatment could involve alterations in the patients' microbiota and the development of resistance to macrolides, resulting in a higher incidence of bacterial exacerbations.[62] Furthermore, although the results of a recent observational study indicate that long-term low-dose azithromycin prophylaxis is associated with a reduced incidence of cardiovascular events within 30 days following COPD exacerbations in patients with COPD and atrial fibrillation,[63] concerns about the cardiac safety of macrolides remain a point of ongoing debate.[64,65] Macrolides can prolong the QT and QTc interval via their effect on the rapid delayed rectifier (I_{Kr}) potassium channel.[66] The risk is higher in patients predisposed to CV events.[67] Consequently, the use of macrolides as anti-inflammatory treatment for patients with COPD and concomitant CVD does not appear to be an appropriate choice.

Other classes that seemed potentially useful as anti-inflammatory agents in COPD, such as CXC chemokine receptor 2 antagonists (danirixin) and selectin antagonists (bimosiamose), have been discontinued due to unfavourable results.[68,69]

Phosphodiesterase Inhibitors

Among the various PDE inhibitors, those that inhibit PDE4 are arguably the most comprehensively studied. This prominence is attributed to the significant expression of PDE4 in T-cells, eosinophils, neutrophils, monocytes, and macrophages, indicating that its inhibition could potentially suppress the activity of both inflammatory and immune cells.[70] Nevertheless, the PDE4 inhibitors that have reached Phase II and Phase III clinical trials have demonstrated a poor success rate, largely due to their unfavourable adverse event (AE) profiles.[71] Roflumilast N-oxide is the only drug from this class that has been approved for the treatment of severe COPD.[72] However, the clinical use of roflumilast is currently limited due to its narrow therapeutic index, with various dose-limiting AEs that may predominantly impact the gastrointestinal system and the central nervous system.[20] In patients receiving roflumilast, gastrointestinal AEs (diarrhoea, nausea) and weight loss are commonly observed, although the degree of weight loss is generally limited. Moreover, the use of roflumilast may also result in the occurence of less prevalent AEs, such as headaches, back pain, and insomnia.

Several inhaled PDE4 inhibitors have been developed with the aim of optimising the therapeutic window.[21] However, the results of some clinical trials indicate that these molecules offer little or no benefit to patients diagnosed with COPD. Nevertheless, the inhaled PDE 4 inhibitor tanimilast (CHF6001), available as powder for inhalation administered via NEXThaler, is currently undergoing phase III clinical trials as a potential therapeutic option for COPD.[22] It is noteworthy that in the phase II PIONEER study, tanimilast did not exhibit any impact on the primary lung function assessment.[23] However, it was well-tolerated, with no indications of gastrointestinal AEs. Subsequent post-hoc analyses that focused on acute exacerbation of COPD (AECOPD) risk identified specific patient subgroups that may potentially benefit from tanimilast.[23]

Tanimilast is directly delivered to the airways, where it can act on the target cells with minimal systemic exposure and an increase in its therapeutic index. However, the predominant local action of tanimilast may be perceived as a limitation in patients with COPD who also present with CVD. Indeed, the preclinical evidence indicates that PDE4 plays an important role in regulating vascular and cardiac functions through intricate adjustments to cyclic adenosine monophosphate (cAMP)-dependent phosphorylation cascades, thus exerting a significant influence on cardiac hypertrophy and arrhythmogenesis.[24] A comprehensive meta-analysis of clinical trials conducted on patients with COPD who were administered roflumilast has indicated that the use of this PDE4 inhibitor is associated with a notable decline in major cardiovascular events.[73] This outcome may be associated with improved endothelial function and the functionality of vascular smooth muscle cells, in addition to the inhibition of interactions between leukocytes and platelets, as well as a decrease in the prothrombotic activity of polymorphonuclear leukocytes and monocytes.[25]

The available experimental data supports the notion that a compound which inhibits both PDE3 and PDE4 simultaneously has the potential to increase the calibre of the airway by relaxing the airway smooth muscle, while also reducing the inflammatory response within the airways.[74,75] This has led to sustained interest in bifunctional PDE3/PDE4 inhibitors, despite the negative findings associated with various tested compounds.[76]

