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REVIEW

Emerging pharmaceutical therapies for COPD

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Abstract: COPD, for which cigarette smoking is the major risk factor, remains a worldwide burden. Current therapies provide only limited short-term benefit and fail to halt progression. A variety of potential therapeutic targets are currently being investigated, including COPD-related proinflammatory mediators and signaling pathways. Other investigational compounds target specific aspects or complications of COPD such as mucus hypersecretion and pulmonary hypertension. Although many candidate therapies have shown no significant effects, other emerging therapies have improved lung function, pulmonary hypertension, glucocorticoid sensitivity, and/or the frequency of exacerbations. Among these are compounds that inhibit the CXCR2 receptor, mitogen-activated protein kinase/Src kinase, myristoylated alanine-rich C kinase substrate, selectins, and the endothelin receptor. Activation of certain transcription factors may also be relevant, as a large retrospective cohort study of COPD patients with diabetes found that the peroxisome proliferator-activated receptor γ (PPARγ) agonists rosiglitazone and pioglitazone were associated with reduced COPD exacerbation rate. Notably, several therapies have shown efficacy only in identifiable subgroups of COPD patients, suggesting that subgroup identification may become more important in future treatment strategies. This review summarizes the status of emerging therapeutic pharmaceuticals for COPD and highlights those that appear most promising.

Keywords: pulmonary, PPAR, phosphodiesterase, emphysema, cigarette, mucus

Introduction

COPD affects ~200 million people worldwide[1] and is the third leading cause of death in the US, claiming ~150,000 lives in 2013.[2] Approximately 6.3% of US adults aged ≥18 years have COPD,[3] and its combined indirect and direct costs in 2010 surpassed $52 billion. More effective treatments for COPD are needed to address this serious health problem. This review summarizes the status of potential therapies currently or recently in clinical trials and highlights those that appear most promising.

COPD pathology

COPD, a complex and heterogeneous chronic progressive inflammatory disease of the distal airways characterized by persistent airflow limitations, typically results from inhaling noxious gases and particles, especially cigarette smoke.[4–6] The resulting inflammatory response involves increased numbers of neutrophils, macrophages, B cells, and $CD4^+$ and $CD8^+$ T lymphocytes in the airways.[7] Histopathological changes include edema, loss of alveoli, and tissue remodeling involving smooth muscle hypertrophy and fibrosis, which are associated with bronchoconstriction and airway mucus hypersecretion exacerbated by reduced clearance.[5–8] The accompanying systemic inflammation and increased reactive oxygen species (ROS) in patients may contribute to such manifestations as cardiovascular complications, loss of skeletal muscle, osteoporosis, and psychosocial effects.

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COPD exacerbations

COPD exacerbations can significantly accelerate lung function decline and overall health. In patients with severe COPD, acute exacerbations requiring hospitalization account for up to 50% of COPD health care costs. Exacerbation risk appears to be associated with serum eosinophilia: in patients with clinical COPD and serum eosinophils above 0.34×10^9 cells/L, risk of severe and moderate exacerbations were increased compared to those in patients with fewer eosinophils.[9] Causes of COPD exacerbations appear multifactorial and elusive but may include bacterial or viral infections, exposure to environmental pollutants, and unidentified factors.[5] Exacerbations are accompanied by a rapid rise of proinflammatory cytokines and chemokines that trigger and sustain rapid influx of neutrophils and their products such as neutrophil elastase into the airways.[10,11] Reduction in the frequency of COPD exacerbation is a primary or secondary end point of several current clinical trials of emerging therapies.[12,13]

Treatment of stable COPD

The American Thoracic Society and other leading pulmonary disease organizations recommend that COPD patients cease smoking and use one or more inhaled bronchodilators.[14] The wide choice of inhaled bronchodilators includes short-acting beta$_2$-agonists (SABA) and long-acting beta$_2$-agonists (LABA), short-acting muscarinic antagonists (SAMA) and long-acting muscarinic antagonists (LAMA), and combinations of β-agonists and antimuscarinic agents. Inhaled corticosteroids (ICS) and combinations of corticosteroids with other agents may also be used. Oral medications, including methylxanthines and a phosphodiesterase 4 (PDE4) inhibitor, may also be used as adjunctive agents or, in the case of systemic corticosteroids, for acute exacerbations.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recently categorized COPD patients into four groups, in which the familiar spirometry-based grades (GOLD I–IV) are supplemented by patients' symptom burden (assessed by the modified British Medical Research Council questionnaire or COPD Assessment Test) and exacerbation history: spirometry and exacerbation history are jointly used to determine the risk of adverse health events.[5] Groups A and C have relatively mild symptoms, while Groups A and B have relatively low risk. GOLD recommends that Groups A and B receive SABA, LABA, SAMA, or LAMA bronchodilators. It recommends that Groups C and D also receive ICS or possibly the PDE4 inhibitor roflumilast. Despite symptomatic relief and reduced rates of exacerbations with current medications, long-term studies of treated COPD patients suggest that medications do not halt the decline of lung function[4] and resulting mortality, although there is limited evidence that fluticasone and/or salmeterol may slow the rate of decline.[15,16] Several groups are pursuing identification of biomarkers for COPD subgroups based on either the etiological agent/event triggering the exacerbation or the physiological targets that may indicate response to a given therapy.[6,17] For example, COPD patients with higher levels of exhaled nitric oxide (FeNO) had a greater probability of the enhanced eosinophilic infiltration[18] that is associated with a greater response to corticosteroids.[19–21] These studies carry significant implications both for current treatment and for the development of novel therapies that may be targeted to specific groups of patients.

