Chronic obstructive pulmonary disease: an update of treatment related to frequently associated comorbidities

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Abstract: Chronic obstructive pulmonary disease (COPD) is associated with a pulmonary inflammatory response to inhaled substances, and individuals with COPD often have raised levels of several circulating inflammatory markers indicating the presence of systemic inflammation. Recently, there has been increasing interest in comorbidities associated with COPD such as skeletal muscle dysfunction, cardiovascular disease, osteoporosis, diabetes and lung cancer. These conditions are associated with a similar inflammation-based pathophysiology to COPD, and may represent a lung inflammatory ‘overspill’ to distant organs. Cardiovascular disease is a significant cause of mortality in COPD, and the concepts of an inflammatory link raise the possibility that treatment for one organ may show benefits to comorbidities in other organs. When considering treatment of COPD and its comorbidities, one approach is to target the pulmonary inflammation and hence reduce any ‘overspill’ effect of inflammatory mediators systemically as suggested by response to inhaled corticosteroids. Alternatively, treatment targeted towards comorbid organs may alter features of pulmonary disease as statins, angiotensin-converting enzyme (ACE) inhibitors and peroxisome proliferator-activated receptor (PPAR) agonists may have beneficial effects on COPD by reducing exacerbations and mortality. Newer anti-inflammatory treatments, such as phosphodiesterase 4 (PDE4), nuclear factor(NF)-kB, and p38 mitogen-activated protein kinase (MAPK) inhibitors, are given systemically and may confer benefits to both COPD and its comorbidities. With common inflammatory pathways it might be expected that successful anti-inflammatory therapy in one organ may also influence others. In this review we explore the concepts of systemic inflammation in COPD and current evidence for treatment of its related comorbidities.

Keywords: angiotensin-converting enzyme inhibitors, anti-inflammatory drugs, chronic obstructive pulmonary disease, comorbidity, peroxisome proliferator-activated receptor agonists, statins, systemic inflammation

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide [Pauwels *et al.* 2001]. The underlying pathophysiological process is believed to reflect an abnormal and destructive inflammatory response to inhaled substances such as cigarette smoke and pollutants. The degree of airflow obstruction as measured by forced expiratory volume in 1 second (FEV₁) is a strong independent predictor of all-cause mortality amongst smokers [Stavem *et al.* 2005]. More recently, interest has been increasing in the associated

comorbidities such as skeletal muscle dysfunction [Kim *et al.* 2008], cardiovascular disease (CVD) [Sin and Man, 2005a], osteoporosis [Bolton *et al.* 2004], type 2 diabetes [Mannino *et al.* 2008] and lung cancer [Wasswa-Kintu *et al.* 2005]. These conditions occur more frequently than expected even when all of the known common risk factors (such as smoking and steroid use) are taken into account. Furthermore, inflammation has also been implicated in these other diseases and the mediators involved have much in common with those in COPD. This raises the possibility of an inflammatory ‘overspill’ affecting distant organs

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or common genetic predispositions [Wouters *et al.* 2009]. Patients with COPD have raised systemic levels of several markers of inflammation including C-reactive protein (CRP), interleukin (IL)-6, fibrinogen, activated leukocytes, and tumour necrosis factor (TNF) α [Gan *et al.* 2004]. Mortality in mild-to-moderate COPD is often not respiratory in origin and cardiovascular mortality provides a significant contribution [Sin *et al.* 2006]. Similarly, vascular disease is a major cause of death in diabetes [Moss *et al.* 1991]. These observations and the concepts of an inflammatory link raise the possibility that effective therapies for one organ may also have a beneficial effect on the other comorbid conditions. This review explores these concepts and the current evidence in more detail.

Inflammation in COPD

The lung inflammatory response is characterized by increased numbers of neutrophils, macrophages and T lymphocytes, and elevated concentrations of pro-inflammatory cytokines such as leukotriene (LT) B₄, IL-1, IL-6 and IL-8 and TNF α [Agusti *et al.* 2003]. Many of these markers of inflammation are also elevated in the systemic circulation, and evidence of activation of circulating inflammatory cells is present in COPD [Barnes and Celli, 2009].

