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Prospects for COPD treatment

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Abstract

The management of chronic obstructive pulmonary disease (COPD) is fundamentally still heavily dependent on the use of bronchodilators and corticosteroids. Therefore, there is a need for alternative, more effective and safer therapeutic approaches. In particular, since inflammation in COPD lungs is often poorly responsive to corticosteroid treatment, novel pharmacological anti-inflammatory approaches are needed to optimally treat COPD patients. There have been multiple attempts to develop drugs that inhibit recruitment and activation of inflammatory cells, such as macrophages, neutrophils and T-lymphocytes, in the lungs of patients with COPD or target inflammatory mediators that are important in the recruitment or activation of these inflammatory cells or released by such cells. This review article focuses on novel classes of anti-inflammatory drugs that have already been tested in humans as possible treatments for patients with COPD.

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Introduction

Although the therapeutic approach to chronic obstructive pulmonary disease (COPD) has improved over the last two decades, it is fundamentally still heavily dependent on the use of bronchodilators and corticosteroids [1].

Bronchodilators are the cornerstone of the symptomatic treatment of COPD, even when there is limited reversibility of airflow obstruction [1]. Over the years, there has been an improvement in the effectiveness of existing bronchodilator drug classes in terms of potency, duration of action and improved delivery devices. Additionally, there has been considerable advances in the development of fixed dose combination inhalers containing both a long-acting β_2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), combinations of a bronchodilator with and inhaled corticosteroid (ICS) and more recently the introduction of so called "triple inhalers" containing fixed doses of a LABA, a LAMA and an ICS which we have reviewed extensively elsewhere [2]. Additionally, a number of bifunctional muscarinic antagonist/β_2-adrenoceptor (AR) agonist compounds called MABAs, which are dimer molecules that induce bronchorelaxant effects by eliciting simultaneous blockade of muscarinic receptors and activation of β_2-ARs in the airways, are interesting advances in the class of bronchodilators [2,3]. MABA compounds promise to be an excellent opportunity to coformulate a "triple therapy" combination with an ICS because they reduce the potential problems of formulating different drugs in one inhaler [3].

Considering the central role of bronchodilators in the management of COPD, there remains an interest in identifying new targets for drugs to induce bronchodilation above the effects induced by current drug classes [4]. We have recently extensively reviewed several new opportunities that are mostly still in the preclinical phase of development, and thus it is currently too early to know what additional beneficial bronchodilator effects these new classes of drug will bring [5].

Corticosteroids are currently the main class of anti-inflammatory drugs used in the treatment of COPD, but they can also induce adverse effects when they are administered chronically at high doses, even when administered by inhalation [6]. This concern has recently become a focus of interest because use of ICSs has been associated with an increased risk of pneumonia in patients with COPD [1,6]. The possibility that the anti-inflammatory effects of corticosteroids could be dissociated from their adverse side effects through an independent modulation of the molecular mechanisms underlying transactivation (mediating side effects) and transrepression (mediating anti-inflammatory actions) has increased efforts in searching for dissociated glucocorticoid receptor (GR) agonists that are able to elicit

prevalently transrepression with negligible transactivating activity. Several nonsteroidal selective glucocorticoid receptor agonists (SEGRAs) are currently under pre-clinical or early clinical development, exemplified by GW870086X, AZD5423, and valsecorat [AZD7594]) as discussed elsewhere [7].

A need for alternative and more effective therapeutic approaches

In view of the suboptimal status of current treatments for COPD, there is an urgent need for alternative, more effective and safer therapeutic approaches that will not only relieve symptoms, but will also affect the natural course of the disease by preventing progression of the disease or even have the ability in reversing the disease process.

In particular, it has been highlighted that since inflammation in COPD lungs is often poorly responsive to corticosteroid treatment, novel pharmacological anti-inflammatory approaches are needed to optimally treat COPD patients [8]. So far attention has largely been focused on inhibition of recruitment and activation of inflammatory cells, such as macrophages, neutrophils and T-lymphocytes, in the lungs of patients with COPD. Furthermore, there have been multiple attempts to develop drugs that target inflammatory mediators thought to be important in the recruitment or activation of these inflammatory cells or released by such cells [9].

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 (Table 1).