Inflammation in COPD

Smoke, from cigarettes, biomass fuel, or air pollution, is a common inducer of inflammation in COPD. The inhaled irritants provoke significant oxidative stress and activate inflammatory cells.[22,23] Excess neutrophils and macrophages, along with T cells, B cells, and dendritic cells, infiltrate the peripheral airways,[24–26] concurrent with the narrowing or obliteration of small bronchioles.[27] A number of inflammatory markers are significantly elevated in the serum of patients with COPD, notably including CD40 ligand, epidermal growth factor (EGF), brain-derived neurotrophic factor (BDNF), a variety of acute-phase proteins, and neutrophil-associated proteins.[28] These molecules may represent targets for future COPD therapies.

Glucocorticoid (GC) resistance

COPD is relatively resistant to modulation by corticosteroids, as even high doses of GCs do not delay or inhibit COPD progression. Histological analysis of lung tissue removed during lung volume reduction surgery of COPD patients indicated that GC treatment significantly reduced the number of airways with lymphoid follicles but had no long-term effect on luminal occlusion or airway wall thickening.[29]

Corticosteroids suppress inflammation both by activating transcription of anti-inflammatory and suppressing transcription of proinflammatory genes.[30] Binding of corticosteroids to the classic glucocorticoid receptor (GRα) leads to activation, which allows release from its cytoplasmic anchor. The receptor is then acetylated, allowing binding to response elements in the promoter elements of target

genes, and recruitment of coactivators such as CREB-binding protein, with consequent transcriptional activation. GC-mediated gene repression requires histone deacetylase 2 (HDAC2) at two distinct steps.[31] First, this acetyl group must be removed by HDAC2 to allow binding to proinflammatory transcription factors such as nuclear factor-κB (NF-κB). Second, activated GR recruits HDAC2, which then deacetylates histones and thus inactivates transcription. Alveolar macrophages (AMs), lungs, and bronchi of COPD patients express lower levels of HDAC2 than those in healthy controls,[32] however, and theophylline treatment, which enhances HDAC activity in AMs, also restores AM GC sensitivity.[33] These effects may underlie the reported ability of theophylline treatment (200–400 mg/day, depending on weight), added to the LABA formoterol and the GC budesonide in a 50-patient (study completion) single-blinded, placebo-controlled study, to improve 6-minute walk distance and forced expiratory volume in 1 second (FEV_1).[34] However, a double-blind, placebo-controlled study in 46 per-protocol patients found no effect of low-dose (100 mg bid) theophylline added to fluticasone plus salmeterol on HDAC activity, inflammatory biomarkers, or frequency of exacerbation.[35]

Observed COPD-associated reductions in HDAC2 are believed to result from oxidative and nitrosative stress,[32] and levels of the antioxidant transcription factor NF-E2–related factor 2 (Nrf2) are similarly reduced in AMs of COPD patients.[36] Treatment with the Nrf2 activator sulforaphane, similar to theophylline treatment, increases HDAC2 activity and restores GC sensitivity.[37]

A number of other mechanisms of GC resistance have also been suggested.[30] Among these may be increased expression of the translationally inactive GRβ, although this remains controversial[30] and GR expression has been found to be reduced in lungs of healthy smokers and COPD patients.[38] Another possibility is posttranslational modifications of GRα by phosphorylation or nitrosylation.[39] Such phosphorylation may be due to p38 mitogen-activated protein kinase (MAPK) activation, and p38 MAPK inhibitors have been shown to reduce the GC resistance seen in some patients with severe asthma.[40]

Restoration of GC sensitivity is an attractive strategy for the development of novel pharmaceutical therapies. As previously noted, the ability of theophylline treatment to accomplish this is controversial.[34,35] However, roflumilast has been shown ex vivo to improve GC sensitivity of neutrophils from COPD patients,[41] and subgroup analysis of two clinical trials showed that patients receiving ICS were among those particularly likely to experience a reduction of exacerbations in roflumilast treatment.[42] A subsequent 1-year trial showed that roflumilast treatment reduced exacerbations in patients also receiving ICS and LABA.[13]

Proinflammatory cytokines and chemokines

Numerous proinflammatory cytokines and chemokines are significantly higher in COPD patients than in healthy controls,[43] and multiple biologics and small molecules that target these mediators are under investigation (Tables 1 and 2). Chemokines significantly contribute to inflammation

Table 1 Developmental status of chemokine receptor inhibitors for COPD

Mediator	Role in COPD	Drug	Clinical development	References
CCR1	Receptor for CCL3 (MIP-1α) and chemoattractant for inflammatory cells. CCR1 is also among receptors binding CCL5 and CCL7.	AZD4818	AZD4818 (4-week treatment) provided no significant benefit to COPD patients (NCT00629239).	46
CCR2	Receptor for CCL2 (MCP-1), which recruits inflammatory cells to lungs in COPD. Increases synthesis of MUC5AC and MUC5B.	AZD2423	AZD2423 (28-day treatment) in DBPCRT (NCT01215279); study has completed but statistical analysis not released.	47, 48
CXCR2 (IL8RB)	Activated by CXCL8 (IL-8), which is higher in BAL and sputum of COPD patients. CXCL8 is chemotactic for neutrophils.	Navarixin (MK-7123); AZD5069	MK-7123 (navarixin; 6-month treatment) in DBPCRT showed statistically significant improvement in postbronchodilator FEV_1 (NCT01006616 and NCT00441701). AZD5069 (4-week treatment) in DBPCRT in patients with moderate-to-severe COPD reduced blood neutrophil counts with no increased infection (NCT01233232).	44, 45

Abbreviations: DBPCRT, double-blind, placebo-controlled, randomized trial; IL-8, interleukin 8.