TNF α in particular has been recognized as part of both the lung and systemic inflammation in COPD [Churg *et al.* 2004; Di Francia *et al.* 1994]. Plasma TNF α and its soluble receptor are increased in COPD patients [Broekhuizen *et al.* 2005; Takabatake *et al.* 2000], and their circulating monocytes and bronchoalveolar lavage T lymphocytes produce more TNF α than those from healthy controls [Barczyk *et al.* 2006; de Godoy *et al.* 1996]. TNF α has been implicated in the pathophysiology of skeletal muscle dysfunction, type 2 diabetes and osteoporosis [Sevenoaks and Stockley, 2006]. However, TNF α inhibitors have not shown significant benefit in patients with COPD from limited randomized controlled trials [Matera *et al.* 2010], although an observational study suggests that etanercept may reduce hospital admissions [Suisa *et al.* 2008]. Barnes has suggested that this may be because COPD is a highly complex inflammatory disease in which many other cytokines and mediators are involved, and that blocking a single cytokine does not have a clinically significant effect [Barnes, 2007]. Alternatively, the relatively low levels seen in COPD and the slow progression of the disease

may mean that TNF α requires long-term inhibition before any effect can be clearly identified.

Patients with COPD also have elevated levels of CRP [Schols *et al.* 1996], which increase with disease severity [Kony *et al.* 2004]. Plasma concentrations of CRP are related to mortality in mild-to-moderate patients [Man *et al.* 2006], although not in severe and very severe patients [de Torres *et al.* 2008]. Persistent systemic inflammation and elevated CRP have been associated with an increased risk of future cardiovascular mortality [Ridker *et al.* 2002], which may explain the increase in mortality early in the disease.

Comorbidities in COPD

Skeletal muscle dysfunction

Muscle wasting is a significant marker of mortality in COPD [Swallow *et al.* 2007] and TNF α is believed to play a key role. TNF α activates the transcription factor NF- κ B which increases activity of the ubiquitin/proteasome (U/P) pathway and subsequently accelerates the regulated degradation of muscle proteins and promotes muscle weakness [Reid and Li, 2001]. In addition, TNF α can induce apoptosis in several cell systems including skeletal muscle in COPD patients with weight loss [Agusti *et al.* 2003]. COPD patients with increased resting energy expenditure and reduced fat-free mass also have increased levels of acute phase reactant proteins and other inflammatory cytokines in their serum including CRP, lipopolysaccharide binding protein (LBP) and IL-8 [Schols *et al.* 1996], indicating an association with a more general inflammatory response.

Cardiovascular disease

COPD is an independent risk factor for CVD, with patients having an increased risk of coronary heart disease (odds ratio [OR] = 2.0, 95% confidence interval [CI]: 1.5–2.5), heart failure (OR = 3.9, 95% CI: 2.8–5.5), arrhythmias (OR = 2.4, 95% CI: 2.0–2.8) and stroke (OR = 1.5, 95% CI: 1.1–2.1) [Finkelstein *et al.* 2009]. Studies by Sin and colleagues have shown that the lower the FEV₁, the higher the risk of CVD [Sin and Man, 2005a, 2005b; Sin *et al.* 2005]. Arterial wall stiffness, which relates to cardiovascular risk, is increased in patients with COPD compared with smokers without COPD [Mills *et al.* 2008], and is related to disease severity [McAllister *et al.* 2007; Sabit *et al.* 2007]. CRP is an independent risk factor for future myocardial

disease [Lagrand *et al.* 1999] and has been implicated in the pathophysiology (along with other cytokines) of atheroma [Sun *et al.* 2005]. The increase in CRP with reducing FEV₁ may therefore explain the association with vascular abnormalities and increased risk of vascular disease. It is of interest to note that statin therapy is also associated with a reduction in CRP [Melbye *et al.* 2007], which may explain (in part) their efficacy.

Osteoporosis

Osteopenia is a feature of COPD even in patients not receiving systemic glucocorticoids and is associated with an increase in circulating TNF α [Bolton *et al.* 2004; Katsura and Kida, 2002]. Impaired FEV₁ has also been shown to be an independent predictor of osteoporosis in studies of patients with and without COPD [Lekamwasam *et al.* 2005]. TNF α and IL-1 have been implicated in the pathophysiology of osteoporosis [Cenci *et al.* 2000] and act as stimulants of osteoclasts which cause bone resorption. The resorption process is driven by receptor activator of NF-kB ligand (RANKL), which is related to TNF α . The selective oestrogen receptor modulator, raloxifene, which is used for the treatment of osteoporosis may modulate TNF α synthesis and is associated with a reduction in TNF α in the plasma [Gianni *et al.* 2004].