Inhibition of recruitment and activation of the cellular components of inflammation

The central role of neutrophils in the pathophysiology of COPD suggests that development of drugs targeting neutrophilic inflammation may be of value. Neutrophils contribute to airway damage through release of proteases and reactive oxygen species, leading to loss of alveoli, increased mucus production and mucociliary dysfunction [10]. Neutrophilic inflammation may be modified by targeting the chemoattractants responsible for neutrophil recruitment into the lung or by directly

Table 1

Novel classes of anti-inflammatory drugs that have already been tested in humans and are possible treatments for patients with COPD.

	Classes of drugs	Subclasses	Drugs
Inhibition of recruitment and activation of the cellular components of inflammation			
	PDE inhibitors	Inhaled PDE4 inhibitors	CHF 6001
		Inhaled PDE3/4 inhibitors	Ensifentrine
Drugs that regulate signaling molecules	Chemokine receptor inhibitors	CXCR2 antagonists	Danirixin
	Anti-IL-17A monoclonal antibodies	Anti-free IL-17A	Secukinumab
		Anti-IL-17RA	Brodalumab
	Selectin antagonists	Pan-selectin antagonists	Bimosiamose Rivipansel
		Specific inhibitors of E-selectin	Uproleselan
	PI3K inhibitors	Selective PI3Kδ inhibitors	Nemiralisib RV1729 Idelalisib Umbralisib Leniolisib
	p38 MAPK inhibitors	Oral	Dilmapimod Losmapimod PH797804 Acumapimod
		Inhaled	AZD7624 CHF6297 PF-03715455
	CFTR modulators		Ivacaftor QBW251
	Anti-IL-5 monoclonal antibodies	Anti-free IL-5	Mepolizumab
		Anti-IL-5R	Benralizumab
Antagonism of products of the cellular components of inflammation			
	MMP inhibitors	Selective MMP-12 inhibitors	V85546
		MMP-9/MMP-12 inhibitors	AZD1236
	NE inhibitors	Oral	Sivelestat Alvelestat BAY 85-8501
		Inhaled	CHF6333 POL6014
	Inhaled AAT replacement therapy		

modulating neutrophil function [9,11]. The clinical development of new drugs that directly inhibit the cellular components of inflammation is quite slow because neutrophils are a challenging target also because an excessive inhibition of neutrophil host defense mechanisms can amplify the risk of infections that are common in patients with COPD [9].

Phosphodiesterase (PDE) inhibitors

PDE4 family is an important intracellular target in most of the inflammatory cells implicated in the pathogenesis of COPD [12], including neutrophils, T cells and macrophages. Roflumilast [13] and cilomilast [14] suppress inflammation in the lungs of patients with COPD, which may well contribute to the ability of this class of drug to reduce acute exacerbation of COPD (AECOPDs) when used chronically [12]. Roflumilast is the only PDE4 inhibitor that has been approved as a treatment of COPD and then only as an add-on therapy on top of standard of care. However, this drug induces a number of clinically relevant side effects, particularly in the gastrointestinal tract, as well as unexplained weight loss and in some cases unwanted psychiatric effects. The adverse effects have stopped the development of many examples of this class of drug [15].

In an attempt to improve the therapeutic window of PDE4 inhibitors, a number of inhaled drugs have been developed but in several clinical trials, these drugs have shown little or no efficacy in patients with COPD [16]. The exception is CHF6001 which inhaled on top of standard of care for 32 days was well tolerated and reduced multiple biomarkers of airway inflammation in induced sputum, and serum surfactant protein D in patients with COPD and chronic bronchitis [17]. CHF6001 is currently in Phase IIb clinical trials for the treatment of COPD [16] and the results from these trials are impatiently awaited.

A compound that simultaneously inhibits PDE3 and PDE4 should increase airway caliber by relaxing the smooth muscle and, at the same time, suppress airway inflammatory responses [3] (Figure 1). A single dose of nebulized ensifentrine, which is a PDE3/4 inhibitor, caused a significant improvement in forced expiratory volume in 1 s (FEV_1) that at the peak was similar to that caused by salbutamol 200 μg in a small group of patients with mild-to-moderate COPD, and significantly reduced the number of neutrophils, total cells, macrophages, eosinophils and lymphocytes in the sputum of healthy individuals 6 h after a challenge with lipopolysaccharide [18]. In other short-term studies, ensifentrine significantly reduced lung volumes and airway resistance compared with placebo, and when added to salbutamol, ipratropium or tiotropium induced additional bronchodilation and a significant additive effect on lung volume [19].

In a four-week Phase IIb dose-ranging study, four ensifentrine doses significantly improved bronchodilation and symptoms, with a dose-ranging effect, and were well tolerated in a large number of patients with moderate-to-severe COPD [20]. Ensifentrine has recently entered Phase III clinical development.

