Drugs of the Future 2007, 32(9): 799-807

CCC: 0377-8282/2007
DOI: 10.1358/dof.2007.032.09.1126938

Review Article

Chronic obstructive pulmonary disease (COPD)

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Abstract

Chronic obstructive pulmonary disease (COPD) includes emphysema and chronic bronchitis, which are characterized by a progressive airflow limitation and chronic inflammation. Although COPD is a major cause of chronic morbidity and mortality throughout the world, its recognition as a public health problem has been neglected. The most important cause by far is cigarette smoking. Despite increasing insight into the pathophysiological mechanisms of COPD, there has been only a limited translation into effective pharmacotherapy. Inhaled anticholinergics remain the mainstay drugs in COPD management due to their capacity to alleviate symptoms, decrease exacerbations and improve quality of life. Future COPD therapy will be based on three drug classes: bronchodilators, antiinflammatory drugs and possibly repair drugs. This review provides an overview on the status of drugs currently in clinical development for COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterized by chronic obstruction of expiratory flow affecting peripheral airways. It is associated with chronic bronchitis (mucus hypersecretion with goblet cell and submucosal gland hyperplasia) and emphysema (destruction of airways parenchyma), together with fibrosis, tissue damage and inflammation of the small airways. COPD is a major worldwide health burden, with increasing morbidity, mortality and healthcare costs. At present, it is the fifth leading cause of death and it is expected to rank third in 2020 (1). Although the major risk factor is cigarette smoke, the host factors that are involved in the pathogenesis of COPD have not yet been fully identified. Despite increasing insight into the pathophysiological mechanisms of COPD, there has been only a limited translation into effective pharmacotherapy.

Pharmacotherapy for COPD is palliative at best, having no impact on slowing the progression of the disease. Therefore, the goals of therapy in COPD patients are to reduce disease progression and mortality, relieve symptoms, improve exercise tolerance and health status, and prevent exacerbations and complications. The current mainstay of treatment is bronchodilator medication for symptom relief. Unlike in asthma, corticosteroids are poorly effective and do not reduce disease progression, although they may reduce exacerbations. In general, current therapy does not suppress airways inflammation to a desired and therapeutically relevant extent. Neither the release of inflammatory mediators nor the numbers of inflammatory cells in the lungs are effectively influenced by available treatments. Additionally, COPD is accompanied by systemic inflammation resulting in weight loss, cachexia and osteoporosis. Consequently, there is an urgent need to develop new and more effective forms of therapy. Herein, we review the status of drugs that have reached clinical development for COPD.

Muscarinic receptor antagonists

The muscle tone in bronchi is regulated mainly by cholinergic activity. Overstimulation of muscarinic receptors leads to airways narrowing. The airways of patients with COPD present increased cholinergic tone, as reflected by the stronger bronchodilating effect of anticholinergic drugs (2). Vagally derived acetylcholine also regulates mucus production in the airways. Acetylcholine, acting through muscarinic receptors, may in part regulate patho-

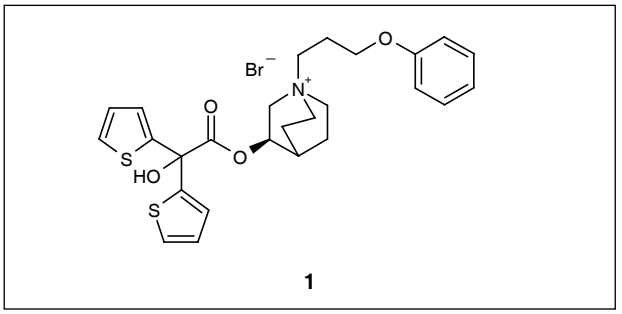
logical changes associated with airways remodeling as well (3).

