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Emerging trends in the therapy of COPD: novel anti-inflammatory agents in clinical development

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During the past ten years, the pharmaceutical industry has focussed on treating chronic obstructive pulmonary disease (COPD) as distinct to asthma, and no novel anti-inflammatory agents have been launched as therapies for this disease. As our understanding of the pathology of COPD has increased it has been established that the progressive pulmonary inflammation that is associated with COPD relates to disease severity. Thus, it is anticipated that drugs that reduce pulmonary inflammation will provide effective, disease-modifying therapies. Here, we consider the potential of anti-inflammatory drugs that are currently in clinical development for COPD and discuss how these might reduce pulmonary inflammation in this disease.

Introduction

As discussed in the accompanying article [1], COPD is a disorder that is characterized by airflow obstruction that is progressive and relatively insensitive to treatment with bronchodilators, which provide mainly symptomatic relief. The lung pathology of COPD is complex and heterogeneous, comprising pulmonary inflammation, small airway remodelling, emphysema and mucous hypersecretion. The characteristic features of inflammation in COPD are described in Table 1.

Inflammation in the lungs of patients with COPD occurs in both small and large airways and is thought to be crucial to the development of the disease pathology: the severity of inflammation is associated with disease severity as measured by spirometry [2]. Key contributors to the progression of airway obstruction in COPD are an increase in the volume of tissue in the small-airway wall, accumulation of mucous exudates and infiltration of the airway wall by cells of the innate and adaptive immune responses [3,4]. Emphysema is defined as dilation and destruction of lung tissue beyond the terminal bronchiole, and its development contributes to a reduction in lung function by decreasing the elastic recoil of the lung. This reduces maximum expiratory flow, which leads to trapping of gas within the lung [5]. Up to 40% of heavy smokers develop emphysema and increased CD8+ lymphocytes [2,6], eosinophils, CD4+ lymphocytes and macrophages are associated with the presence of emphysema [7].

Recent literature indicates that antigen-driven cellular-mediated immunity is involved in severe COPD, and that this might be responsible for the persistent inflammation that is characteristic of severe emphysema [8]. The role of the B-cell follicles, which are present in increasing numbers in the small airways as COPD progresses in severity, in the development of a specific antigenic response is under investigation. Studies in emphysema patients and mice exposed to tobacco smoke (TS) show the presence of B-cell follicles that undergo antigen-specific proliferation. The specific antigens involved in this proliferative response are unknown but might include bacteria, viruses, components of TS and, potentially, the breakdown products of the extracellular matrix [9,10].

Aims of therapy

The aim of therapy in COPD is to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status, improve exercise tolerance and, ultimately, prevent the accelerated decline in lung function that might reduce mortality. Reducing the frequency and severity of exacerbations is an increasingly important target therapy because the prognosis for patients following exacerbations is poor. Current therapy focuses mainly on reducing symptoms using short-acting and long-acting bronchodilators either as monotherapies or combinations of

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TABLE 1

Characteristics of pulmonary inflammation associated with COPD

Site of inflammation	Feature	Refs
Small airways	Fibrosis Smooth muscle hypertrophy Goblet cell hyperplasia Inflammatory cells involved include CD4+ T cells, CD8+ T cells, B-cell follicles, macrophages and neutrophils (more severe disease)	[2,4,48,49]
Large airways	Involves macrophages, CD8+ T cells and plasma cells	[48]

long-acting β_2 adrenoceptor agonist bronchodilators with inhaled corticosteroids (ICS). The disappointing anti-inflammatory data for ICS either alone or in combination with β_2 adrenoceptor agonists has intensified the search for an effective anti-inflammatory drug for COPD and this goal remains a key objective for the pharmaceutical industry.

New anti-inflammatory agents in clinical development

COPD is a chronic inflammatory disorder, thus, a key question is whether novel anti-inflammatory agents can halt or slow the decline in lung function that does not appear to be modified by currently prescribed therapies. A schematic of the airway inflammation in COPD and the approaches that are being developed clinically is outlined in Box 1.

Our current understanding of the relationship between inflammatory biomarkers measured in sputum, bronchoalveolar lavage (BAL) and bronchial biopsies, and the clinical outcomes including disease progression, disease severity and response to therapy is limited, and more work is required to understand these key relationships. This is essential to evaluate fully the anti-inflammatory approaches that are in clinical development. Trials examining the predictive value of inflammatory biomarkers are underway but only a few of the markers that have been identified are associated with disease severity [11].