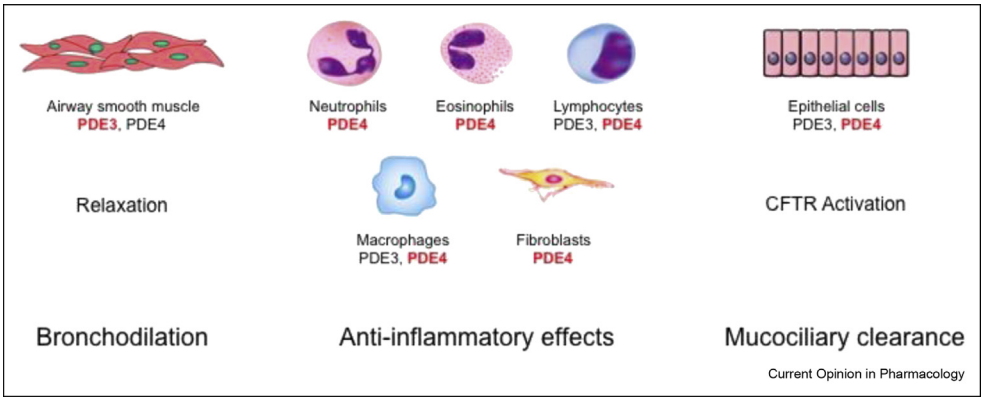
Drugs that regulate signaling molecules

Multiple signaling molecules help regulate various cells implicated in airways inflammation and remodeling and are plausible molecular targets for the treatment of COPD [21].

Chemokine receptor inhibitors

Inflammatory chemokines induce neutrophil migration and activation in the lung. Chemokines, divided into CXC, CC, C and CX3C families based on the number and spacing of conserved cysteines at the amino terminus [22], signal through G-protein-coupled CXC

Figure 1



Combined inhibition of phosphodiesterase (PDE)3 and PDE4 has additive and synergistic anti-inflammatory and bronchodilatory effects versus inhibition of either PDE3 or PDE4 alone. Furthermore, it increases mucociliary clearance. In red, the main PDE involved in the activity of the specific cell.

chemokine receptor 1 (CXCR1) or 2 (CXCR2). In particular, CXCR2 and its ligands have been implicated in the pathogenesis of COPD [23] and CXCR2 is expressed on monocytes.

Interleukin (IL)-8 (CXCL8) is a chemokine that has been demonstrated to specifically recruit neutrophils into inflamed tissues. A fully human monoclonal antibody (mAb) that only recognizes free CXCL8 [24] has been tested in a Phase II pilot study in patients with COPD and the results from this trial suggested that neutralization of CXCL8 may improve dyspnea, although it did not improve lung function or health status [25]. The clinical failure of this mAb is likely due to the fact that the active form of CXCL8 is bound to proteoglycans on the endothelial surface [9]. Blocking the ligand–receptor interaction with mAbs or small molecular inhibitors to prevent the recruitment and activation of leukocytes induced by chemokines has the potential to overcome this issue [11].

The neutrophil CXCR2 receptor is another promising target as a treatment for COPD. Several CXCR2 antagonists, such as SCH5 27123, SB-656933, QBM076, AZD5069 and navarixin, have been investigated as potential treatments for COPD, but the Phase II studies had to be terminated due to adverse events [26]. Futher small-molecule chemokine receptor antagonists (repertaxin and danirixin) have been developed as a potential therapeutic approach for the treatment of other inflammatory diseases and may have benefit in patients with COPD [26].

Danirixin has been evaluated in two 52-week randomized control trials (RCTs) in stable COPD patients. In the first trial, it significantly improved symptoms (breathlessness, cough and sputum) and also decreased the number of days free from AECOPDs compared with placebo [27]. However, in a 24-week, dose-finding Phase II study that enrolled over 600 COPD patients at high risk of AECOPDs (NCT03034967), danirixin did not significantly improve AECOPD or change respiratory symptoms measured by Evaluating Respiratory Symptoms tool in COPD compared to placebo. Consequently, the second 52-week RCT (NCT03170232) that was evaluating the effects on lung function and quality of life in mild to moderate COPD patients was terminated [28].