Anticholinergics act by producing a competitive blockade of acetylcholine at muscarinic acetylcholine receptors, inhibiting bronchoconstriction and bronchial hypersecretion, and thereby increasing airflow. Ipratropium is available in most countries and oxitropium is also available in many countries outside the U.S. The duration of action of these anticholinergics is short (approximately 5-8 h). Tiotropium, administered once daily, is an effective bronchodilator for patients with COPD, and unlike other anticholinergics, it acts through prolonged antagonism of the M_3 receptor, thus sustaining airways patency for 24 h. Tiotropium may also slow the decline in FEV_1 (4).

Several other anticholinergics are in development. LAS-34273 (aclidinium, **1**; Almirall, Forest), a novel M_3 receptor antagonist, has been reported to have a fast onset of action and to provide 24 h of bronchodilatation (5). The compound is now in phase III studies in the United States and Europe. In contrast to the nonselective ipratropium, revatropate (**2**; Pfizer) showed selectivity for M_1 and M_3 receptors in guinea pig trachea, without influencing the M_2 autoreceptor. Early clinical studies in COPD patients showed that inhaled revatropate was an effective and well-tolerated bronchodilator (6). It appears, however, that the development of this compound has been discontinued.

Racemic glycopyrrolate is an "old" drug, available since the 1950s, for use when a rapid anticholinergic effect is desired, for example during anesthesia. Recently, it has been demonstrated that in animals, racemic glycopyrrolate-induced bronchodilatation lasted longer than with ipratropium, but somewhat less than with tiotropium (7). Moreover, it is likely that glycopyrrolate, at appropriate doses, can be administered once daily. In sputum cells obtained from COPD patients, M_3 receptor expression was seen to be increased. Additionally, enhanced acetylcholine-induced LTB_4 production was observed in peripheral blood monocytes, indicating that muscarinic antagonism may contribute to reduce neutrophil infiltration and activation in COPD (8). Indeed, (*R,R*)-glycopyrrolate acts synergistically with the phosphodiesterase type 4 (PDE4) inhibitor rolipram and the steroid budesonide to inhibit the release of inflammatory mediators from blood monocytes (9).

Novartis licensed a formulation of glycopyrrolate, NVA-237 (**3**), from Arakis (subsequently acquired by Sosei). Comprised of racemic glycopyrrolate in a controlled-release formulation, this product is now in phase II clinical trials (ClinicalTrials.gov Identifier NCT00501852 and NCT00510510).



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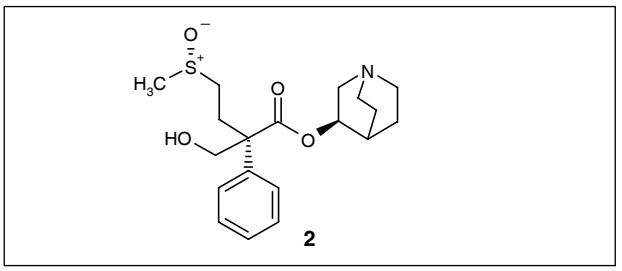

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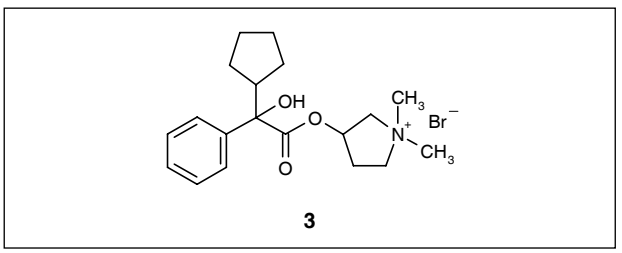

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Long-acting β-agonists

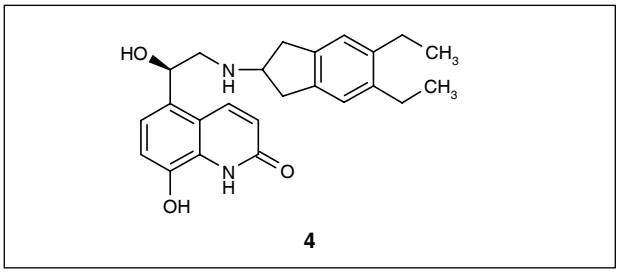
There is evidence that inhaled corticosteroids, probably in combination with β_2-adrenoceptor agonists, could suppress systemic inflammation in COPD (10). Long-acting β_2-agonists (LABAs), such as formoterol and salmeterol, are now recommended in patients with moderate and severe COPD. They provide comparable bronchodilatation over 12 h and have tolerable side effects. Besides bronchodilatation, LABAs can increase mucociliary transport and reduce bacterial damage.