In the next section, we review the status of anti-inflammatory drugs currently in clinical development for COPD and estimates of when these compounds will reach the market are included in Figure 1. Other anti-inflammatory mechanisms in development

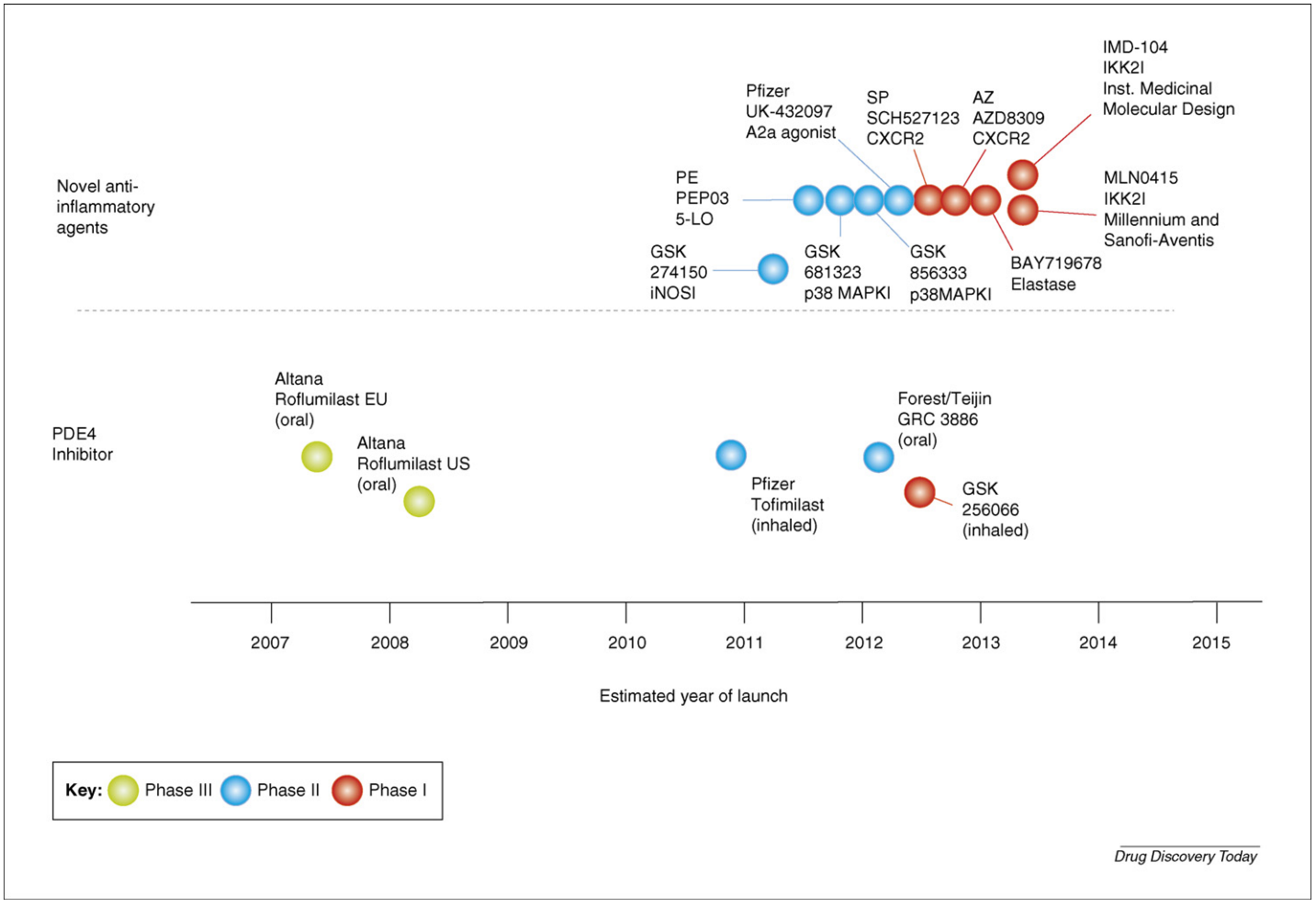

FIGURE 1

The current status of anti-inflammatory therapies in clinical development for COPD. Two main categories of therapy are shown: novel anti-inflammatory agents and PDE4 inhibitors (oral or inhaled). Status: phase III (green circles); phase II (blue circles) and phase I (red circles). Estimates for year of launch have been made based on publicly available information.