However, it is recognized that PDE3 is present in both cardiac and vascular tissues. Isoforms within the PDE3 family are of particular importance in cyclic nucleotide-mediated signalling in cardiac myocytes.[29] Conventional inhibitors of PDE3 induce an increase in cAMP levels within the cells, irrespective of their location. The increase in cardiac myocytes may produce a mixture of pro-apoptotic, pro-hypertrophic, and inotropic effects, which may induce pathological changes in the myocardium, thereby increasing the likelihood of malignant arrhythmias.[29] Moreover, the evidence indicates that the simultaneous inhibition of both PDE3 and PDE4 can result in a synergistic effect, increasing the spontaneous beating frequency of sinoatrial node cells by approximately 50%.[30]

To address this issue, the development of a dual PDE3/PDE4 inhibitor for inhalation has been proposed as a strategy to minimise systemic exposure.[26] Ensifentrine (RPL554) is currently the only PDE3/PDE4 compound approved for the maintenance treatment of COPD.[77] The findings from the phase III ENHANCE 1 and 2 studies fully support its efficacy when used in conjunction with other maintenance therapy classes.[27] Findings from various trials revealed that ensifentrine had no substantial effect on vital signs or cardiac repolarization.[28] Moreover, patients receiving ensifentrine did not display any changes in morphology, rhythm disturbances, or other parameters measured by ECG. It would be interesting to investigate whether concomitant inhibition of PDE3 and PDE4 by inhalation confers a real advantage over PDE4

inhibition alone in COPD patients presenting with concomitant CVD. Furthermore, it would be beneficial to ascertain whether any difference can be ascribed to a different impact on the pulmonary inflammatory process or even on cardiac activity.

p38 Mitogen-Activated Protein Kinase Inhibitors

The activation of p38 MAPK in alveolar macrophages and various inflammatory cells is triggered by airborne pollutants, cigarette smoke, and microbial pathogens.[78] This activation of the p38 signalling pathway results in the enhanced production of cytokines and chemokines, notably IL-1β, IL-8, and TNF-α, which have been linked to the neutrophilic endotype of COPD.[79] It may therefore be postulated that the targeting and inhibition of p38 MAPK is a promising therapeutic strategy for individuals suffering from COPD.[14,79] By reducing the activity of this pathway, it may be possible to mitigate the inflammatory responses that contribute to the progression of the disease.[11]

In a phase II study evaluating the efficacy of acumapimod, a p38α inhibitor, in individuals with AECOPDs, the primary endpoint, defined as improvement in forced expiratory volume in the first second (FEV_1) at Day 10, was not achieved.[80] However, a significant enhancement in FEV_1 was observed with the 75 mg repeat dose in comparison to placebo at Day 8. Furthermore, the Exacerbations of Chronic Pulmonary Disease Tool exhibited numerical fluctuations relative to placebo, although these did not attain a level of statistical significance. A systematic review with meta-analysis that included 10 randomized controlled trials (RCTs) in patients with COPD showed that p38 MAPK inhibition was safe when compared with placebo, but this approach at best only caused a post-bronchodilator improvement in forced vital capacity.[31]

CHF6297 represents a novel and selective p38α inhibitor, formulated for inhalation as a dry powder. This compound displays considerable promise for the treatment of chronic and acute pulmonary inflammatory disorders, including COPD, severe asthma, and AECOPD.[32] In studies conducted on rats, the administration of the micronized dry powder formulation via a nose-only inhalation device resulted in the inhibition of lipopolysaccharide-induced neutrophil influx in the bronchoalveolar lavage fluid (BALF). Furthermore, intratracheal administration in rats demonstrated the capacity to mitigate IL-1β-induced neutrophil influx and the rise in IL-6 levels within the BALF. In mice exposed to tobacco smoke, CHF6297 was observed to effectively inhibit the corticosteroid-resistant neutrophil influx in the BALF. Furthermore, in a murine model of asthma exacerbated by influenza A virus, it was demonstrated to significantly reduce airway neutrophilia in comparison to vehicle-treated mice. It is of particular importance to note that when CHF6297 was administered concurrently with budesonide at a dose that was ineffective when administered alone, it augmented the anti-inflammatory properties of the steroid.