Type 2 diabetes mellitus

There is an increased prevalence of diabetes amongst patients with COPD [Mannino *et al.* 2008; Rana *et al.* 2004], which is also seen in patients with mild disease who are not taking corticosteroids. The pathogenesis may relate to the specific systemic inflammation in COPD since an increased risk was not found in asthmatic patients [Rana *et al.* 2004]. Furthermore, patients with non-insulin-dependent diabetes have increased circulating levels of IL-6 and CRP [Pickup *et al.* 1997] indicating the presence of systemic inflammation. Sonnenburg and colleagues suggested that TNF α activates NF-kB leading to cytokine production, upregulation of adhesion molecules and increasing oxidative stress [Sonnenberg *et al.* 2004]. This pathway may interfere with glucose metabolism and insulin sensitivity, and can be antagonized by adiponectin which reduces NF-kB activation [Sevenoaks and Stockley, 2006]. Indeed, the relationship between TNF α and insulin resistance is supported by the insulin-resistant obese mouse which becomes insulin sensitive following anti-TNF α therapy [Araujo *et al.* 2007].

Lung cancer

Smoking is a shared risk factor for both COPD and lung cancer. However, reduced FEV₁ increases the risk for lung cancer in the general population independent of smoking history, and there is an inverse relationship between the degree of airflow obstruction and the incidence of lung cancer [Wasswa-Kintu *et al.* 2005]. Chronic inflammation may also play a role in the pathogenesis of lung cancer and NF-kB activation may be an important factor [Sin *et al.* 2006]. Mukhopadhyay and colleagues suggested that alterations in the normal NF-kB regulation pathway may play a role in the development of non-small cell lung cancer (NSCLC) [Mukhopadhyay *et al.* 1995]. Since many cytokines including TNF α activate NF-kB a common mechanism can be envisaged. The protease-antiprotease imbalance is also an important factor since a deficiency of α 1-antitrypsin and/or an excess of neutrophil elastase are significantly associated with lung cancer risk [Yang *et al.* 2005].

Other comorbidities

Depression and anxiety are both common in patients with COPD, with a prevalence of up to 80% [Kunik *et al.* 2005]. These conditions are often underdiagnosed in clinical practice and may impact on quality of life. The aetiology of depression in COPD is likely to be multifactorial [Norwood, 2007].

Patients with chronic bronchitis and emphysema develop peptic ulcer disease more frequently than controls [Arora *et al.* 1968] and are more likely to have positive serology for *Helicobacter pylori* [Roussos *et al.* 2005]. Further, FEV₁ is lower in patients with peptic ulcer disease [Kellow *et al.* 1986]. Gastro-oesophageal reflux disease is common in patients with COPD and is associated with increased frequency of exacerbations [Rascon-Aguilar *et al.* 2006]. This may reflect inhalation of gastric acid; however, it needs to be recognized and adequately treated in this patient group.

COPD is also associated with normocytic anaemia [Cote *et al.* 2007], which is an independent risk factor for reduced functional capacity. The exact mechanism is largely unknown although it is generally considered a feature of 'chronic disease.'

COPD therapy and relation to comorbidities

There are various approaches to the treatment of COPD and its comorbidities. One approach is to target the pulmonary inflammation and hence reduce any 'overspill' effect of inflammatory mediators systemically. The concept of 'overspill' has been reviewed in detail elsewhere [Sinden and Stockley, 2010]. An alternative approach is to target treatment towards systemic effects and monitor the features of pulmonary disease.

Systemic treatments for comorbidities, such as statins, angiotensin-converting enzyme (ACE) inhibitors and peroxisome proliferator-activated receptor (PPAR) agonists may have beneficial effects on COPD with reduced exacerbations and mortality [Mancini *et al.* 2006]. Newer anti-inflammatory treatments, such as phosphodiesterase (PDE) 4, nuclear factor(NF)-kB, and p38 mitogen-activated protein kinase (MAPK) inhibitors, may potentially confer benefits to

both COPD and comorbidities [de Boer *et al.* 2007], but risk adverse effects due to their systemic distribution. With common pathways of inflammation, it might be expected that anti-inflammatory therapy that is successful in one organ may also influence others with the same pathophysiology. Unfortunately, randomized controlled trials in patients with chronic disease often exclude those with significant comorbidities. These concepts are summarized in Figure 1.