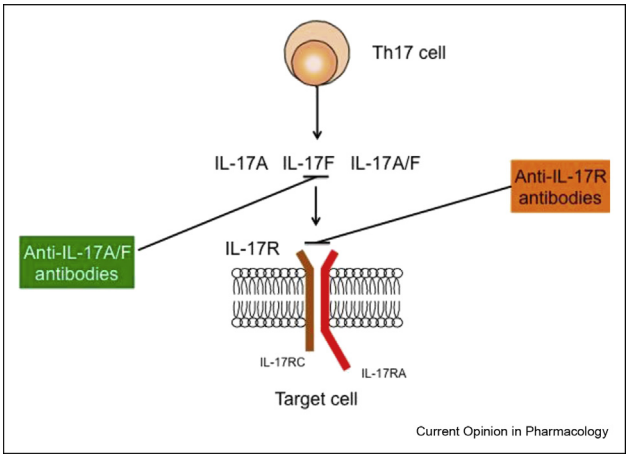
Also a 26-week Phase IIb RCT in symptomatic patients with mild to moderate COPD at risk for AECOPDs failed to show any benefit on the incidence and severity of respiratory symptoms, but reported a high incidence of AECOPDs and incidence of pneumonia [29]. Moreover, a 14-day Phase II RCT (NCT03250689) that evaluated the effect of danirixin on neutrophil extracellular trap formation in stable COPD patients was terminated as a result of a change in the benefit–risk profile [28].

Anti-IL-17A monoclonal antibodies

The interleukin (IL)-17 superfamily triggers production of numerous chemokines, resulting in neutrophil and macrophage recruitment as part of "host defense" [30]. It comprises of six members (IL-17A–17F) and five receptors (IL-17RA–17RE) [30]. IL-17A is the most potent member [30]. It is produced by Th17 cells and a number of other cell types, including γδT cells, lymphoid tissue inducer cells, innate lymphoid cells, and natural killer cells [30]. IL-17A is able to induce factors such as IL-6, IL-8, granulocyte macrophage colony stimulating factor and granulocyte colony stimulating factor that are important in neutrophil recruitment, survival and activation. Its serum levels are increased in patients with stable COPD and correlate directly with the stage of COPD, and inversely with predicted FEV_1 percentage [30]. There is evidence that blocking IL-17A using a neutralizing antibody significantly decreases neutrophil recruitment and the pathological score of airway inflammation in tobacco-smoke-exposed mice [31]. Therefore, targeting IL-17A maybe a possible new approach to treating patients with COPD [32] (Figure 2).

To this end, a number of monoclonal antibodies (mAbs) against free IL-17A and IL-17RA are in development [30,32]. However, neutralizing IL-17A with secukinumab, an anti-IL-17A mAb, did not attenuate acute ozone-induced airway neutrophilia in healthy subjects [33]. Furthermore, there is concern that targeting the

Figure 2



All of the IL-17 isoforms exist as homodimers, but IL-17A and IL-17F can also form a heterodimer, IL-17A/F. A heterodimer of IL-17RA and IL-17RC is the receptor for IL-17A. Secukinumab and CNTO-6785 bind IL-17A and block the binding of both IL-17A and IL-17A/F to their receptor. Brodalumab binds IL-17RA and blocks the binding of IL-17A and IL-17A/F to their receptor.

IL-17 pathway may result in further exacerbation of bacterial infection in the context of COPD by dampening "host defense." Nonetheless, a study using a nontypeable *Haemophilus influenza*e AECOPD model in mice showed that IL-17$^{-/-}$ mice and mice treated with an IL-17-neutralizing antibody were protected against enhanced pulmonary neutrophilia [34].

CNTO 6785 is a fully human immunoglobulin G1 lambda mAb that binds to human IL-17A with high affinity and specificity, and prevents IL-17A from binding to its receptors on the cell surface [35]. In a Phase II proof-of-concept RCT, this antibody did not demonstrate significant efficacy above the standard of care compared with placebo in patients with moderate-to-severe symptomatic COPD [35]. Furthermore, an increased rate of AECOPDs was observed.

Secukinumab and brodalumab, an anti-IL-17RA mAb, have been tested in patients with asthma, but not yet in patients with COPD. Secukinumab was examined in subjects with severe asthma not adequately controlled despite high doses of ICSs and LABAs [36]. Patients who responded to secukinumab had enriched nasal epithelial neutrophilic inflammation, significantly lower total IgE levels when compared to nonresponders and downregulated markers of IgE-driven systemic inflammation. Brodalumab did not result in a significant effect on multiple parameters in patients with inadequately controlled moderate-severe asthma but might have had some effect in a subset of patients whose disease was considered highly reversible [37].