In any case, the use of p38 MAPK inhibitors may prove beneficial in the treatment of COPD patients with a concomitant CVD. Indeed, the activation of p38 MAPK is implicated in the development of heart failure (HF) and cardiac arrhythmias through several key mechanisms, as outlined in reference.[33] Firstly, it has been demonstrated to enhance cardiac fibrosis by inducing the production of TNF-α and IL-6 in cardiomyocytes. Secondly, it facilitates fibroblast differentiation. Thirdly, it stimulates the production of transforming growth factor-β in cardiac myofibroblasts. Furthermore, it diminishes cardiac contractility due to the dephosphorylation of α-tropomyosin and troponin I. The propensity for cardiac arrhythmias is attributed to a reduction in the expression and activity of sarcoplasmic reticulum Ca^{2+}-ATPase, an increase in the expression of sodium calcium exchanger 1 and connexin 43 (Cx43), and alterations in Cx43 phosphorylation.

Phosphoinositide 3-Kinase Inhibitors

The enzyme PI3K is responsible for catalysing the formation of phosphatidylinositol-3,4,5-triphosphate, which is essential for the activation of macrophages and neutrophils.[81] Furthermore, it plays a pivotal role in the hyperphosphorylation and ubiquitination of histone deacetylase 2, thereby modulating the sensitivity of inflammatory cells to corticosteroids.[81] In patients with COPD, the activity of PI3K is markedly increased.[81] Neutrophils from these patients demonstrate enhanced migratory speed and reduced directional accuracy towards cytokine gradients, effects that are reversed through the inhibition of PI3Kδ.[82] Furthermore, the inhibition of PI3Kδ has been demonstrated to decrease the secretion of pro-inflammatory cytokines and enhance survival rates in the context of infections.[83]

Two RCTs demonstrated that nemiralisib influenced the migratory patterns of neutrophils in patients with stable COPD.[34] Conversely, no such alteration was noted in patients suffering from AECOPD, despite an improvement in lung function in this group.

There are several PI3K inhibitors under development.[11,14] CHF6523 is an inhaled PI3K inhibitor that is currently in the clinical development stage, with research focused on its safety and tolerability in patients suffering from COPD. The PI3Kγδ inhibitor AZD8154 has been assessed in healthy volunteers, while RV1729, another inhibitor of the same subtype, is being studied in the COPD patient population. GSK045, which selectively inhibits PI3Kδ, and ZSTK474, a pan-PI3K inhibitor, are additional candidates being evaluated for their potential to inhibit PI3K in the treatment of COPD.

The development of PI3K inhibitors may prove beneficial in the treatment of patients with COPD and CVD. The PI3K/Akt signalling pathway plays a pivotal role in the pathological mechanisms involved in the development of atherosclerosis, including the formation of atherosclerotic plaques and their subsequent rupture.[35] It is noteworthy that the PI3Kγ isoform, which is predominantly expressed in haematopoietic cells, significantly contributes to the promotion of inflammation associated with atherosclerosis. Furthermore, the PI3K/Akt pathway is integral to the progression of cardiac fibrosis. The simultaneous inhibition of both the PI3K/Akt and mammalian target of rapamycin pathways has been demonstrated to mitigate the fibrotic process.[35]

Biologic Therapies

A subset of patients with COPD exhibits elevated eosinophil levels in the blood and airways.[84] Additionally, there are subjects with varying degrees of combined neutrophil/eosinophil inflammation.[80] In such cases, mAb therapy targeting type (T)2 cytokines may offer a promising therapeutic avenue.[85]

Targeting IL-5

In patients with COPD, there is a notable correlation between the levels of IL-5 present in sputum and the quantity of eosinophils.[86] Additionally, it has been observed that soluble IL-5 receptor subunit α (IL-5Rα) increases during AECOPDs caused by viral infections.[87] As eosinophils undergo rapid apoptosis in the absence of IL-5,[88] targeting IL-5 may serve to inhibit or lessen the inflammation associated with eosinophils.