Chronic diseases such as COPD, CVD and diabetes are common especially in an elderly population and often coexist. These conditions share common preventable risk factors such as cigarette smoking and obesity. There is an urgent need for clinicians managing such chronic diseases to consider and treat comorbid conditions, and be aware that current clinical guidelines often do not take account of the coexistence of other conditions.

Figure 1. Treatment of chronic obstructive pulmonary disease (COPD) and its comorbidities. Inhaled corticosteroids reduce lung inflammation (1). Therapy targeted towards lung inflammation may also reduce systemic inflammation as a result of 'overspill' of inflammatory mediators leading to comorbidity (2). Comorbid conditions have a similar inflammation-based pathophysiology to COPD. Therapies targeted towards these comorbid conditions, e.g. statins, angiotensin-converting enzyme (ACE) inhibitors, peroxisome proliferator-activated receptor (PPAR) agonists, also have benefits for pulmonary disease (3). Systemic anti-inflammatory treatments may confer benefits to both COPD (4) and its comorbidities (5), but risk adverse effects due to their widespread distribution.

Smoking cessation

Cigarette smoking is a major cause of COPD, CVD and lung cancer. Smoking cessation is the only accepted intervention to reduce disease progression in COPD [Scanlon *et al.* 2000], although recent subanalysis of the TORCH (Towards a Revolution in COPD Health) study suggests that inhaled combinations of a long acting β_2 -agonist and corticosteroid may also have an effect [Celli *et al.* 2008]. Further, smoking cessation has similar beneficial effects on comorbidities such as CVD and lung cancer. Anthonisen and colleagues showed in a 14.5-year follow up of COPD patients that smoking cessation, which should reduce lung inflammation, also reduces all-cause mortality, particularly that due to myocardial infarction and cancer [Anthonisen *et al.* 2005]. Halvorsen and colleagues conducted a study to determine the effect of smoking cessation on markers of inflammation and endothelial cell activation and found that smoking cessation led to a reduction in soluble intercellular adhesion molecule 1 (sICAM-1) and a decrease in the gene expression of IL-8, although this was not statistically significant [Halvorsen *et al.* 2007]. Cigarette smoking alone is associated with increased levels of inflammatory markers (CRP, white cell count, fibrinogen), increased coagulation activation, and increased plasma viscosity and haematocrit, which have all been associated with increased risk of CVD. Smoking cessation is associated with a reduction in these haemostatic and inflammatory markers [Wannamethee *et al.* 2005], suggesting the mechanism for the reduction in the risk of CVD following smoking cessation is reducing the inflammation.

Both non-pharmacological and pharmacological approaches can be taken to assist smoking cessation. In clinical trials, treatment with nicotine replacement therapy and bupropion approximately doubles quit rates, whereas therapy with varenicline increases quit rates by threefold over those achieved by placebo and non-pharmacological measures [Chandler and Rennard, 2010].

Inhaled therapy

Corticosteroids. Inhaled corticosteroids were first implicated in reducing mortality following subanalysis of the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) study, a randomized double-blind placebo controlled study of fluticasone propionate in patients with

moderate-to-severe COPD [Briggs *et al.* 2006; Burge *et al.* 2000]. This led to the design of the TORCH study [Calverley *et al.* 2007], which was a randomized double-blind trial and included 6112 patients with moderate-to-severe COPD and supported a reduction in all-cause mortality rate in those receiving combination therapy (salmeterol and fluticasone propionate) compared with placebo, although this failed to achieve conventional levels of statistical significance ($p=0.052$). Subsequently, the randomized double-blind INSPIRE (Investigating New Standards for Prophylaxis in Reducing Exacerbations) study [Wedzicha *et al.* 2008] found a lower mortality (especially cardiovascular) in patients taking combination therapy (salmeterol/fluticasone) compared to those receiving tiotropium, although the trial was not initially powered to detect a difference in mortality as it was not the primary outcome. Meta-analysis has suggested that mortality is increased with anticholinergics [Singh *et al.* 2008]; however, this is unlikely to explain the difference since a randomized double-blind trial of 5993 patients with COPD, the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) study [Celli *et al.* 2009; Tashkin *et al.* 2008], if anything showed a trend towards reduced mortality in subjects receiving tiotropium compared with placebo. The difference observed in the INSPIRE study may therefore reflect the anti-inflammatory properties of the inhaled corticosteroid, although this remains speculative as inflammatory mediator measurement was not included in the study design.