BOX 1

Airway inflammation in COPD and emerging anti-inflammatory therapy

Exposure to TS in susceptible individuals causes an abnormal inflammatory response that appears to be self perpetuating and is perhaps linked to bacterial or viral infection (Figure I). Alveolar macrophages and pulmonary epithelial cells release a variety of inflammatory mediators in response to TS, which activate and stimulate migration of pulmonary inflammatory cells, including neutrophils, macrophages and lymphocytes. The chronic and persistent inflammation that ensues is thought to be responsible for the symptoms of disease and the progressive decline in lung function that is seen in COPD patients. The loss of airway function appears to be related to the destruction of alveoli resulting in a loss of elasticity linked to increased protease activity; and obstruction and fibrosis of the small airways as a result of inflammation and mucus hypersecretion.

Emerging anti-inflammatory therapies currently under clinical investigation attack the chronic pulmonary inflammation via several strategies. Targeting chemokines such as monocyte chemotactic protein-1 (MCP-1), IL-8 and Leukotriene B4 (LTB4) can reduce the influx of inflammatory cells into the lungs from the circulation by reducing the chemotactic gradient. Reducing the numbers of neutrophils in the lung can also be accomplished using 5-Lipoxygenase (5-LO) inhibitors or CXCR2 antagonists. Reduction of pleiotropic inflammatory mediators, such as Interleukin-1β (IL-1β) and TNFα, using monoclonal antibodies that target the ligand can also reduce the inflammatory burden in the lung. Broad-spectrum anti-inflammatory agents that reduce the synthesis of these mediators in the lung, such as PDE4 inhibitors, p38 inhibitors, IKK2 inhibitors, Adenosine receptor 2a (A2a) agonists and iNOS inhibitors, might also be effective. Inhibiting the NE activity in the lung increased by the presence of inflammation might reduce lung tissue damage and the number of lung neutrophils. Reducing the severity of inflammation in the lung could then improve lung function and reduce the progression of disease.