A Cochrane systematic review indicates that mepolizumab, a humanized mAb of the IgG_{1k} class that blocks free IL-5, and benralizumab, a fully humanized afucosylated immunoglobulin (Ig)$G_{1κ}$ mAb that binds to a specific epitope within the extracellular domain on IL-5Rα, which is near the IL-5 binding site and thus inhibits IL-5R signalling, may reduce the incidence of moderate and severe AECOPD in a highly selected group of individuals with COPD and elevated blood eosinophil levels.[36]

At present, there is no evidence to suggest that biologics targeting IL-5 or its receptor, including mepolizumab, reslizumab, and benralizumab, are associated with an elevated risk of CVD.[89] This observation is consistent with the lack of a causal association between genetically predicted IL-5 inhibition and the risk of CVD, as demonstrated in a Mendelian randomization study.[38] Nevertheless, there is substantial documentation to support the notion that IL-5 plays a role in the protection against atherosclerosis. Recent research has demonstrated that plasma IL-5 levels are altered in numerous CVDs, including atherosclerosis and myocardial ischemia, and that these changes may have influenced disease development.[37,90–92] A study of a large randomly selected population-based cohort representative of a middle-aged Finnish population revealed a correlation between human plasma IL-5 levels and antibodies binding to oxidized low-density lipoprotein, as well as a reduction in subclinical atherosclerosis.[90] A prospective investigation involving 696 individuals revealed that those with higher IL-5 levels were less likely to have carotid plaque at the time of the initial examination.[37] Moreover, IL-5 expression was markedly diminished in aorta samples from patients with acute aortic dissection in comparison to those from normal donors.[93] In patients with an established diagnosis of coronary artery disease, it was found that plasma IL-5 levels were decreased, and IL-5 was negatively associated with proinflammatory cytokines.[94] In an experimental setting, it was demonstrated that in IL-5 knockout mice, the absence of IL-5 was associated with an increase in plaque formation in regions experiencing oscillatory blood flow.[37] Additionally,

administration of recombinant mouse IL-5 was observed to improve cardiac performance post-MI in a mouse MI model, which was completely abolished by eosinophil depletion.[95]

These findings suggest the possibility that the inhibition of IL-5 could, in theory, increase the likelihood of CVD, although the existing studies have not found strong evidence linking anti-IL-5 therapies to increased CVD risk. The dearth of evidence may be attributed to the fact that clinical studies on anti-IL-5 mAbs have primarily focused on outcomes pertaining to asthma and other allergic conditions, with a paucity of data on CV events. This is partly due also to the fact that the enrolled population was, for the most part, relatively young and without a concomitant CVD. Furthermore, the majority of studies have had a relatively short duration, and long-term cardiovascular endpoints were often not the primary focus, which has resulted in an inadequate data set on potential CVD risks. Further investigation is necessary to gain a deeper understanding of the precise role of IL-5 in patients with COPD and CVD.

Targeting IL13/IL4

Mounting evidence highlights the importance of targeting IL-13 and IL-4 in the context of COPD, as this approach addresses multiple pathological mechanisms that contribute to the disease's progression.[39,95] Dupilumab, a fully humanised mAb that specifically targets the type 2 IL-4 receptor (IL4Rα), has been demonstrated to effectively reduce airway eosinophilia in the majority of patients by blocking the actions of IL-4 and IL-13. The results of the pivotal phase III RCTs, BOREAS,[40] and NOTUS [96] reinforce the notion that the blockade of IL-4 and IL-13 in COPD patients exhibiting T2 inflammation can result in significant clinical improvements for this specific patient population.[97] This therapeutic strategy targets critical inflammatory pathways, which may lead to a reduction in AECOPDs, an improvement in lung function, and an overall enhancement in disease management.[97]

From a cardiological perspective, however, the utilisation of IL13/IL4-targeted mAbs may not be unanimously accepted, as there are conflicting results in the available literature.

In light of experimental evidence, it has been postulated that IL4 and IL13 may play a role in the activation and reparative polarisation of macrophages, which have been observed to have a limited inflammatory effect on the myocardium.[98] Indeed, experimental evidence indicates that IL4Rα signalling may have a protective function in mice following MI.[41] Furthermore, the complete absence of IL4Rα in mice has been associated with an exacerbation of HF following MI. In addition, the absence of IL4Rα signalling in myeloid cells, which have been identified as the primary target cell types for IL4R signalling, has been shown to result in impaired cardiac function following MI.[99] This is mainly due to an inability to manage inflammation effectively. The pivotal function of IL-13 signalling in macrophages in the context of the post-MI damage response has also been elucidated.[42] In neonatal mice, the signalling axis involving IL-13 and IL-4Rα is evident. The deletion of IL-13 receptors (IL13R) in macrophages impairs cardiac function and results in larger scars early after neonatal MI. However, this signalling pathway decreases significantly when the mice reach adulthood. Reactivation of this pathway in adult cardiac macrophages has been found to improve recovery outcomes after MI. It is hypothesised that these cells contribute to tissue repair and extracellular matrix deposition through the activation of myofibroblasts.[98] Furthermore, it is postulated that strategies to activate IL-13 signalling in macrophages may represent a promising avenue for therapeutic intervention in the treatment of human ischemic HF.[42]