Table 2 Developmental status of cytokine inhibitors for COPD

Mediator	Role in COPD	Drug	Clinical development	References
IL-1	Promotes proinflammatory responses. Elevated in stable COPD and further increased in exacerbations.	Canakinumab, a human anti-IL-1β monoclonal antibody	A phase I/II RDBPCES of canakinumab (NCT00581945) (45-week treatment), no statistical analysis provided for lung function changes.	49, 50
IL-5	Mediates eosinophil maturation and mobilization; eosinophils increased during some exacerbations.	Mepolizumab (MAb against IL-5), benralizumab (MEDI-563; MAb against IL-5Rα)	Mepolizumab (26–52-week treatment) tested as adjunct in DBPCRT targeting COPD exacerbation rate, studies completed, but results not posted (NCT02105948, NCT01463644, and NCT02105961). Benralizumab (≤56-week treatment) has completed a trial for moderate-to-severe COPD (NCT01227278), but no evidence of efficacy was observed; studies for exacerbation reduction and other effectiveness measures (NCT02155660 and NCT02138916) are ongoing.	9, 51
IL-13	Plasma but not sputum concentrations inversely correlated with FEV_1 in COPD. IL-13 induces goblet cell hyperplasia and mucus hypersecretion.	Lebrikizumab, a humanized anti-IL-13 MAb	There is a study of lebrikizumab (24-week treatment) for decline in frequency of COPD exacerbations and lung function (NCT02546700).	100–102
IL-17A	One study found IL-17 reduced in sputum of severe COPD patients but another found numbers of $CD4^+$ Th17 cells in the airways correlated with airflow limitations.	CNTO6785	CNTO6785 (12-week treatment) is being investigated in moderate-to-severe COPD in DBPCRT (NCT01966549). No results reported yet.	43, 53, 58
Tumor necrosis factor	Higher levels in sputum and serum of COPD patients; augments inflammation.	Infliximab, etanercept	Infliximab (6-month treatment) (NCT00056264) showed no clinical benefit but toxicity – higher rate of pneumonia and malignancies; however, difference in malignancy rate diminished greatly on long-term follow-up (NCT00380796), making the results difficult to interpret. Etanercept (90-day treatment) (NCT00789997) was not more efficacious than prednisone for the treatment of exacerbations.	28, 103–105

Abbreviations: IL, interleukin; RDBPCES, randomized, double-blind, placebo-controlled, exploratory study; MAb, monoclonal antibody; DBPCRT, double-blind, placebo-controlled, randomized trial; FEV_1, forced expiratory volume in 1 second; Th17, T helper 17.

by attracting neutrophils and other inflammation-related cells, and an antagonist of the CXCR2 receptor for interleukin (IL)-8 and other chemokines[44] has been found beneficial in COPD patients. A different CXCR2 inhibitor reduced blood neutrophil counts with no increased rate of infection,[45] but compounds blocking CCR1[46] and CCR2[47,48] (NCT01215279) had no effect.

IL-1 expression was significantly higher in lung and sputum from COPD patients compared to non-COPD controls.[49] However, treatment with a monoclonal antibody (MAb) inhibiting IL-1β (canakinumab)[50] remains an open question in COPD patients (Table 2).

IL-5 is largely produced by eosinophils and is therefore low in typical COPD. A subset of COPD patients have elevated eosinophil numbers and IL-5 levels in their blood and airways; these patients are at increased risk for acute exacerbations.[9,51] Two MAbs targeted to IL-5 have been investigated for their ability to reduce exacerbation rate in COPD patients, but one showed no evidence of efficacy and results for the other are not yet available (Table 2).

Secretion of IL-17A is a canonical marker of T helper 17 (Th17) lymphocytes, which are distinct from Th1 and Th2 cells. However, most of the cells secreting IL-17 in patients with very severe COPD were identified as mast

cells.[52] This study also found that levels of IL-17A in lungs of COPD patients correlated with functional decline, with elevations becoming significant in patients with severe and very severe disease. Another study found that the numbers of $CD4^+IL\text{-}17^+$ cells in the alveolar walls and small airways of COPD patients and $CD4^+IL\text{-}17^+$ numbers in small airways positively correlated with airflow limitations.[53] These results are compatible with the finding that Th17 cells were present in the lungs of patients with emphysema but not normal controls and that IL-17A-induced secretion of the elastin-degrading enzyme matrix metalloprotease 12 by lung macrophages.[54] The levels of IL-17A were also elevated in the sputum of patients with acute COPD exacerbations associated with *Haemophilus influenzae* infection but not other acute exacerbations.[55] Other studies have not similarly distinguished among causes of acute exacerbations, likely accounting for findings that the ratio of regulatory T cells to IL-17 levels in peripheral blood was similar in COPD patients with and without current acute exacerbations, although exacerbations significantly increased levels of transforming growth factor β (TGF-β).[56] Indeed, one study was unable to detect IL-17 in sputum or serum of COPD patients with or without exacerbations.[57] Another study found that the sputum of patients with severe COPD had significantly higher levels of IL-8 but 4.8-fold lower levels of IL-17 compared to that of patients with mild COPD and healthy controls.[58] T cells from many COPD patients have also been reported to produce less IL-17A and IL-22 (also a signature cytokine of Th17 cells) than those of most normal smokers.[59] These complex and apparently contradictory findings underline the uncertainty of the role of IL-17 in COPD. Nevertheless, an IL-17 modulator is currently in clinical trials for COPD (Table 2).