The goal in the development of novel LABAs is to prolong the duration of action and allow once-daily administration. Several compounds (*e.g.,* indacaterol [**4**], carmoterol [**5**], milveterol [**6**]) are now in development and are expected to be introduced to the market before 2010. The once-daily administration of a LABA will lead to increased convenience for patients and enhance the probability of combining them with other bronchodilators such as tiotropium or glycopyrrolate.

To our knowledge, apart from these improvements, there are currently no new classes of bronchodilator drugs in clinical testing. It is unlikely that better and stronger bronchodilators than β_2-adrenoceptor agonists or selective antimuscarinic agents (M_3 receptor antagonists) will be found.

Combination therapies

Combination therapy offers the potential to target several components involved in the pathological mechanism of COPD at once. At present, combinations of LABAs with anticholinergics and LABAs with inhaled corticosteroids are commercially available.



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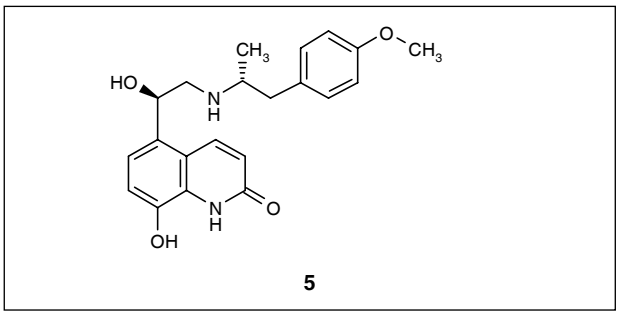

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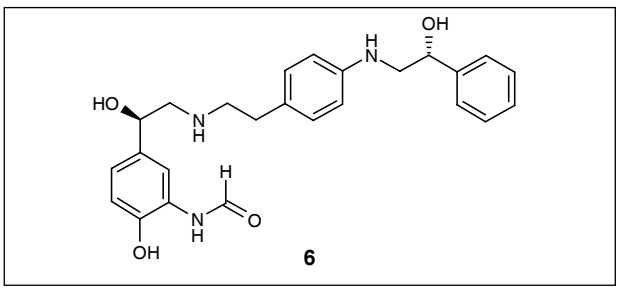

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A combination of bronchodilating agents with different mechanisms of action could potentially provide a greater clinical effect than the single agents alone. Clinical trials suggest many potential benefits for combinations of short-acting bronchodilators in patients with COPD (11, 12). Information on combining long-acting anticholinergic drugs with LABAs is scarce, but the combination of two long-acting agents (*e.g.,* formoterol + tiotropium) may provide additional benefit by improving airways obstruction (13, 14).

There is also evidence that combining LABAs and inhaled corticosteroids has improved efficacy over treatment with the individual agents alone (15-17). In a recent study, the addition of fluticasone/salmeterol to tiotropium therapy did not statistically significantly influence rates of COPD exacerbation but did improve lung function, quality of life and hospitalization rates in patients with moderate to severe COPD (18).

Combination therapies should form an integral part of novel future treatment strategies. It is unlikely that inhaled bronchodilator therapy will be replaced by an oral treatment. Antiinflammatory compounds currently in development are potential candidates for combination with bronchodilators, although patient compliance will be reduced if they cannot be administered by inhalation. For oral administration, only drugs with an outstanding antiinflammatory effect will be acceptable. This is also valid for compounds that may influence the extrapulmonary systemic component of COPD.