This experimental evidence has been confirmed in humans. Findings from an observational study suggest that humans receiving dupilumab are at an elevated risk of developing HF following ischaemic episodes.[41] Nevertheless, conflicting evidence exists indicating that dupilumab treatment may have a protective effect on the cardiovascular system by downregulating biomarkers associated with atherosclerosis and cardiovascular comorbidities.[100] In addition to the documentation that treatment with dupilumab demonstrated a significant modulation of atherosclerosis-related genes in patients with atopic dermatitis compared to placebo[101] and suppressed key immune and atherosclerosis/CV risk proteins,[102] there are several reports of favourable clinical outcomes in patients treated with this mAb despite suffering from a CVD.[103]

Indeed, it has been documented that dupilumab markedly decreases serum concentrations of CCL17, a chemokine produced by conventional dendritic cells, which signals through CCR4 on regulatory T cells (Treg)[104] and promotes atherosclerosis by impairing Treg function.[105] The precise mechanisms by which this occurs remain to be fully

elucidated. Furthermore, dupilumab does not inhibit the circulation of IL-13, which remains capable of binding to IL13Rα2.[43] This receptor is known as a non-signalling decoy receptor, exhibiting a 400-fold higher affinity for IL-13 in comparison to IL4Rα/IL13Rα1. This could mitigate the cardiac risk from blocking IL4Rα.

Targeting Thymic Stromal Lymphopoietin

TSLP, an IL-7-like cytokine, is acknowledged as a pivotal upstream epithelial alarmin that plays a crucial role in the regulation of T2 immune mechanisms.[106] TSLP exerts influence over a diverse range of cells, including dendritic cells, T-cells, mast cells, innate lymphoid cells, and eosinophils. This leads to the secretion of various interleukins, including IL-4, IL-5, and IL-13. This interaction is critical for the development of airway eosinophilia and hyperresponsiveness. Furthermore, TSLP can induce a range of pathogenic effects that extend beyond the realm of T2 inflammation. Viruses and T1 cytokines can also induce COPD epithelial cells to overproduce TSLP.[107]

Tezepelumab, a first-in-class human $IgG_{2/\lambda}$ mAb that binds to TSLP and inhibits its interaction with the TSLP receptor complex, has recently been documented to result in a nominally significant reduction of 37% in the rate of moderate or severe AECOPDs in comparison to placebo.[44] In patients with a blood eosinophil count of 300 cells/μL or greater, tezepelumab resulted in a statistically significant reduction of 46% in the incidence of moderate or severe AECOPDs.

It must be noted that in patients presenting with an MI, plasma TSLP concentrations were significantly elevated in comparison to those observed in individuals with unstable angina.[45] Furthermore, lower levels of TSLP were correlated with a higher incidence of major adverse cardiac events following MI. A comprehensive understanding of the interplay between TSLP levels and other established prognostic factors may facilitate improvements in both the prognostic assessment and management of MI.

Targeting IL-33

IL-33 functions as an alarmin, triggering an immune response to potential harm by enhancing the inflammatory response. Its pro-inflammatory effects are mediated through the activation of its receptor.[108] The stimulation of lung epithelial and endothelial cells by IL-33 results in the production and release of IL-6 and IL-8, which attract neutrophils that cause damage to lung tissue through the action of elastases and proteases. This process contributes to the development of pulmonary fibrosis and has a detrimental impact on lung function. Furthermore, in non-atopic patients with COPD, IL-33 has been linked to the development of eosinophilic airway inflammation.[109]

Tozorakimab, a human IgG_1 mAb that binds to the reduced form of IL-33 to block signalling via the membrane-bound receptor, serum stimulated-2 (ST2) pathway, and also prevents the formation of the oxidized form of IL-33, thereby attenuating signalling via the advanced glycation end products/epidermal growth factor receptor pathway,[110] significantly reduced serum IL-5 and IL-13 levels at all dose levels compared to placebo in patients with COPD and also numerically lowered blood eosinophil levels.[48]