ABT-122 (IL-17A and TNF-α bispecific dual variable domain immunoglobulin), COVA322 (bispecific IL-17A/TNF-α inhibitor), ALX-0761 (anti-IL-17A/F bispecific nanobody), bimekizumab (anti-IL-17A/F bispecific mAb), NI-1401 (anti-IL-17A/F bispecific mAb) and SCH 900,117 are other candidates targeting IL-17A [38], but to date there is no report of the effectiveness of any of these agents in patients with COPD.

Selectin antagonists

Selectins are essential for migration of inflammatory cells from the bloodstream into pulmonary tissue; they mediate transient adhesive interactions pertinent to inflammation [9]. There are three members of the selectin family (E-, L-, P-selectin). E- and P-selectin are expressed on endothelium, whilst L-selectin is expressed constitutively on circulating leukocytes. An overabundance of molecules that inhibit selectin-ligand interactions have been developed, but only a few compounds have showed promising results in clinical trials [39]. Inhaled bimosiamose is a synthetic pan-selectin antagonist that has shown encouraging results in a Phase IIa trial in patients with COPD. After its administration for 4 weeks on top of standard bronchodilator therapy, it induced an attenuation of airway inflammation and small lung function improvements [40]. Also, uproleselan, a specific inhibitor of E-selectin, and rivipansel (GMI-1070), a pan-selectin antagonist, have been tested in humans, but not yet in patients with COPD [39].

Phosphoinositide 3-kinase (PI3K) inhibitors

PI3K catalyzes the production of phosphatidylinositol-3,4,5-triphosphate (PIP3) and is important in the activation of macrophage and neutrophils [41]. Since PI3K function may be altered in COPD [41], the inhibition of the δ isoform of PI3K, which plays a recognized role in regulating neutrophil trafficking and directional movement and also hyperphosphorylation and ubiquitination of histone deacetylase 2 that cause a reduction in its activity and, consequently, in glucocorticoid sensitivity [41], has been suggested as a possible therapeutic strategy for this disease [9].

Some small-molecule inhibitors of PI3Kδ are in clinical development. Two of them, ZSTK474 that is a pan PI3K inhibitor, and GSK045, a selective PI3Kδ inhibitor, reduced matrix metalloproteinase 9 (MMP-9) activation and reactive oxygen species production in neutrophils obtained from patients with either stable COPD or during an AECOPD, while corticosteroids had no effect in the same assays [42].

In healthy smokers, nemiralisib, a potent inhaled PI3Kδ inhibitor that is > 1000-fold more selective at PI3Kδ than 250 other kinases [43], showed acceptable tolerability and a well-defined pharmacokinetic profile with significantly higher levels of the drug in the lung compared with plasma. This drug inhibited PI3Kδ in the target organ, as proved by the reduction of PIP3 in sputum, with a linear relationship observed between plasma exposure and reduction in PIP3 levels [44]. However, it has also been reported that despite good lung retention of this drug, as documented by the presence of nemiralisib in bronchoalveolar lavage at 24 h, target engagement (reduction of PIP3 in sputum) was only present at 3 h [45].

Four Phase II RCTs (NCT02294734, NCT02130635, NCT02522299, NCT03345407) have investigated the pharmacokinetic behavior and efficacy of nemiralisib mainly in patients with moderate to severe AECOPDs [28].

In a 3-month study of patients with an AECOPD (NCT02294734), inhaled nemiralisib administered as add-on to standard care improved lung function parameters measured by high-resolution computed tomography compared with placebo and reduced the risk and severity of subsequent exacerbation events [46]. A second RCT found a reduction in sputum IL-6 (29%)

and IL-8 (32%) levels following inhalation of nemiralisib for 14 days in patients with stable COPD [47]. Nemiralisib was rapidly absorbed into plasma following a single inhaled nemiralisib 100−2000 μg with a maximum peak at approximately 2 h. Following repeat administration, accumulation in plasma was approximately 2−3 fold from Day 1 to Day 7. Short post-inhalation cough was reported.

Another Phase II study (NCT02522299) showed that treatment with nemiralisib 1000 μg via DISKUS or 700 μg via ELLIPTA did not improve trough FEV_1 or in the use of rescue medication, compared to placebo [28]. C_{max} was 508.4 pg/mL for nemiralisib administered via DISKUS and 1103.4 pg/mL for nemiralisib via ELLIPTA. Adverse events were present in both groups. A large Phase II RCT (NCT03345407) investigated the efficacy and safety of nemiralisib administered from 12.5 μg to 750 μg via the ELLIPTA inhaler to COPD patients with history of AECOPDs, but the study recruitment was terminated due to an unfavorable benefit-risk profile [28].