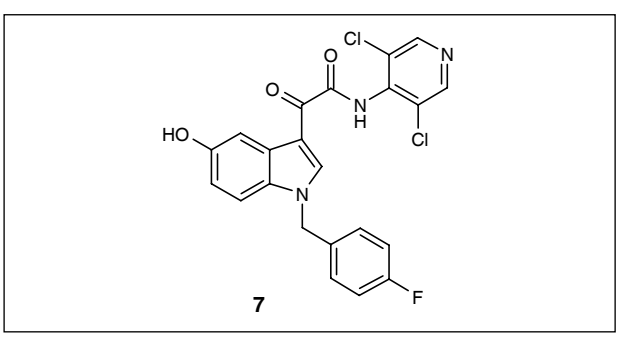
Phosphodiesterase (PDE) inhibitors

Intracellular levels of cyclic nucleotides are closely regulated by distinct families of PDEs, which are responsible for the hydrolysis of intracellular cyclic nucleotides, such as cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), to inactive 5'-monophosphates. Inhibitors of PDEs cause elevation of cAMP and cGMP, which leads to a variety of cellular effects, including airways smooth muscle relaxation and inhibition of cellular inflammation or immune responses (19).

Type 4 PDEs have the ability to modulate the release of inflammatory mediators through cAMP-dependent and -independent mechanisms. The first generation of PDE4 inhibitors, such as rolipram, selectively targeted PDE4 but caused severe side effects. The second generation of oral PDE4 inhibitors, such as cilomilast and roflumilast, have reached clinical trials and have demonstrated beneficial effects in asthma and COPD. However, the efficacy of these PDE4 inhibitors may be limited by their potential for side effects (20).

In analogy to inhaled corticosteroids, a simple way of minimizing side effects without reducing efficacy is to administer the compound by inhalation. It is hard to understand why this approach has not been chosen as a viable solution in the past decade. One compound was developed, AWD-12-281 (**7**; GlaxoSmithKline, elbion) (21), but its enzyme-inhibitory activity was too weak. Therefore, its lack of significant clinical efficacy was not surprising. The basic idea of synthesizing a compound with high enzyme-inhibitory potency and extremely low bioavailability is still valid and fulfills the requirements directed to inhaled corticosteroids as well. Topical administration of PDE4 inhibitors may provide a considerably better side effect profile with increased efficacy. The next few years should allow the clarification of the potential role of PDE4 inhibitors as novel nonsteroidal antiinflammatory drugs for COPD. It is, however, also possible that PDE4 may turn out not to be a realistic target to replace theophylline, although the necessary efforts should be made.

The development of inhibitors of other PDE isozymes or dual inhibitors may represent another route to effective



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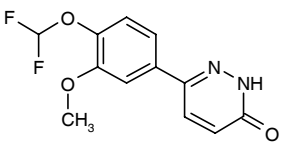

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treatments. A dual PDE3/PDE4 inhibitor may provide bronchodilating and bronchoprotective effects in addition to the beneficial antiinflammatory effects of PDE4 inhibition. However, combination of these two properties is associated with several problems, mainly side effects caused by dual PDE inhibition. Already 15 years ago, it was shown that zardaverine (**8**; Nycomed), a dual PDE3 and PDE4 inhibitor, had modest and short-lasting bronchodilating activity. Its development was discontinued due to classical PDE4-associated side effects (nausea, vomiting) (22).

PDE3A is the main subtype of PDE3 expressed in platelets and cardiac ventricular myocytes and is responsible for the functional changes caused by PDE3 inhibition (23). Another subtype, PDE3B, is probably involved in adiposity and diabetes mellitus (24). Indeed, PDE3B-selective inhibitors have been synthesized by Edmondson *et al.* for the treatment of obesity (25). In terms of asthma and COPD, the role of selective inhibition of PDE3B remains to be elucidated.