Based on an IL-18-overexpressing transgenic mouse model that develops emphysema and airway remodeling,[60] Kang et al[60] and Nakajima and Owen[61] proposed that IL-18 is a master regulator of lung pathology in COPD. A phase I safety and tolerability clinical trial (NCT01322594) of the MAb MEDI2338 (targeted to IL-18) in COPD patients found no serious adverse events, but there have been no efficacy studies.[62]

Tumor necrosis factor α (TNF-α) plays multiple roles in COPD inflammatory pathology, and the levels of interferon γ (IFNγ) and TNF-α in the intraepithelial T cells from bronchi of COPD patients with GOLD II–III disease showed a significant negative correlation with FEV_1.[63] Nevertheless, studies with infliximab showed no clinical benefits on FEV_1, dyspnea, or exacerbations and were associated with higher rates of pneumonia and malignancy (Table 2). Similarly, treatment with etanercept, a fusion protein that competitively binds TNF-α, was not superior to prednisone in COPD exacerbations and in fact was less effective among patients with eosinophilia (Table 2).

Taken together, these data show that an increased level of a specific cytokine or chemokine during COPD exacerbations or stable COPD does not necessarily predict the efficacy of its specific inhibitor in COPD patients. Whether modulators of specific cytokines or chemokines can provide improved efficacy in a subgroup of patients is a possibility and warrants further investigation.[6]

Signaling molecules

Multiple signaling molecules help regulate inflammation and airway remodeling and represent plausible targets for the development of therapeutic candidates. Candidate drugs include inhibitors of p38 MAPK and related kinases, phosphoinositide kinase δ (PI3Kδ), leukotriene B_4, selectins, and vasoactive intestinal peptide (Table 3). Although several oral and inhaled p38 MAPK inhibitors have been discontinued, the inhaled narrow spectrum kinase (p38α + Src family) inhibitor JNJ49095397 (previously RV568) shows promising activity in COPD patients; conference presentations have indicated that RV568 significantly increased FEV_1 and inhibited IL-1β (90% at 800 μg dose) and CXCL8 expression (73%).[64] However, a recent conference report performed in over 200 COPD patients (half placebo, half 400 μg dose) showed no benefit with RV568 on lung function or EXACT-PRO.[65] PI3Kδ participates in many functions of lymphoid and myeloid cells: B-cell development, migration and activation of natural killer (NK) cells and T cells, neutrophil oxidative burst, macrophage activation triggered by immune complexes, and degranulation and maturation of mast cells.[66] Specific PI3Kδ inhibitors are being developed,[67] and studies on the effects of such inhibitors in COPD are in progress. Efficacy data remain limited, however (Table 3). Selectins are essential for migration of inflammatory cells from the bloodstream into pulmonary tissue; the selectin modulator bimosiamose reduced inflammation in COPD patients and thus warrants further testing (Table 3).[68]

Similar to the glucocorticoid receptor, peroxisome proliferator-activated receptor γ (PPARγ), also a member of the nuclear hormone receptor superfamily, exerts potent antioxidant and anti-inflammatory effects via multiple mechanisms, including downregulation of NF-κB and other proinflammatory transcription factors. Lung tissue and bronchial epithelial cells from COPD patients express significantly lower levels of PPARγ than those of nonsmoking controls.[69] In vitro treatment of COPD patient and control bronchial epithelial cells

Table 3 Developmental status of proinflammatory signaling pathway inhibitors for COPD

Mediator	Role in COPD	Drug	Clinical development	References
MAPK (p38 mitogen-activated protein kinase)	Higher MAPK in lungs activates proinflammatory response in AMs and lymphocytes.	Acumapimod, dilmapimod (SB-681323), losmapimod, PH-797804, GSK-610677, AZD-7624	Acumapimod (BCT197A2201) reportedly remains in active development, although phase II results have not been reported and there are no current clinical trials. Dilmapimod (SB-681323) significantly reduced TNF-α production in COPD (NCT00144859) but its development was discontinued. Losmapimod did not induce a significant improvement in exercise tolerance or lung function (NCT01218126) and was discontinued. PH-797804 (6-week treatment) (NCT00559910) significantly improved lung function and dyspnea in moderate-to-severe COPD in DBPCRT but was discontinued. Development of GSK-610677 was discontinued following an unreported phase I trial (NCT00694902). Results of a phase II study of AZD-7624 (NCT02238483) have not been reported.	64, 106–109
Narrow spectrum kinase inhibitors	p38α and Src family kinases such as Hck are involved in the production of proinflammatory cytokines from macrophages, smooth muscle cells, and human airway epithelial cells. Cigarette smoke activates c-Src and augments airway inflammation and destruction of lung tissue.	JNJ49095397/RV568	RV568 (14-day inhaled treatment) significantly increased FEV_1 and reduced sputum malondialdehyde and serum myeloperoxidase in COPD patients. A recent conference report, however, in over 200 COPD patients showed no benefit with RV568 for 12 weeks with respect to lung function or EXACT-PRO (NCT01867762, NCT01475292, and NCT01661244).	64, 66, 110
PI3Kδ (phosphoinositide-3-kinase δ)	Involved in maturation and effector functions of B cells and other leukocytes.	GSK2269557, RV1729	GSK2269557 (treatment up to 84 days in NCT02522299 or 28 days in NCT02294734) DBPCRTs in patients with acute exacerbations of COPD in progress. RV1729 (treatment up to 28 days) is being tested in NCT02140346 with limited efficacy data being gathered in a predominantly phase I study.	66, 67
IKK (inhibitor of nuclear factor kappa-B kinase)	IKK is an upstream activator of the proinflammatory transcription factor NF-κB. IKKα and IKKβ activity is elevated in patients with COPD.	IMD-1041, an IKKβ inhibitor	IMD-1041 in DBPCRT (NCT00883584) has no follow-up information posted since April 2009; unclear whether study was performed.	111
LTB_4 receptor	LTB_4 levels are elevated in sputum, breath, and BAL of COPD patients; highest LTB_4 levels seen in exacerbations. LTB_4 is chemotactic for neutrophils and T cells. AMs bearing the BLT1 receptor are more common in COPD patients.	BIIL 284	BIIL 284 (12-week treatment) was assessed for effects on lung function, exercise endurance, sputum, and safety in COPD patients (NCT02249247); a 14-day study assessed effects on biomarkers (NCT02249338) – results of neither study have yet been published. Other LTB_4 receptor antagonists have not demonstrated beneficial results.	4, 112