RV1729, a PI3Kδ(/γ) inhibitor, has been tested in a Phase I trial in COPD patients to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of repeat doses of this drug administered for 28 days (NCT02140346), but no results have been reported yet.

Other PI3Kδ-selective compounds tested in humans include idelalisib, which is approved for treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma, umbralisib, which is in Phase II trials for the treatment of leukemia and lymphoma, and leniolisib, in Phase II/III trials for the treatment of primary Sjögren's syndrome and activated PI3Kδ syndrome/lymphadenopathy and immunodeficiency [48]. However, these compounds, as far as we know, have not yet been tested in COPD patients.

It has been suggested that PI3Kδ inhibitors that can be administered by inhalation will have an improved safety profile and may be more appropriate for patients who are primarily affected by airway infections, potentially limiting the progression of bronchiectasis [49].

p38 MAPK inhibitors

Mitogen-activated protein kinases (MAPKs) play a key role in chronic inflammation. MAPK pathways are mediated through extracellular-signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38, which is considered to be a central regulator of inflammation [50]. p38 MAPK subgroup includes four isoforms (α, β, γ, δ). p38α MAPK seems to play a prominent role in COPD [51]. The p38 MAPK pathway is activated in COPD by several extracellular stimuli that, in turn, stimulate inflammatory gene transcription.

Several p38 MAPK inhibitors have been tested in patients with COPD. Dilmapimod, losmapimod, PH797804 and acumapimod are all oral p38 MAPK inhibitors. In a 4-week treatment in patients with COPD, dilmapimod induced a reduction in sputum neutrophils and in serum fibrinogen, but not in serum C-reactive protein (CRP), IL-8, IL-1β, or IL-6, with an improvement in forced vital capacity, but not in FEV_1 [52]. Losmapimod is a dual p38α/β inhibitor that caused an 11% reduction in plasma fibrinogen, with a trend toward lower CXCL8, IL-6 and CRP plasma levels, and produced some improvement in lung hyperinflation in patients with COPD [53]. However, in patients with severe COPD the drug failed to meet the primary outcome, which was an increase in exercise tolerance, and there were no trends in improvement of an extensive range of lung function measures or in the plasma levels of fibrinogen and CRP [54]. PH797804, which is an inhibitor of p38α, produced significant improvements in trough FEV_1 and in dyspnea in patients with COPD [55]. When studied in moderate to severe COPD patients on a background of ICS/LABA, PH797804 caused a decrease in serum CRP [56]. In a Phase II RCT, repeated single-dose of acumapimod on Days 1 and 6 showed an improvement in FEV_1 at Day 8 that was clinically relevant compared with placebo, along with consistent numerical differences in EXACT-PRO, in patients with moderate or severe AECOPD [57].

Inhaled delivery of p38 MAPK inhibitors may enhance p38 inhibition in the lung while reducing unwanted systemic effects. Several inhaled p38 MAPK inhibitors have been tested in COPD. AZD7624, a dual p38α/β inhibitor, had a greater effect than budesonide on cytokine production from bronchial epithelial cells in COPD patients [58], but failed to provide any benefit in a 3-month AECOPD Phase IIa RCT [59]. RV568, a dual p38α/γ inhibitor, significantly reduced sputum malondialdehyde compared to placebo in patients with COPD, although there were no changes in sputum cell counts and only a modest FEV_1 increase [60]. Safety, tolerability and efficacy of CHF6297, a p38α inhibitor, has been assessed in a recent Phase II RCT in COPD patients (NCT02815488), but the results of the trial are yet to be reported. PF-03715455 is another dual p38 α/β inhibitor whose safety and efficacy has been assessed in a Phase II RCT (NCT02366637) in subjects with moderate to severe COPD. However, the effect of PF-03715455 on trough FEV_1 was not significantly different from placebo [28].

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators

Developed primarily for the treatment of cystic fibrosis, CFTR modulators have the potential to be useful in COPD because dysfunction of CFTR induced by smoking-related oxidative stress is associated with

reduced lung function, disease severity and clinical symptoms in COPD [61].