PDE7 is involved in T-cell activation. It was thought that combined inhibition of both PDE4 and PDE7 isozymes might be more effective in asthma and COPD than a single inhibitor. The initial euphoria was followed by a lack of activity and the development of this approach has apparently been discontinued.

Tumor necrosis factor-α (TNF-α) inhibitors

TNF-α appears to play a role in the pathogenesis of COPD as a primary mediator driving the characteristic inflammation. A number of studies have reported increased production of TNF-α in patients with COPD, and have related this increase to the systemic manifestations of the disease (reviewed in 26). Furthermore, preclinical data suggested TNF-α to be a relevant target for COPD, *e.g.,* TNF-α double receptor-knockout mice are protected from both the acute and chronic effects of cigarette smoke exposure (27). However, a small pilot study evaluating the effect of three infusions of the TNF inhibitor infliximab (5 mg/kg) in patients with COPD demonstrated no beneficial therapeutic response or effect on sputum neutrophils (28). A larger study in subjects with moderate to severe COPD also did not detect beneficial responses following treatment with infliximab (29). In addition, more cases of cancer and pneumonia were observed in the infliximab-treated subjects. Taken together, these observations argue against the use of infliximab in moderate to severe COPD. However, the lack of clinical benefit does not exclude a role for TNF-α in the pathogenesis of COPD. The treatment period of 6 months may have been too short to demonstrate changes in health status. Nevertheless, it is also possible that other mediators in addition to TNF-α may be sufficient to cause COPD symptoms. Altogether, while single patients may benefit from anti-TNF treatment, the use of anti-TNF-α antibody therapy appears unwarranted in patients with moderate to severe COPD.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibitors

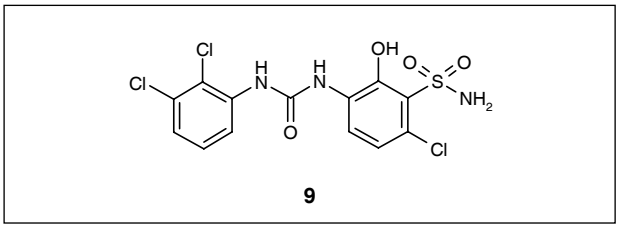
GM-CSF plays an important role in the pathogenesis of chronic lung disease as a major regulator governing the functions of granulocyte and macrophage lineage populations. The inflammation in COPD is dominated by neutrophils, macrophages and T-cells (30). It has been proposed that proinflammatory cytokines, such as IL-8, TNF-α, macrophage inflammatory protein 2 (MIP2) and GM-CSF, play a key role in the pathophysiology of COPD (31). If so, antagonizing these cytokines could represent a promising strategy to inhibit lung obstruction/destruction in COPD. Neutralization of GM-CSF by the monoclonal antibody 22E9 was highly effective in preventing neutrophil influx and reducing the levels of MIP2 and TNF-α in bronchoalveolar lavage fluid (BALF) of lipopolysaccharide (LPS)-challenged mice (32, 33), indicating that neutralization of GM-CSF may represent a novel treatment strategy for COPD (34). Accordingly, MT-203, a human GM-CSF-neutralizing antibody, is now in development at Micromet and Nycomed and is expected to enter clinical trials in 2008.

Chemokine antagonists

Several chemokines have been reported to be increased in COPD patients. Monocyte chemotactic protein-1 (MCP-1) and its receptor CCR2 have been found to be increased in macrophages and epithelial cells from COPD patients (35). MCP-1 concentrations are increased in the sputum from COPD patients and are positively correlated with neutrophil number and negatively correlated with FEV_1 (36). Accordingly, Novartis is testing an MCP-1-neutralizing antibody, ABN-912, in phase I studies.