(*Continued*)

Table 3 (*Continued*)

Mediator	Role in COPD	Drug	Clinical development	References
5-LO (5-lipoxygenase)	Involved in synthesis of leukotrienes.	5-Lipoxygenase inhibitor (zileuton) used clinically for asthma	Zileuton (14-day treatment) reduced urinary LTE_4 levels in hospitalized COPD patients with acute exacerbations in DBPCRT (NCT00493974) but did not significantly shorten stay or reduce treatment failure.	113
Prostaglandin D_2 receptor or chemoattractant receptor-homologous molecule expressed on Th2 (CRTh2) receptor	Highly expressed on eosinophils, basophils, Th2 (not Th1) lymphocytes, and subset of monocytes. Blocking this receptor inhibits chemotaxis of these cells. CRTh2 is expressed on mucosal epithelia and mononuclear infiltrates from COPD lungs.	AZD1981	AZD1981 (4-week treatment) did not induce significant differences in lung function, quality of life variables, nor use of reliever medication in COPD patients in DBPCRT (NCT00690482).	114
Adenosine A_{2A} receptor	Inhibits neutrophil superoxide production, phagocytosis, adhesion, and cytokine release.	UK-432097 (agonist)	UK-432097 (6-week inhaled treatment) in DBPCRT (NCT00430300) showed no significant differences in FEV_1, use of rescue bronchodilator, or quality of life parameters.	115
Selectins	Involved in migration of leukocytes from blood to surrounding tissues. Overexpressed in lung tissue of COPD patients.	Bimosiamose	Inhalation of bimosiamose (28-day treatment) attenuated inflammation by significantly reducing numbers of macrophages and concentrations of CXCL8 in sputum of COPD patients in DBPCRT (NCT01108913). Adverse events were similar between the groups.	68
Vasoactive intestinal peptide (VIP)	Bronchodilatory and immunomodulatory effects in the lungs. Anti-inflammatory activity requires activation of both VPAC1 and VPAC2 receptors, With VPAC1 being particularly elevated in AMs of COPD patients.	VIP; available derivatives have not been tested in human COPD	VIP (3-month inhaled treatment) was tested in DBPCRT in severe COPD patients (NCT00464932). Study was completed in 2006 but no results are available.	116–119

Abbreviations: AM, alveolar macrophage; TNF-α, tumor necrosis factor α; DBPCRT, double-blind, placebo-controlled, randomized trial; FEV_1, forced expiratory volume in 1 second; NF-κB, nuclear factor-κB; Th, T helper.

with PPARγ agonists including 10-nitro-oleic acid (a possible endogenous ligand) or rosiglitazone (a thiazolidinedione) blocked cigarette smoke-induced production of cytokines, chemokines, and ROS, and accompanying suppression of HDAC2 levels.[69] The PPARγ agonist rosiglitazone dose dependently inhibited LPS-induced production of TNF-α and CCL5 by AMs of COPD patients, smokers, and never-smokers, shifting them toward an anti-inflammatory M2 phenotype, while both rosiglitazone and pioglitazone attenuated pulmonary inflammation in a tobacco smoke mouse model.[70] PPARγ also appears to play a central role in the development of emphysema. PPARγ is downregulated in lung myeloid dendritic cells of smokers with emphysema and endogenous PPARγ agonist activity is reduced in plasma of those with emphysema, while treatment with the thiazolidinedione ciglitazone reverses emphysema in a mouse model.[71] A retrospective epidemiological study of veterans with both diabetes and COPD indicated that the 7,887 veterans treated with a PPARγ agonist for their diabetes (97.1% rosiglitazone) significantly reduced the risk of COPD exacerbations in comparison to those receiving other diabetes medications (n=42,347; incidence rate ratio [IRR]=0.85; CI: 0.80–0.91) (Table 4).[72] Taken together, these data support further studies of PPARγ agonists in COPD patients with early signs of emphysema.

COPD also involves progressive increase in pulmonary arterial pressure, and 20%–91% (depending on definition, COPD severity, and method of measurement) of COPD patients have progressed to pulmonary hypertension.[73] Endothelin signaling plays a major role in vascular remodeling and hence in development of pulmonary hypertension.[74,75] An 18-month treatment with the

endothelin antagonist bosentan improved measures of pulmonary hypertension compared to those at baseline, especially in GOLD grade III and IV COPD patients, while pulmonary hypertension worsened in placebo-treated patients (Table 4).[74] However, bosentan can actually worsen hypoxemia in COPD patients without pulmonary hypertension.[76]

Although statins are known to have anti-inflammatory properties, simvastatin treatment (40 mg/day) of COPD