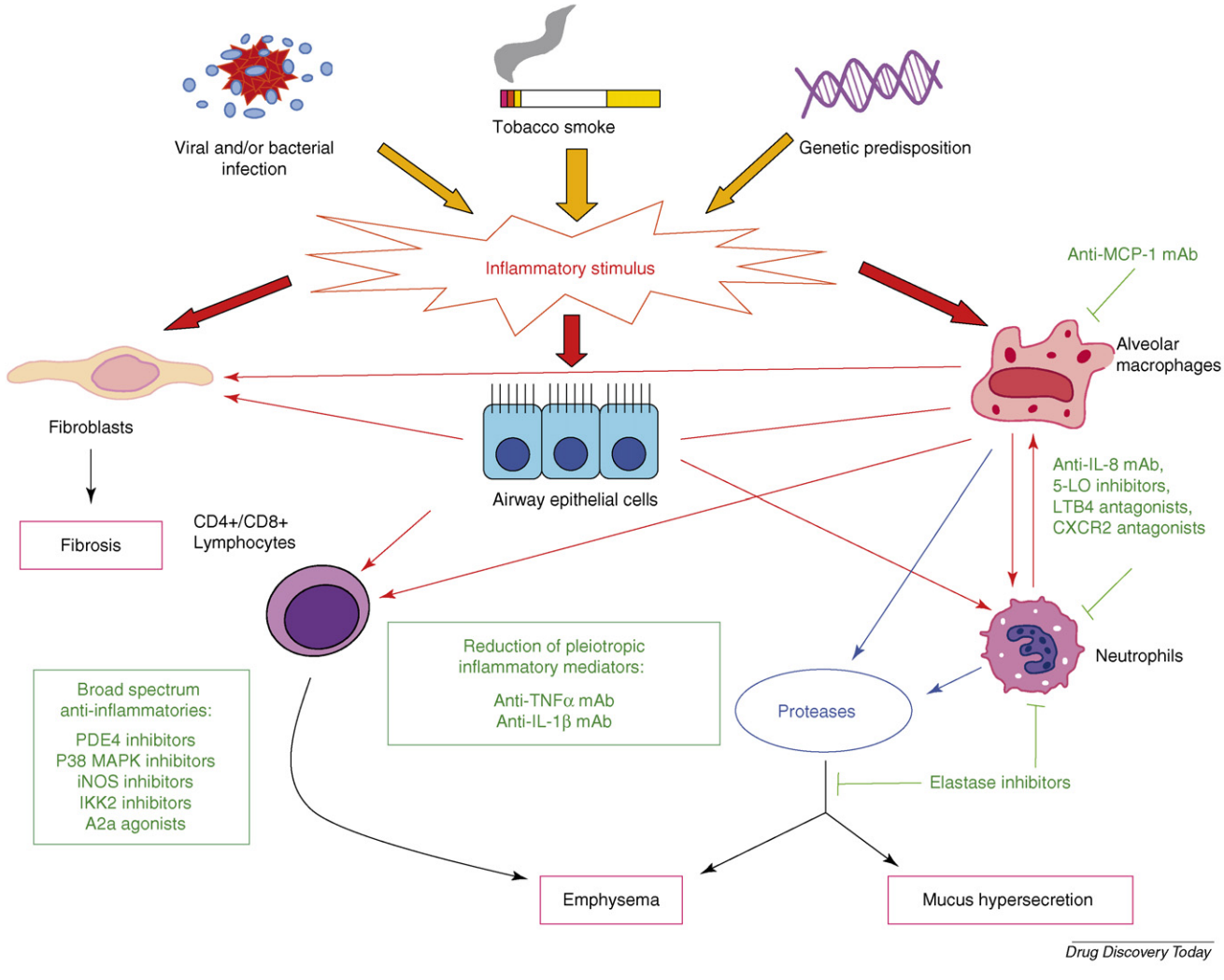

FIGURE I

TABLE 2

Other anti-inflammatory mechanisms in clinical development for COPD

Mechanism	Phase of development/company	Evidence in support of mechanism	Refs
Inhibition of p38 MAP kinase	GSK856553 in Phase II/GSK GSK681323 in Phase II/GSK	See text	
CXCR2 antagonism	SCH527123 in Phase I/Schering Plough AZD8309 in Phase I/AZ	See text	
Inhibition of IL-1 signalling	Monoclonal antibody to IL-1. Phase I/Novartis	IL-1β in the sputum of stable COPD patients correlates with neutrophil number, IL-8 and TNFα Mice that overexpress IL-1β in lung epithelium during adulthood develop pulmonary inflammation, emphysema, and airway remodelling Pulmonary inflammation induced by multiple TS exposure in mice is inhibited by treatment with an anti-IL-1β monoclonal antibody IL-1 receptor-knockout mice have significantly reduced emphysema following chronic exposure to TS	[50–53]
MCP-1 neutralization	Anti-MCP-1 antibody ABN912 Phase I/Novartis	MCP-1 and receptor, CCR2, is increased on macrophages and epithelial cells from COPD patients MCP-1 concentration is increased in the sputum from COPD patients MCP-1 concentration correlates with neutrophil number and FEV_1	[54,55]
TNFα neutralization	Infliximab Phase II/Centocor Etanercept Phase II (?)/Wyeth	TNFα double receptor-knockout mice are protected from both acute and chronic effects of TS exposure Infliximab apparently inactive in COPD trials up to 24 weeks Etanercept reduces inflammation and improves lung function in severe asthma	[56–59]
5 Lipoxygenase inhibition	PEP03 inhaled Phase II trials for COPD/PharmaEngine	Sputum levels of LTB4 are elevated in COPD Neutrophils from COPD patients produce increased amounts of LTB4 First generation inhibitors were associated with hepatotoxicity	[60,61][a]
iNOS inhibitors	1. GW-274150 Phase II/GSK? 2. SC-51 Phase I (asthma)/Pfizer	Immunoreactivity for iNOS in airway inflammatory cells of COPD patients is greater than in healthy smokers Role for iNOS in neutrophil recruitment induced by inhaled LPS	[62,63]
Adenosine 2A receptor agonists	UK-432097 in Phase II/Pfizer	A2A-receptor density is increased in lungs of COPD patients but the binding affinity is reduced. Receptor density is associated with airflow limitation CGS21680 reduces activation of lung neutrophils induced by LPS *in vivo*	[64,65]
IKK2 inhibitors	IMD1041 in Phase I/Institute of Medicinal Molecular Design, Inc MLN0415 in Phase I/Millennium and Sanofi-Aventis	IKK2 activity is required for NF-κB activation which is increased in the lungs of COPD patients IKK2 inhibitors block LPS induced lung neutrophila *in vivo*	[66,67]

[a] http://www.clinicaltrials.gov/ct/show/NCT00219648.

for COPD that are not described in the text are included in Table 2.