In a phase II trial lasting up to 52 weeks, itepekimab, a human IgG_4 mAb targeting IL-33, did not demonstrate a significant reduction in the annualised rate of moderate-to-severe AECOPDs when used as an adjunct to standard care, in comparison to placebo.[46] However, it did show a notable reduction in the occurrence of AECOPDs and an improvement in lung function in individuals with a history of smoking who had COPD. Similarly, astegolimab, an anti-ST2 mAb administered subcutaneously through an infusion pump every four weeks to patients with moderate-to-severe COPD during a 48-week treatment period, did not result in a significant reduction in the incidence of AECOPD.[47] However, it did lead to an improvement in both health status and lung function.

Nevertheless, in spite of the uninspiring nature of these data, tozorakimab, itepekimab and astegolimab are currently the subject of phase III clinical trials for the treatment of COPD.

Within the cardiovascular system, IL-33 plays a pivotal role in cardioprotection, facilitating tissue repair and inhibiting the death of cardiomyocytes.[49] The administration of recombinant IL-33 to mice that had undergone transverse aortic constriction surgery resulted in improved survival rates. In contrast, mice that lacked the ST2 receptor exhibited increased cardiac fibrosis. Furthermore, IL-33 has been demonstrated to prevent cardiomyocyte apoptosis in the context

of ischemia/reperfusion injury. Additionally, IL-33 enhances the expression of anti-inflammatory cytokines IL-10 and IL-4 while reducing the levels of the T1 inflammatory cytokine interferon-γ in cardiac tissues.

This effect of IL-33 on the heart raises the question of the usefulness of blocking the action of this cytokine in the presence of CVD also considering that there is evidence that IL-33 levels are lower in patients diagnosed with HF than in healthy controls, suggesting a potentially critical role for this cytokine in the development and progression of HF.[50] However, experimental evidence exists that challenges this hypothesis. Specifically, treatment with recombinant IL-33 protein has been shown to promote atrial remodelling through ST2 signalling.[51] This suggests that blocking the IL-33/ST2 axis may represent a novel therapeutic approach for patients with atrial arrhythmias and elevated serum IL-33.

Targeting IL-17A

It is established that the cytokine IL-17A is instrumental in the expression of a number of pivotal factors, including IL-6, IL-8, granulocyte macrophage colony-stimulating factor, and granulocyte colony-stimulating factor.[111] These factors are indispensable for the recruitment, survival, and activation of neutrophils. In patients diagnosed with stable COPD, there is an increase in serum levels of IL-17A that correlates directly with disease progression and inversely with the predicted percentage of FEV_1.[111]

CNTO 6785 is the only anti-IL-17A mAb that has been studied in individuals diagnosed with COPD.[52] While it produced a slight increase in FEV_1, yet it did not have a notable impact on the other primary or secondary endpoints. Furthermore, more AECOPDs appeared in the CNTO 6785 arm than in the placebo arm at week 16.

Nevertheless, the blockade of IL-17A may prove beneficial in the case of a patient with concomitant CVD.[53] Indeed, IL-17A, whether functioning independently or in conjunction with TNF-α, exerts an influence on all three layers of the vascular wall. In the endothelial cell-rich intima, it promotes inflammatory responses and apoptosis, and contributes to coagulation and thrombosis. In the media, which is composed of vascular smooth muscle cells, it further amplifies inflammation and apoptosis. In the adventitial layer, it drives collagen production, stimulates lipolysis, and alters glucose metabolism. The effects of IL-17A extend to the cardiac wall as well, where it induces apoptosis in cardiomyocytes and stimulates inflammation and collagen production in cardiac fibroblasts. Furthermore, it facilitates the recruitment of leukocytes throughout all layers of the vascular structure.

Targeting the Products of the Cellular Components of Inflammation

A variety of approaches have been undertaken with the aim of developing therapies that are specifically targeted at the products resulting from cellular inflammation. Some of these therapies have undergone evaluation in human subjects.