Two CFTR potentiators, ivacaftor (VX-770) and QBW251, have been evaluated in patients with COPD. In the pilot Phase I RCT, ivacaftor did not improve FEV_1 compared to placebo, but improved symptoms and sweat chloride levels, and caused a ~20% improvement in CFTR activity, with no real safety concerns [62]. In a Phase II RCT, after 28 days of treatment, QBW251 produced small improvement over placebo in the change from baseline in pre- and post-bronchodilator FEV_1. It also improved sweat chloride and inflammatory markers (fibrinogen), and decreased sputum colonization, although no difference was found in the primary outcome of lung clearance index [63].

Anti-IL-5 monoclonal antibodies

Persistent eosinophilic inflammation can be a feature of some patients with COPD and is associated with an increased risk of AECOPDs [64]. These patients have increased IL-5 concentrations in sputum [65]. IL-5 is central in the differentiation and maturation of eosinophils in bone marrow and the survival of this cell type in tissues [66]. Thus, anti-IL-5 treatments with mepolizumab, a humanized mAb that recognizes free IL-5, and benralizumab, a humanized mAb directed at the α subunit of the IL-5R, have been studied in patients with COPD, mainly those with increased blood and airway eosinophils [67,68].

The effect size observed in these trials was smaller than that seen with these drugs in patients with severe asthma, but with benefits directly related to the intensity of eosinophilic inflammation. Consequently, a Phase III study is evaluating the efficacy and safety of a benralizumab in patients with moderate to very severe COPD with a history of frequent AECOPDs and elevated peripheral blood eosinophils (≥300/μL) (NCT40536349).

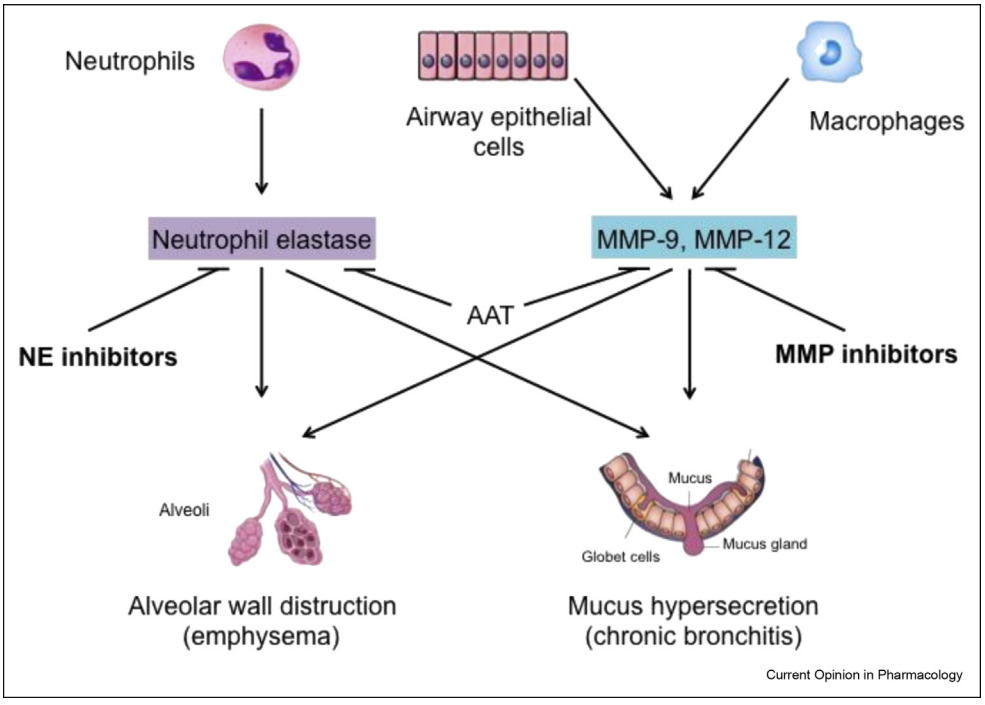
Antagonism of products of the cellular components of inflammation

MMPs, especially MMP-9 and MMP-12, and neutrophil elastase (NE) are produced by neutrophils and macrophages [69] (Figure 3). These enzymes are strongly implicated in the inflammatory pathway characterizing COPD, with effects not only on proteolysis but also on perpetuation and regulation of inflammation.

Matrix metalloproteinase inhibitors

Matrix metalloproteinase inhibitors (MMPs) are recognized as promising diagnostic and therapeutic targets in

Figure 3



Several proteases, such as neutrophil elastase (NE) and metalloproteinases (MMP-9 and MMP-12) are implicated in COPD so that blocking a single enzyme with a NE inhibitor or a MMP inhibitor may not have a major therapeutic effect. α_1-Antitrypsin (AAT) inhibits NE and suppresses MMP-12 production by macrophages.