Phosphodiesterase 4 inhibitors

Phosphodiesterases (PDEs), including the isoenzyme PDE4, hydrolyse the intracellular second messenger 3′-5′-cyclic adenosine monophosphate (cAMP) to an inactive 5′ monophosphate. Elevation of intracellular cAMP has broad anti-inflammatory effects [12]. PDE4 is the predominant PDE isoenzyme in most inflammatory cells that have a role in the pathogenesis of COPD, and its activity is elevated in pulmonary macrophages from patients with COPD [13]. Several *in vitro* inflammatory cell-based functional assays and *in vivo* animal models of inflammation have demonstrated that PDE4 inhibitors have broad anti-inflammatory activity. This profile has led to interest in developing a safe, well tolerated inhibitor of PDE4 to treat respiratory disease.

In agreement with clinical studies, corticosteroids have limited anti-inflammatory efficacy in TS models in both mice and guinea pigs [14,15]. By contrast, the *in vivo* efficacy of PDE4 inhibitors in animal models of COPD is well documented. Roflumilast, which is currently in Phase III trials for COPD, inhibits TS-induced inflammation in mice and guinea pigs, and prevents the development of emphysema in mice [16,17].

There are currently five oral PDE4 inhibitors in clinical development for COPD (Table 3) and the major hurdle in their development has been overcoming the dose-limiting side-effects, which include nausea, emesis and headache. Evidence indicates that these side-effects, at least in part, are caused by inhibition of the PDE4D isozyme whereas the anti-inflammatory activity results from inhibition of the PDE4B isozyme. However, it remains to be established whether PDE4B-selective inhibitors would have a greater therapeutic index, which allows higher doses and improved efficacy [18]. In addition to the commonly reported side-effects, vascular inflammation or arteritis [19] and cardiac dysfunction [20] are also a concern with chronic therapy.

Four, 24-week, Phase III trials have assessed the efficacy of the PDE4 inhibitor cilomilast and one of these studies has been published recently [21]. In this study, outcome measures included trough forced expiratory volume in one second (FEV_1) and total score in the St. George's Respiratory Questionnaire (SGRQ). A key

TABLE 3

PDE4 inhibitors in clinical development

Compound ID	Administration route	Company	Clinical phase	Comment
Roflumilast	Oral	Altana	Phase III	Tanabe developing in Japan
Cilomilast	Oral	GSK	Phase III	FDA issued approvable letter in 2003
C3193	Oral	Merck	Phase II suspended?	Removed from company website. Last activity 2005
GRC3886	Oral	Glenmark	Phase II	Licensed to Forest/Teijin
Tetomilast (OPC6535)	Oral	Otsuka	Phase II	Also in clinical development for ulcerative colitis
Tofimilast	Inhaled	Pfizer	Phase II	For potential combination with an M_3 receptor antagonist?
GSK256066	Inhaled	GSK	Phase I	Phase II for asthma
GSK842470	Inhaled	GSK/Elbion	Phase II	Suspended?

secondary end-point was the frequency of COPD exacerbations. Over 24 weeks cilomilast improved baseline FEV_1 by 40 ml compared to placebo. The difference in total SGRQ score was 4.1 U (a difference of 4 U is accepted as clinically relevant). In addition, 12% of subjects in the cilomilast group were exacerbation-free at 24 weeks. A review of all four 24-week studies (www.fda.gov/ohrms/dockets/ac/03/slides/3976S1_01_Glaxo-Ariflo.ppt) shows that the improvement in FEV_1 compared to placebo was similar (30–40 ml over 24 weeks) across studies but significant improvements in SGRQ were achieved in only two studies.