It has been demonstrated that several proteases, including neutrophil elastase (NE), matrix metalloproteinase (MMP)-9, and MMP-12, are associated with COPD.[11] Considering the intricate proteolytic relationships among α1-antitrypsin (AAT), MMPs, and NE, targeting a single enzyme, whether through an NE inhibitor or an MMP inhibitor, may be insufficient for achieving notable therapeutic results. Indeed, AZD1236, a dual MMP-9/12 inhibitor, was ineffective in patients with moderate-to-severe COPD.[54] Also alvelestat, an oral potent and selective inhibitor of human NE, did not induced changes in lung function or inflammation even when added to budesonide/formoterol maintenance therapy in patients with COPD[55] Conversely, AAT has been demonstrated to function as an inhibitor of NE and a suppressor of macrophage MMP-12 synthesis.[57]

It is disappointing that the reduced efficacy of NE inhibitors and MMP inhibitors in COPD will likely preclude the specific evaluation of these agents in patients with concomitant COPD and CVD. Nevertheless, it has been proposed that NE inhibition may represent a novel approach to the treatment of MI. Indeed, there is evidence to suggest that NE may contribute to myocardial injury by provoking an overactive inflammatory response and suppressing the protein kinase Akt signalling in cardiomyocytes.[112] MMPs play a complex role in the development of atherosclerotic plaques, exerting both beneficial and detrimental effects.[56] Their favourable actions include the promotion of proliferation and longevity of vascular smooth muscle cells, which contribute to plaque stabilisation. This suggests that their use in the cardiopathic patient may be favourable. Conversely, the continuous degradation of the extracellular matrix and the continuous influx of monocytes and macrophages may increase the risk of plaque rupture, which contraindicates their use in the presence of CVD.

Augmentation therapy with intravenous purified AAT is central in the treatment of AAT deficiency despite reaching the lungs in a relatively inactive form.[14,57] The development of AAT formulations for inhalation could potentially address this issue by delivering treatment directly to the target organ. Evidence suggests that significantly higher concentrations of AAT can be achieved in the airway epithelial lining fluid by inhalation compared to intravenous administration.[57] The administration of inhaled AAT for a period of 50 weeks resulted in a statistically significant reduction in the incidence of symptomatic exacerbations classified as Anthonisen type I.[58] However, while there was a trend towards improvement in FEV_1, the treatment had no discernible effect on the time to first exacerbation.

The evidence suggests that individuals with AAT deficiency are more likely to require hospitalisation due to HF and have a higher mortality rate associated with HF.[58] This indicates the feasibility of utilising AAT replacement therapy that could potentially mitigate the cardiovascular damage. The hypothesis was validated through studies conducted on murine models of acute myocardial injury, which revealed that AAT might possess the capability to diminish the size of the ischemic area and sustain systolic function, regardless of the effects attributed to NE.[59] Consequently, administering AAT to patients suffering from ST-segment elevated MI, alongside conventional therapeutic protocols, demonstrated good tolerance and efficacy in alleviating the inflammatory processes linked to the cardiac event.[60]

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[113] 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.

Given that the existing literature contains conflicting data on the cardiac response to activation or suppression of many of the targets that appear to be beneficial in the treatment of COPD, we believe that further investigation of these novel molecules in patients with CVD, is warranted. This evaluation should be conducted at a relatively early stage of their clinical development process. Our rationale is based on the recognition that patients with COPD and comorbid CVD often present significant challenges to manage, necessitating treatments that improve both pulmonary and cardiac function without causing adverse cardiac effects.

Abbreviations

AAT, α1-antitrypsin; AE, adverse effect; AECOPD, acute exacerbation of COPD; BALF, bronchoalveolar lavage fluid; cAMP, cyclic adenosine monophosphate; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Cx43, connexin 43; FEV_1, forced expiratory volume in the first second; HF, heart failure; Ig, immunoglobulin; IL, interleukin; IL-4Rα, IL-4 receptor subunit α; IL-5Rα, IL-5 receptor subunit α; IL-13R, IL-13 receptor; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; MI, myocardial infarction; MMP, matrix metalloprotease; NE, neutrophil elastase; PDE, phosphodiesterase; PI3K, phosphoinositide 3-kinase; RCT, randomized controlled trial; ST2, tumor suppressor protein 2; T, type; TNF-α, tumor necrosis factor-α; TSLP, thymic stromal lymphopoietin.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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