The CXC chemokine IL-8 is a potent neutrophil-recruiting and -activating factor that exerts its effects on neutrophils by binding to the chemokine receptors CXCR1 and CXCR2 on the neutrophil surface (37). IL-8 levels are markedly elevated in the sputum of patients with COPD and are correlated with disease severity (38). IL-8-blocking antibodies were developed that inhibited neutrophilic inflammation in experimental animal studies (39). The effect of an anti-IL-8 monoclonal antibody was studied in COPD patients by the former Abgenix (now part of Amgen). This antibody was well tolerated and improved symptoms of dyspnea, but did not improve lung function (40). Newer results are not available, although phase II trials for rheumatoid arthritis and psoriasis were also disappointing.

Other CXC chemokines, such as GRO-α, GRO-β, GRO-γ, NAP-2, ENA-78 and GCP-2, are also ligands for CXCR2, and several pharmaceutical companies have focused on developing CXCR2 antagonists. Such antagonists might reduce the action of these mediators, in addition to IL-8. In rats, a specific CXCR2 antagonist, SB-332235 (**9**; GlaxoSmithKline), effectively inhibited cigarette smoke-induced neutrophilia in a dose-dependent manner (41), but no development has been reported for several years. A further study found similar efficacy for another CXCR2 antagonist in mice (42). GlaxoSmithKline has had at least three oral CXCR2 antagonists in the pipeline for COPD (SB-656933 [**10**], SB-225002 [**11**] and SB-265610 [**12**]), but none presently appear to be in development; AstraZeneca's oral CXCR2 antagonist AZD-8309 has also been discontinued. Currently, Schering-Plough's oral CXCR2 antagonist SCH-527123 (**13**) is in phase II development for COPD (37).



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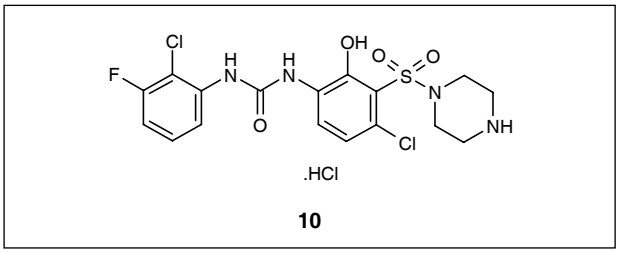

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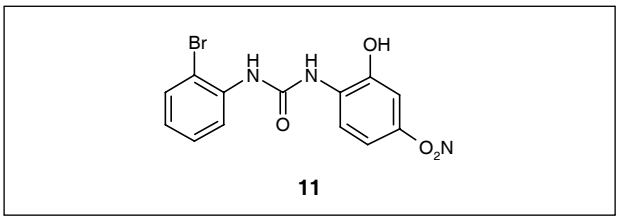

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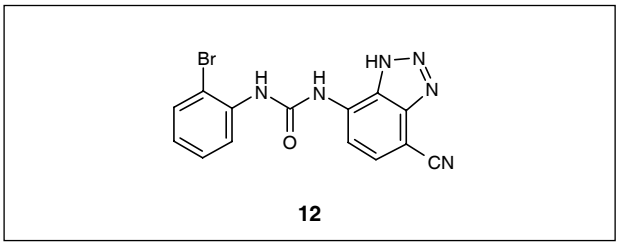

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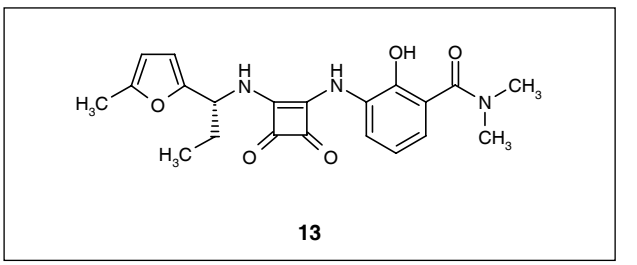

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Protease inhibitors

Protease inhibitors offer promise in the treatment of emphysema. Therapy with the naturally occurring α_1-protease inhibitor resulted in a reduced loss of lung tissue in patients with moderate emphysema, indicating potential for this type of therapy. Although we have not been able to find further clinical trials, several protease inhibitors still appear to be interesting candidates. However, none of the numerous candidates has reached the clinical stage. In addition to neutrophil elastase, other proteolytic enzymes such as the matrix metalloproteinases (MMPs), a family of zinc-dependent proteinases, have been explored as potential therapeutic targets for intervention in COPD for over 20 years (43). A significant problem in the development of such antagonists is the occurrence of side effects, because MMPs exert multiple effects required for normal cell function and also host defense mechanisms.