Another PDE4 inhibitor, roflumilast, has been evaluated in a 24-week, multi-centre, Phase III trial of 1411 moderate to severe COPD patients (the RECORD trial) [22]. The primary outcomes were post-bronchodilator FEV_1 and health-related quality of life, measured by the SGRQ. Secondary outcomes included other parameters of lung function and COPD exacerbations. Post-bronchodilator FEV_1 at the end of treatment significantly improved with roflumilast at 250 μg (64 ml improvement) and 500 μg (88 ml improvement) compared with placebo. Pre-bronchodilator FEV_1 at the end of treatment also improved significantly with roflumilast at 250 μg (74 ml improvement) and 500 μg (97 ml improvement) compared with placebo. A post-hoc analysis indicates that lung-function improvement is greater in patients with moderate (FEV_1 >50% predicted) than severe COPD (FEV_1 <50% predicted). Although the improvement in SGRQ total score, compared with placebo, is similar for both doses of drug, it did not achieve statistical significance. Mean exacerbation rate was 34% less in the group that received 500 μg of roflumilast than in the placebo group owing to a reduction in mild exacerbations; the frequency of severe exacerbations was unaffected.

To reinforce the outcome of the RECORD trial, two additional Phase III trials (the US 'OPUS' study and the European 'RATIO' study) were initiated, which defined exacerbations as one of the primary measures of efficacy. The key outcome measures of these 1-year trials with roflumilast (500 μg) were reported in abstract form at the 2006 annual conference of the American Thoracic Society. In patients with severe to very severe COPD, moderate exacerbations were reduced by 18%, whereas in a subgroup of very severe patients with a high exacerbation rate there was a 36% reduction compared to placebo [23]. Roflumilast increased pre- and post-bronchodilator FEV_1 by 36 ml and 39 ml, respectively. Reported adverse events were mainly diarrhoea and nausea, which were mainly mild to moderate and resolved during continuous treatment [24].

Although the clinical benefit of roflumilast is less in the 1-year studies than in the shorter RECORD study, roflumilast was more effective in patients with severe disease and, in many cases, activity was seen in patients already being treated with an ICS/β_2 agonist combination and oral steroids. The level of efficacy that is achievable in patients with severe to very severe disease that are already on steroid therapy needs to be resolved because it might be more difficult to deliver additional, clinically significant outcomes in patients who are very ill. Indeed, there is an argument to be made for treating COPD patients with anti-inflammatory agents before they reach the moderate to severe category because treatment at this stage might have greater potential for reducing the decline in lung function.

The relationship between the improvement in clinical outcomes and anti-inflammatory activity has been investigated for both cilomilast and roflumilast in short-term studies. Treatment with cilomilast (15 mg, twice daily) for 12 weeks had no effect on sputum neutrophils, macrophages, elastase, interleukin 8 (IL-8) and lung function. However, bronchial biopsies demonstrated that cilomilast treatment was associated with significant reductions in the number of CD8+ T cells (48%) and CD68+ T cells (47%) [25]. Treatment with roflumilast for 4 weeks improved post-bronchodilator FEV_1 by 68.7 ml compared with placebo and significantly reduced the absolute number of neutrophils and eosinophils per gram of sputum by 36% and 50%, respectively, which was paralleled by reductions in IL-8 (26%) and neutrophil elastase (NE; 30%) [26]. This data indicates that the health-related outcomes observed in longer-term trials might be related, at least in part, to the anti-inflammatory activity of roflumilast.

In November 2005 it was reported that Altana Pharma had withdrawn the European Marketing Authorisation Application (MAA) for Daxas® (roflumilast). It was also reported than the submission of a new MAA would be pursued when further clinical data were available to strengthen the anti-inflammatory product profile and possible market potential of Daxas®. Although PDE4 inhibitors increase post-bronchodilator FEV_1 reproducibly in COPD patients, this is a relatively small effect and is below the minimum clinically important difference specified in the Global Initiative for Chronic Obstructive Lung Disease guidelines [27]. Robust reductions in the frequency of exacerbations in COPD patients are likely to be the minimum requirement for regulatory submission of PDE4 inhibitors and perhaps all new anti-inflammatory agents.