COPD. In fact, MMP inhibition might be an effective strategy to treat COPD [70], although few clinical studies have been performed with MMP inhibitors, due to the potential for off-target effects [71].

The development of drugs inhibiting MMPs is still at an early stage. V85546, a selective MMP-12 inhibitor, and AZD1236, a MMP-9 and MMP-12 inhibitor, are two small molecules that have been tested in humans. V85546 completed phase I clinical testing [72], whereas AZD1236 showed no clinical efficacy in the short term after 6-weeks treatment in patients with moderate-to-severe COPD and did not affect any pro-inflammatory biomarkers including sputum expression of MMP-8 and MMP-9 proteins and the activity of MMPs [73,74].

Neutrophil elastase inhibitors

NE is the primary enzyme present in azurophil granules in the neutrophil cytoplasm. Its activity in the lung may lead to lung parenchyma destruction and increased production of inflammatory mediators [75]. Consequently, compounds have been developed to antagonize NE not only to protect the lungs from NE-mediated tissue damage but also to control over exuberant inflammatory responses [76].

At present, only sivelestat (ONO-5046) is on the market in Japan and South Korea for the treatment of acute lung injury and in acute respiratory distress syndrome in patients with a systemic inflammatory response [77]. There are also a number of other NE inhibitors currently in various stages of clinical development that, however, are not specifically focused on COPD.

Alvelestat is currently in clinical trials that aim to reduce lung damage and slow the progression of lung disease in patients with α_1-antitrypsin (AAT) deficiency [77]. However, this drug did not show clinical benefit and effect on biomarkers of inflammation or tissue degradation when added to tiotropium in patients with COPD [78]. Furthermore, alvelestat had no effect on lung function, respiratory signs and symptoms or SGRQ-C score when added to budesonide/formoterol maintenance therapy [79].

Safety and tolerability of BAY 85-8501 have been successfully evaluated in patients with noncystic fibrosis bronchiectasis in a Phase IIa RCT [80]. CHF6333, the first inhaled NE inhibitor under development is currently in Phase I clinical trials [77]. Single ascending doses of inhaled POL6014 have been positively tested in healthy volunteers and in subjects with cystic fibrosis [81].

Inhaled α_1-antitrypsin replacement therapy

AAT deficiency in COPD patients is another pending issue [82]. It is a common but under-recognized genetic condition that predisposes to COPD. The circulating human protein AAT is an effective inhibitor of NE, providing greater than 90% of the defense against the elastolytic burden in the lower airways posed by NE [83]. Furthermore, AAT is an important controller of neutrophilic inflammation, particularly in the lungs [84].

Augmentation therapy with intravenous purified AAT is central in patients with AAT deficiency, although it arrives at the lung in a relatively inactive state [85]. The development of AAT formulations to be administered by inhalation could overcome this problem by acting directly on the organ of interest [85]. Some data show that much higher local AAT levels in the airway epithelial lining fluid have been achieved with the inhaled route compared to delivery with the intravenous route [86]. However, in AAT deficiency patients with severe COPD and frequent AECOPDs, AAT inhalation had no effect on the time to first AECOPD during treatment for 50 weeks [87]. Characteristics of the protein such as particle size, density, lipophilicity and charge still need to be optimized to achieve stability of the formulation, and then tested with a suitable drug delivery system to achieve dosing consistency in order to provide an opportunity for the inhaled AAT to have a biochemical effect in reaching and maintaining protective AAT levels in lung tissue [88].

Conclusion

In recent years, the search for drugs beyond the use of bronchodilators and ICSs in the treatment of patients with COPD, such as IL-1β, IL-13, TNF-α, IκB kinase 2, inducible nitric oxide synthase, β_2-integrin, secretory phospholipase A2 and adenosine receptor 2a, has led to the discovery and study of a large number of molecules with different pharmacological properties that could potentially be used in the treatment of COPD. Many of these approaches have failed to reach the clinical development stage or have failed in the clinic, and so we have deliberately limited this review to therapeutic possibilities already tested in humans and which, in our opinion, have the possibility of further development in COPD.

However, even if only a small number of the drugs we have described succeed in becoming approved medicines for the treatment of COPD, we can say that the much-desired "light at the end of the tunnel" invoked several years ago by Peter Barnes [89] is really appearing.

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Conflict of interest statement

Nothing to be declared.

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- • of special interest
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