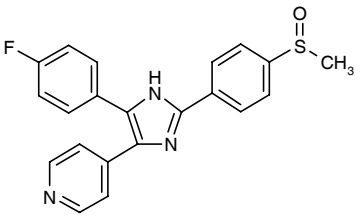
p38 MAP kinase inhibitors

Among intracellular signaling pathways found to be activated in COPD, the p38 MAP (mitogen-activated protein) kinase pathway is considered to be a central regulator of inflammation (44). The p38 subfamily of the MAP kinase superfamily comprises four isoforms, of which p38α is thought to be responsible primarily for regulating inflammation, whereas the functions of the other isoforms in inflammation remain elusive (45).

Owing to its vital role in inflammation, p38 is an obvious therapeutic target for potential drugs to treat inflammatory diseases (46). Many strategies have been applied to the design of inhibitors of p38α. The inhibitors vary not only in chemical structure, but also in how they interact with the protein; however, the common mechanism of inhibition is competition with ATP. p38 inhibitors produce antiinflammatory effects in animal models of inflammatory diseases, mainly by inhibiting the expression of inflammatory mediators; as a result, p38 inhibitors from various pharmaceutical companies have been involved in preclinical or clinical trials (47).

Several small-molecule inhibitors of p38 kinase have been developed showing a broad range of antiinflammatory effects. For example, GlaxoSmithKline's SB-203580 (**14**) and SB-239063 (**15**) reduced inhaled LPS-induced neutrophil infiltration and inhibited cytokine secretion in BALF (48, 49).

Although several oral inhibitors of p38 MAP kinase are in clinical development for arthritis and cancer, only two compounds are being developed for COPD. SB-681323 (GlaxoSmithKline) has been studied in a 4-week



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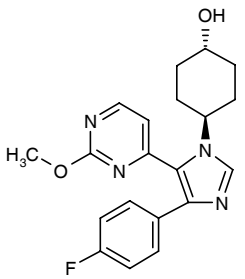

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phase II trial in which the efficacy outcome measures included lung function, sputum and serum biomarkers of inflammation, including C-reactive protein (CRP), but results have not been published. A follow-up compound, SB-856553, recently entered phase II trials, which indicates that there is significant confidence in this mechanism within GlaxoSmithKline. In view of the potential for systemic side effects with orally administered kinase inhibitors in general, there might be an opportunity to develop inhaled inhibitors of p38 for COPD. However, since all available p38 inhibitors compete with ATP, severe side effects due to cross-reactivity with other kinases or nonkinase cellular proteins are likely to occur. Alternative approaches would be to design new inhibitors that are not based on competition with ATP, or that target other molecules in the p38 MAP kinase pathway (47).

Phosphatidylinositol 3-kinase inhibitors

Phosphatidylinositol 3-kinase (PI3K) represents a family of intracellular signaling proteins that control a variety of important cellular functions, such as proliferation, apoptosis and migration. Recent findings suggest an involvement of PI3K in the pathogenesis of numerous diseases, including cancer, heart failure and autoimmune/inflammatory disorders (50). A particular isoform, PI3Kγ, is involved in neutrophil recruitment and activation. Knockout of the PI3Kγ gene results in inhibition of neutrophil migration and activation (51). Data from animal studies suggest that PI3Kγ inhibitors may be of interest for the treatment of COPD and the development of selective PI3Kγ inhibitors will facilitate studies to prove this concept (52).