In an attempt to reduce the potential for systemic side-effects and to administer relatively higher doses to the lungs, inhaled

PDE4 inhibitors are being developed (Table 3). GSK842470 (AWD-12–281) has been licensed from Elbion and reached Phase II for asthma and COPD but there are unconfirmed reports that it has no advantage over oral inhibitors of PDE4. Currently GSK (Phase I) and Pfizer (Phase II) are reported to have inhaled PDE4 inhibitors in clinical development for COPD.

Whether either oral or inhaled PDE4 inhibitors deliver the anticipated potential of inhibiting this target in COPD patients will become clearer over the next 3–5 years. It is anticipated that an inhaled PDE4 inhibitor will result in the development of combination products that include bronchodilator drugs of either the long-acting muscarinic acetylcholine receptor antagonist class or long-acting β_2 adrenoceptor agonist class.

Inhibitors of p38 mitogen-activated protein kinase

The p38 mitogen-activated protein kinase (MAPK) has four isoforms (p38 MAPKα–p38 MAPKδ) that regulate transcription through phosphorylation of transcription factors. In assays to assess the function of pulmonary inflammatory cells, inhibition of p38 MAPK blocks the release of tumour necrosis factor α (TNFα) by lipopolysaccharide (LPS)-stimulated alveolar macrophages [28], IL-6 release by bronchial epithelial cells in response to cigarette smoke [29] and activation of neutrophils [30].

The potential therapeutic utility of inhibition of p38 MAPK in respiratory disease is supported by data from several *in vivo* pulmonary inflammatory models, including LPS-induced pulmonary neutrophilia [31]. A recent study has examined the efficacy of a selective inhibitor of p38 MAPKα in a mouse model of COPD [32]. In this model SD282 inhibits TS-induced pulmonary neutrophilia and macrophage recruitment, and decreases the concentration of phospho-p38 MAPK in macrophages and epithelial cells. Although several oral inhibitors of p38 MAPK are in clinical development for arthritis and cancer only two compounds are being developed for COPD. GSK681323 has been studied in a 4-week, Phase II trial in which the efficacy outcome measures include lung function, sputum and serum biomarkers of inflammation, including C-reactive protein (CRP), but results have not been published. A follow-up compound GSK856333 has entered Phase II trials recently, which indicates that there is significant confidence in this mechanism within GSK. 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 MAPK for COPD.

IL-8 neutralization and CXCR2 antagonists

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, [33]. IL-8 is increased in the sputum of COPD patients and its concentration correlates with disease severity [11]. Patients with higher baseline levels of IL-8 are also at higher risk of future exacerbations [34].

The effect of neutralizing IL-8 using a monoclonal antibody has been explored in COPD patients by Abgenix (now part of Amgen). In a 3-month study ABXIL8 was well tolerated and improved symptoms of dyspnoea but did not improve lung function [35]. Further development has not been reported and ABXIL8 does not feature as part of the Amgen pipeline. Whether the lack of conclusive efficacy is caused by the characteristics of the antibody itself is unclear although the efficacy in Phase II trials for rheumatoid arthritis and psoriasis was also disappointing.

The CXC chemokines GROα, GROβ, GROγ, NAP-2, ENA-78 and GCP-2 are also ligands of CXCR2 [36] and so an effective CXCR2 antagonist will reduce signalling mediated by these mediators in addition to IL-8. Development of receptor antagonists has focussed on selective CXCR2 antagonists and blockade of this receptor *in vivo* inhibits neutrophil recruitment into the lungs. In rodent TS models, selective CXCR2 antagonists inhibit pulmonary neutrophilia [37,38].

GSK have had at least three oral CXCR2 antagonists in clinical development for COPD (GSK656933, SB225002 and SB265610) but none now feature in their pipeline. Currently there are two oral CXCR2 antagonists in clinical development for COPD, AZD8309 (AstraZeneca) and SCH527123 (Schering Plough) both of which are in Phase I development.

Neutrophil elastase inhibitors

Neutrophil elastase (NE) is a serine protease that is synthesized by neutrophils and secreted following neutrophil activation. A major action of NE is degradradation of matrix proteins and it is a key enzyme in the development of hereditary emphysema caused by deficiency of α-1 antitrypsin (AAT). Although the role of NE in the development of non-hereditary emphysema is unclear, it has a broad range of actions that are consistent with a pro-inflammatory role in COPD [39]. NE increases matrix metalloproteinase (MMP) activity by directly activating MMPs such as MMP-9 and by inactivating the endogenous MMP inhibitor, TIMP-1, thus, potentially enhancing the role of MMPs in COPD [40]. NE also stimulates mucin secretion [41] and modulates apoptosis of human lung epithelial cells [42]. Therefore, NE might have a role in emphysema and lung remodelling through matrix degradation and by inducing apoptosis.