Table 4 Developmental status of miscellaneous inflammatory modulators for COPD

Mediator	Role in COPD	Drug	Clinical development	References
PPARγ (peroxisome proliferator-activated receptor γ)	Cigarette smoke downregulates PPARγ. Reduced PPARγ expression and activity seen in COPD.	Thiazolidinediones: rosiglitazone and pioglitazone	Retrospective cohort study of patients with diabetes and COPD showed that patients who filled ≥2 thiazolidinedione prescriptions (97.1% rosiglitazone) had a significantly lower number of COPD exacerbations than those receiving other diabetic medications.	69, 72
IgE activity	The high affinity IgE receptor is overexpressed on myeloid and plasmacytoid dendritic cells (DCs) of current smokers. Expression on plasmacytoid DCs correlates with COPD stage.	Omalizumab	The clinical trial of omalizumab (NCT00851370) was withdrawn due to lack of patients meeting inclusion criteria (elevated IgE and positive skin prick test to environmental allergens).	120
RARγ (retinoic acid receptor γ)	Regulates function of multiple cells of the immune system.	Palovarotene	RARγ agonist (2 year treatment) was tested for ability to improve lung function in patients with emphysema in DBPCRT (NCT00413205); in patients with lower lobe emphysema, palovarotene significantly reduced the decline in lung function (from conference report). In another study, over 1 year, palovarotene failed to show a significant benefit on lung density in moderate-to-severe emphysema secondary to severe alpha-1 antitrypsin deficiency.	121, 142, 143
Angiotensin receptor	Angiotensin II receptor blockers reduce in-hospital mortality during first COPD exacerbation.	Losartan	Open-label clinical trial of losartan (4-week treatment) (NCT02416102) to assess effects on mucociliary dysfunction (nasal potential difference, IL-8 and TGF-β in nasal discharge) in COPD patients is recruiting; a 4-year study of losartan for prevention of emphysema progression (NCT02696564) is not yet recruiting.	122
Endothelin	Vasoconstrictor, contributes to pulmonary hypertension in COPD.	Bosentan	Bosentan (18-month treatment) halted progression of PH and led to improvements in most patients, especially those in GOLD grades III and IV. A study of bosentan effects on acute exacerbations and lung function in patients with GOLD III or IV COPD and pulmonary hypertension was initiated but status is unknown (NCT02093195).	73–75
Statins	Statins exert anti-inflammatory effects by several mechanisms independent of cholesterol lowering.	Simvastatin, rosuvastatin	Although retrospective studies suggested that statins may reduce frequency of exacerbations, hospitalization, and mortality in COPD patients, a recent prospective large randomized trial of simvastatin in COPD patients (NCT01061671) did not detect significant differences.	77, 78, 123, 124

(*Continued*)

Table 4 (*Continued*)

Mediator	Role in COPD	Drug	Clinical development	References
			Another 3-month study of simvastatin found no effect in inflammatory biomarkers. Rosuvastatin (12-week treatment) in DBPCRT (NCT00929734) reduced biomarkers of systemic inflammation and improved endothelial function in a prespecified subgroup (patients with supramedian circulating hsCRP levels).	
T cells	T cells infiltrate airways, and are key mediators in the immune response; numbers of senescent cells, which produce increased amounts of proinflammatory and cytotoxic mediators and are relatively resistant to GC treatment, are elevated in blood and lungs of COPD patients.	Cyclosporine, an immunosuppressant affecting T-cell responses	A phase I dose-escalation study of inhaled cyclosporine (28-day treatment) in severe COPD patients (NCT00783107) also evaluated inflammatory biomarkers; no results of 2009 study are available. An ongoing phase II DBPCRT (16-week treatment) (NCT00974142) is evaluating oral cyclosporine in severe COPD.	125, 126

Abbreviations: Ig, immunoglobulin; IL, interleukin; TGF-β, transforming growth factor β; GOLD, Global Initiative for Chronic Obstructive Lung Disease; DBPCRT, double-blind, placebo-controlled, randomized trial; hsCRP, high-sensitivity C-reactive protein.

patients at high risk for exacerbation did not increase the time to first exacerbation nor reduce the number of exacerbations.[77] However, rosuvastatin (12-week treatment) improved endothelium-dependent vascular function in a prespecified subgroup (patients with supramedian circulating high-sensitivity C-reactive protein [hsCRP]) but not in the total COPD population in a double-blind, placebo-controlled trial.[78] This study found no statistically significant effect on pulmonary function parameters, however.

PDE inhibitors

The 11-membered phosphodiesterase enzyme family (PDE1-11) differentially hydrolyzes cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), which regulate many cellular processes including release of inflammatory mediators and relaxation of smooth muscles.[10] PDE3 appears to be involved in bronchoconstriction since its inhibitors induce bronchodilation in humans.[10] PDE4 is expressed in most inflammatory cell types and is a main target for emerging COPD therapies (Table 5), with the PDE4 inhibitor roflumilast having been approved by the FDA as a COPD treatment. In vitro studies of low-dose combinations of PDE4 and PI3Kδ inhibitors significantly reduced cigarette smoke extract-induced apoptosis of lung epithelial cells, neutrophil elastase production, and macrophage secretion of TNF-α, phosphorylated protein kinase B, and matrix metalloproteinase 9 (MMP-9).[79]

Gastrointestinal adverse effects can be a significant problem with roflumilast, but PDE4 inhibitors with inhaled or nebulized (eg, RPL554, GSK-256066) formulations appear to have more tolerable side effect profiles than orally administered roflumilast.[80,81]

The severity of emphysema and small airways disease is associated with higher expression of multiple MMPs.[82] However, despite promising results in an animal model,[83] an inhibitor of MMP-9 and -12 has not shown significant benefit for COPD patients in a clinical trial (Table 6).