Nuclear factor-κB inhibitors

Nuclear factor-κB (NF-κB) is a major family of transcription factors activated during the inflammatory response in COPD. Bronchial biopsies in smokers with normal lung function and COPD patients show increased expression of NF-κB, predominantly in the bronchial epithelium (53). Furthermore, activated NF-κB was detected in sputum macrophages, but not in sputum neutrophils, during exacerbations of COPD (54).

NF-κB normally resides in the cytoplasm and is held in an inactive state by its inhibitor chaperone IκBα. Phosphorylation of IκBα results in ubiquitination and proteolysis of IκBα, which then releases NF-κB to promote gene transcription. The multisubunit IκBα kinase responsible for this phosphorylation contains two catalytic subunits, termed IKK1 and IKK2 (55). NF-κB is a key transcriptional regulator of multiple proinflammatory mediators, such as TNF-α, interleukins, intracellular adhesion molecules (ICAMs), vascular cell adhesion molecules (VCAMs), MMPs and cyclooxygenases (56).

The most promising approach to inhibiting NF-κB is inhibition of IKK2 using small-molecule inhibitors. Several companies initiated drug discovery programs targeting IKK2 (57). Experiments in preclinical models suggest that inhibiting IKK2 is a rational approach to treat COPD (58). So far, only an IKK2 inhibitor from the Institute of Medicinal Molecular Design (IMD-1041) and another (MLN-0415) from Millennium Pharmaceuticals and sanofi-aventis have been reported to be in phase I clinical evaluation, although no results are available (37). As a caveat to this approach, it is still unclear what toxicities will be associated with IKK inhibitors, although teratogenicity and susceptibility to infection could be problematic.

Stimulation of repair mechanisms

Drugs that stimulate alveolar repair could represent a definite qualitative therapeutic improvement. Retinoids promote alveolar septation in the developing lung and stimulate alveolar repair in some animal models of emphysema. However, no definitive clinical benefits were observed in COPD patients treated with *all-trans*-retinoic acid (59).

Vascular endothelial growth factor (VEGF) plays a central role in the life and death of pulmonary vascular endothelial cells. VEGF is a trophic factor required for the survival of endothelial cells and is abundantly expressed in the lung. In an animal model, chronic treatment with the VEGF receptor blocker SU-5416 (semaxanib) led to enlargement of the air spaces, indicative of emphysema (60). Furthermore, VEGF was considerably decreased in the BALF of smoking patients (61). Based on these findings, it is likely that topically applied VEGF agonists may represent interesting future anti-COPD drugs.

Outlook

COPD remains a major health problem and new and improved treatments are desperately needed. The causal

link between the chronic inhalation of cigarette smoke and COPD is beyond doubt, and smoking cessation remains the most important goal for patients.

Inhaled anticholinergics remain the mainstay for COPD management due to their ability to alleviate symptoms, decrease exacerbations and improve quality of life. It remains to be demonstrated whether the natural history of COPD can be modified by correcting the decline in FEV_1, as hoped, and whether mortality is influenced not just by FEV_1 but also by other equally important factors that might indirectly affect airflow limitation.

Future COPD therapy will also be based on two (perhaps three) drug classes (bronchodilators, antiinflammatory and repair drugs). With regard to β_2-mimetics, there is no need to develop new compounds. Among the antimuscarinic compounds, glycopyrrolate may find its therapeutic place beside tiotropium and ipratropium. Of the antiinflammatory drugs, there is general hope that at least one PDE4 inhibitor will soon be approved. Taking a 5-year development period into consideration, it is unlikely that other antiinflammatory drugs will be used in clinical practice. To our knowledge, none of the repair drugs has a realistic chance to be approved in the foreseeable future.

In summary, the future of COPD therapy is not very promising, with no new drugs on the horizon. Both the pharmaceutical industry and academia should therefore reinforce their research activities to find novel and viable targets and corresponding compounds.

Acknowledgements

This work was supported by the DFG (SFB 643, B2).

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