In TS models the NE-knockout mouse is partially protected from developing emphysema, an effect that is accompanied by inhibition of both neutrophil and macrophage recruitment [43]. Treatment with AAT inhibits development of emphysema and reduces pulmonary recruitment of neutrophils and macrophages [44]. Similarly, a small-molecule inhibitor of NE, ZD0892, reduces TS-induced emphysema and pulmonary-cell recruitment in a guinea pig model [45]. These studies indicate that inhibition of NE is anti-inflammatory in addition to preventing the development of emphysema.

The search for potent, safe, oral inhibitors of NE has lasted for more than 20 years and many of the compounds that progressed into clinical development have failed because of poor pharmacokinetics and low therapeutic index. More recently, both GSK (GW311366) and ONO Pharmaceuticals (ONO6818) have had orally active compounds in Phase I/II development. However, these also failed in early clinical trials and no oral NE inhibitors have been evaluated fully in Phase II trials for COPD. The AstraZeneca protease inhibitor AZD3342 (which is thought to be an NE inhibitor) was scheduled to progress to Phase II studies in the second half of 2006. However, as of April 2007, the AstraZeneca website (http://www.astrazeneca.com/article/511390.aspx) indicates that this compound no longer appears to be in clinical development.

TABLE 4

Neutrophil elastase inhibitors in clinical development

Compound ID	Administration route	Company	Clinical phase[a]	Comment
Prolastin	Injection	Talecris	Launched	Treatment for anti-trypsin-deficient emphysema. Licensed from Bayer
AZD3342	Oral	AZ	Discontinued; was in Phase I	NE thought to be target. New molecule in preclinical development
BAY719678	Oral	Bayer	Phase I (for pulmonary hypertension in COPD)	From Bayer website, accessed 2007 (http://www.investor.bayer.com/user_upload/1418/)
DX890 (EPI-HNE-4)	Inhaled	Dyax	Phase II cystic fibrosis	Recombinant protein
rAAT	Inhaled	Baxter/Arriva	Phase II COPD and emphysema	Recombinant AAT

[a] For COPD unless indicated.

Protein inhibitors of NE administered via nebulization are also being pursued (Table 4) and there is data to support the use of inhaled, recombinant AAT in mouse TS models [46]. The probability of developing an inhaled combination product that contains a biological NE inhibitor and a bronchodilator is low. However, safe, long-acting, inhaled inhibitors of NE with low systemic bioavailability that are suitable for combination with bronchodilators are being pursued by Argenta Discovery [47].

The recent evidence to support NE inhibitors as anti-inflammatory agents opens the possibility of evaluating inhibitors in short-term, Phase II, proof of concept trials over 4–6 weeks rather than in long-term trials in which lung function decline is the major clinical outcome. With this realization, the potential of NE inhibition, as either an oral or an inhaled drug should be elucidated in the next 2–5 years.

Conclusions and future perspectives

Several anti-inflammatory mechanisms are being investigated clinically in COPD patients and data generated in the next 5 years should indicate whether significant anti-inflammatory activity can be achieved in COPD patients and whether this leads to improved clinical outcomes. Orally administered drugs have the advantage of improving compliance compared to inhaled medications and might reduce the chronic systemic inflammation that occurs in COPD as well as reducing the inflammation within the lungs. Injectable therapies might also have the advantage of targeting both systemic and pulmonary inflammation. However, as demonstrated by oral steroids and PDE4 inhibitors, systemic side-effects might limit the therapeutic dose significantly and, consequently, reduce efficacy. Inhaled anti-inflammatory drugs have the potential to reduce pulmonary inflammation while having low systemic exposure and an improved therapeutic index. In addition, once proof of concept has been established for the inhalation approach, the potential for combining with inhaled bronchodilators can be explored with the aim of providing patients with an optimal combination that delivers both symptomatic relief and disease-modifying therapy in a single product. These combinations might prove more efficacious than the current combination of ICS and β_2 adrenoceptor agonist that is prescribed widely to patients with COPD.

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