Oxidative stress and antioxidants

Oxidants, both from inhaled pollutants and produced as part of the inflammatory response, are major contributors to COPD pathophysiology. Furthermore, inflammation-associated production of ROS and reactive nitrogen species (RNS) is accompanied by downregulation of the antioxidant transcription factor Nrf2. ROS activates the proinflammatory transcription factors activator protein 1 (AP-1) and NF-κB, with consequent production of inflammatory proteins and mediators. Excess ROS in COPD patients also directly contributes to airspace epithelial injury and inactivates anti-proteases that help prevent emphysema.[84] Therapeutic agents that activate Nrf2 and thus neutralize the excess oxidants may prove beneficial to COPD treatment.[85]

The antioxidant transcription factor Nrf2, the primary mechanism for limiting oxidative stress, is reduced in COPD patients.[36] Kelch-like ECH-associated protein 1 (Keap1) sequesters Nrf2 in the cytoplasm and under healthy conditions targets Nrf2 to Cullin-3 for ubiquitination and degradation.[86] Keap1 monitors oxidative stress through its multiple cysteines with distinct stressors binding one or more

Table 5 Developmental status of cAMP and cGMP phosphodiesterase inhibitors

Mediator	Role in COPD	Drug	Clinical development	References
PDE4 (phosphodiesterase subtype 4)	Hydrolyzes cAMP, an inhibitor of inflammatory pathways; expressed in a wide variety of cells.	Roflumilast, a selective PDE4 inhibitor; GSK-256066; CHF6001; MK0359; MK-0873; tofimilast; UK-500,001; tetomilast (OPC-6535, PDE4 inhibitor with modest PDE3 inhibitory activity); oglemilast; QAK423A; TPI 1100.	Roflumilast is only US FDA approved PDE4 inhibitor; it reduced exacerbation frequency and also produced clinically significant improvements in dyspnea. GSK-256066 (4-week inhaled treatment) in DBPCRT (NCT00549679) improved residual volume and showed a nonsignificant trend toward augmenting postbronchodilator FEV_1. Preclinical testing of CHF6001 (inhaled) shows efficacy and low toxicity in several rat models of pulmonary inflammation. It is in clinical testing (28-day treatment) (NCT01730404) but no results have been reported. Numerous other PDE inhibitors are in clinical testing, including MK-0359 (NCT00482235); MK-0873 (NCT00132730); tofimilast (NCT00219622); UK-500,001 (NCT00263874); tetomilast (OPC-6535) (NCT00874497), terminated, NCT00917150); oglemilast (NCT00671073); QAK423A (NCT01197287); and TPI 1100 (NCT00914433).	10, 42, 80, 99, 127–129
PDE3/PDE4	PDE3 degrades both cAMP and cGMP. It is expressed on airway smooth muscle cells and acts as a bronchoconstrictor. Combined PDE3/PDE4 inhibition is often additive or synergistic.	RPL554	RPL554 (up to 94-day treatment) is being investigated as an adjunct to salbutamol and ipratropium in COPD patients in DBPCRT (NCT02542254).	10
PDE5	PDE5 promotes pulmonary arterial vasoconstriction and vessel wall hypertrophy.	Tadalafil (inhibits PDE5)	Tadalafil, which is approved for pulmonary arterial hypertension, in DBPCRT (12-week treatment) (NCT01197469) did not improve exercise capability or quality of life. Another study (NCT01862536) is in progress.	130

Abbreviations: FEV_1, forced expiratory volume in 1 second; DBPCRT, double-blind, placebo-controlled, randomized trial; FDA, Food and Drug Administration.

specific cysteines. Following binding of these stress-related compounds, release of Nrf2 from Keap1 occurs, which transfers to the nucleus and activates multiple antioxidant enzymes and phase II proteins that counteract oxidative stress.[86] This makes the Nrf2/Keap1 system an attractive therapeutic target in COPD and other inflammatory diseases. The natural product sulforaphane activated Nrf2 in AMs isolated from COPD patients, denitrosylated HDAC2, and restored sensitivity to the glucocorticoid dexamethasone in a glutathione-dependent manner.[37] A study of the effect of two doses of sulforaphane on Nrf2 expression in 89 COPD patients was recently completed, and sulforaphane administered for four weeks to patients with COPD did not induce the expression of Nrf2 target genes or have an effect on oxidative stress, airway inflammation, or lung function. (NCT01335971).[87]

Erdosteine and N-acetylcysteine directly scavenge ROS via their thiol groups (of the metabolite in the case of erdosteine) and also have mucolytic activity. High-dose (900 mg/day) erdosteine increased the ability of salbutamol to improve $\%FEV_1$ reversibility,[88] and long-term treatment reduces exacerbations and improves quality of life.[89] High-dose (600 mg bid) N-acetylcysteine reduces the number of exacerbations patients experience;[12,90,91] reported effects with a lower dose (600 mg/day) have been inconsistent.[92–94]

Mucus hypersecretion

Mucus hypersecretion can be modulated by blocking its overproduction and/or by inhibiting its secretion (Table 7). Hypothetically, a rebound effect after cessation of an inhibitor of mucin secretion may involve a rapid release of produced but unsecreted mucin. In contrast, the rebound effect after cessation of an inhibitor of mucin production may involve a lag phase for mucin production and a more gradual increase of mucin secretion. Multiple mucins comprise the gel-forming layer of normal airway mucus. Numerous signals can promote

Table 6 Developmental status of elastin-degrading protease inhibitors for COPD

Mediator	Role in COPD	Drug	Clinical development	References
Neutrophil elastase	Abundant in neutrophils; can degrade extracellular matrix and damage/destroy lung parenchyma; affects mucus secretion.	AZD9668 AZD6553	AZD9668 (12-week treatment) showed no effect on pulmonary function or quality of life when combined with tiotropium (NCT00949975) or budesonide/formoterol (NCT01023516); there was likewise no effect on airway remodeling (NCT01054170) and studies found no decrease in degradation as assessed by urinary desmosine. AZD6553 clinical trial (NCT01068184) was terminated due to PK inconsistent with pharmaceutical properties.	131, 132
Matrix metalloproteinases (MMPs)	Higher levels of multiple MMPs in lungs of COPD patients; involved in matrix breakdown and tissue remodeling.	AZD1236 (anti-MMP-9 and -12); GS-5745 (anti-MMP-9)	In a 6-week DBPCRT (NCT00758706) of AZD1236 (anti-MMP-9 and -12) in moderate-to-severe COPD patients, reduction in urinary desmosine did not reach statistical significance and there was no effect on COPD clinical symptoms. Another study (NCT00758459) has completed but statistical analysis not released. A 28-day safety and PK study of GS-5745 in COPD patients (NCT02077465) has been completed.	82, 133

Abbreviations: PK, pharmacokinetics; DBPCRT, double-blind, placebo-controlled, randomized trial.

mucus secretion: bacterial products, cytokines, cholinergic agonists, elastases, matrix metalloproteases, and activation of epidermal growth factor receptor (EGFR).[95,96] Cigarette smoke induces EGFR- and hypoxia inducible factor-1 (HIF-1)-mediated signaling[95] and thus can promote hyperplasia of mucin-producing goblet cells.[97] Supporting this concept, nuclear HIF-1α was expressed in the majority of goblet cells in areas of remodeled airway tissues showing goblet cell hyperplasia from COPD patients but not in subjects without COPD.[97] IL-13, an essential component of COPD-associated inflammation, promotes goblet cell production of mucins.[98] After the mucins are expressed, glycosylated, and packaged in mucin granules, myristoylated alanine-rich C kinase substrate (MARCKS) mediates movement of intracellular mucin granules to the goblet cell apical membrane and is therefore essential for mucin exocytosis and secretion.[98]

Summary

The heterogeneity of COPD presentation augments the challenges in identifying and developing therapeutic compounds for the treatment of COPD patients. It also emphasizes the importance of tailoring therapy to individual patients and their disease status, which may involve considerations beyond the standard GOLD categories. Several distinct emerging therapies have shown efficacy in at least some COPD patients. The length of treatment (>3 months) and the inhaled route of administration can be associated with a higher probability of observing a positive effect on COPD variables and a reduced side effect profile, respectively. Although some of the emerging compounds showed significant activity in the total COPD population tested,[45,68,74,88,99] sometimes only in connection with assessed biomarkers rather than clinically significant outcomes, subgroup analysis showed that most compounds were significantly affected in one or more of the following subgroups: smokers or ex-smokers,[44,99] patients with chronic bronchitis or emphysema,[80,99] use of standard COPD therapies,[99] patients with alteration of relevant biomarkers,[78] or at different COPD grades.[74] These data suggest that subgroup analyses and the possibility of individualized therapy can benefit developers of emerging therapies by identification of the patients most likely to benefit from a new therapy.

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Disclosure

The authors report no conflicts of interest in this work.

Table 7 Developmental status of modulators of mucus-mediated airway obstruction for COPD

Mediator	Role in COPD	Drug	Clinical development	References
Epidermal growth factor receptor (EGFR)	EGFR regulates mucin stores in airway epithelium, which are significantly increased in COPD.	BIBW 2948 (inhibits EGFR autophosphorylation)	Inhalation of BIBW 2948 (4-week treatment) in DBPCRT (NCT00423137) reduced internalization of EGFR but did not reduce mucin stores; BIBW 2948 treatment was associated with higher discontinuation rate (24%) than placebo (4.3%). FEV_1 in the higher dose group significantly declined by visit 5 but returned to baseline by visit 7.	134
Myristoylated alanine-rich C kinase substrate (MARCKS)	Mediates movement of mucin granules to the apical membrane as part of mucin exocytosis.	BIO-11006	A 21-day phase II DBPCRT of BIO-11006 (inhaled) in COPD (NCT00648245) has been completed; a 2011 abstract reported improved lung function and reduced mucus hypersecretion.	98, 135, 136
Epithelial sodium channel	Role in homeostasis of mucus hydration, ciliary beating, and clearance of mucus.	GS-5737; compound A	Study of effects of GS-5737 on ciliary action in healthy controls (NCT01793649) was terminated. Preclinical study of compound A shows improved ciliary movement, mucus clearance, and airway hydration.	137
Multiple mechanisms				
Anti-inflammatory and mucolytic	Inflammation, oxidative stress and mucus hypersecretion are well-established in COPD.	N-acetylcysteine (NAC)	The 1-year DBPCRT PANTHEON trial found 600 mg bid NAC reduced exacerbations in patients with GOLD II–III COPD (Chinese Clinical Trials Registry TRC-09000460), as did a smaller study (NCT01136239) that found a reduction only in high-risk patients but also observed improvement in airway function. However, two lower dose studies (600 mg/day) (NCT00184977; not registered) found no benefit while another (not registered) did.	12, 90–94, 138, 139
Mucolytic, anti-inflammatory, antioxidant, promotes activity of antibiotics	Inflammation, oxidative stress, and mucus hypersecretion are well-established in COPD.	Erdosteine	DBPCRT (NCT00338507) to test daily erdosteine for 28 days. After 4 weeks, erdosteine treatment significantly reduced plasma oxidant levels and increased $\%FEV_1$ reversibility by salbutamol treatment. In other reported studies, addition of erdosteine for 7–10 days reduced duration of acute exacerbations, while long-term treatment in stable COPD reduced exacerbations and improved quality of life.	88, 89
Cystic fibrosis transmembrane conductance regulator (CFTR)	One study found that CFTR is downregulated in smokers with and without COPD; another found that expression of CFTR inversely correlated with emphysema severity.	Ivacaftor potentiates chloride transport	A pilot DBPCRT of ivacaftor (NCT02135432) (treatment up to 2 weeks) with outcome assessed by sweat chloride has been completed.	140, 141

Abbreviations: DBPCRT, double-blind, placebo-controlled, randomized trial; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

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