There remains conflicting evidence regarding use of inhaled corticosteroids and mortality; however, overall the data suggest that inhaled therapy has a clinical benefit both for COPD and comorbidities such as cardiovascular disease. The effect may reflect a reduction in 'overspill' inflammation from the lungs to the systemic circulation. Sin and colleagues demonstrated that inhaled corticosteroids are associated with a reduction in CRP levels in COPD patients [Sin *et al.* 2004]. A reduction in CRP and subsequent reduction in cardiovascular mortality is clearly consistent with the pathophysiology described earlier. Further studies that are sufficiently powered to detect a difference in mortality rates would be needed to clarify this issue, although the initiation of suitably powered, placebo-controlled clinical trials of inhaled therapies may now prove unacceptable in view of the widely

accepted local benefits of inhaled corticosteroids, such as reduced exacerbation frequency, improved health status and spirometric values [Calverley *et al.* 2007].

Bronchodilators. Tiotropium is a long-acting anticholinergic drug that has been shown to improve FEV₁, decrease dyspnoea, improve exercise tolerance and improve health status in randomized double-blind placebo controlled studies [Casaburi *et al.* 2002]. The UPLIFT study [Tashkin *et al.* 2008], which was a randomized double-blind trial comparing 4 years of therapy with either tiotropium or placebo in patients with COPD found improvements in lung function and quality of life, and reduced exacerbations and related hospitalizations. As mentioned above, a trend was found towards reduced mortality in patients receiving tiotropium compared with placebo using the analysis according to the protocol, although this did not reach statistical significance.

Long-acting β_2 -agonists (LABAs) are effective bronchodilators in patients with COPD. Presently, there are two agents used in this class: salmeterol and formoterol. Salmeterol is a partial agonist with a slow onset of action whereas formoterol is a complete agonist and has an onset of action similar to that of short-acting β_2 -agonists [Lotvall, 2001]. Placebo-controlled trials have demonstrated an improvement in health-related quality of life [Aalbers *et al.* 2002; Dahl *et al.* 2001; Rennard *et al.* 2001] and possibly exacerbation frequency. It is uncertain whether LABAs have anti-inflammatory effects *in vivo* or have any beneficial effects on COPD comorbidities. Some concerns have been raised about cardiovascular morbidity as a result of β_2 -agonist studies in asthma, particularly in patients not taking an inhaled steroid. However, salmeterol 50 μ g twice daily and formoterol 12 μ g twice daily appear to be both effective and safe in treating patients with asthma and COPD [Sovani *et al.* 2004].

Systemic therapy for comorbidities

Statins. Statins were introduced into clinical practice for their cholesterol-lowering properties and have a proven prognostic benefit in ischaemic heart disease (IHD) [Smith *et al.* 2006a]. However, statins also have anti-inflammatory properties and retrospective studies have shown that they improve survival in patients following

an exacerbation of COPD even in the absence of IHD [Soyseth *et al.* 2007]. Furthermore, combined use of statins and inhaled corticosteroids has been shown to have a more favourable prognosis than use of statins alone [Soyseth *et al.* 2007]. The beneficial effects of statins in COPD may (at least in part) be due to their anti-inflammatory properties, as statins are associated with a reduction in CRP levels [Melbye *et al.* 2007]. Neutrophil-mediated inflammation is central to the lung pathology in COPD [Ichinose, 2009] and, in addition, it has been shown that neutrophil migration into the mouse lung following lipopolysaccharide (LPS)-induced inflammation is inhibited by statins [Young *et al.* 2009]. A further study in rats showed that statins protected against smoking-induced lung damage and exhibited some anti-inflammatory effects on the lung [Lee *et al.* 2005]. In a human study, statin users had reduced levels of neutrophils and lymphocytes in bronchoalveolar lavage fluid (BALF) compared with non-users [Johnson *et al.* 2003] indicating a potential beneficial mechanism.

A number of observational studies suggest that patients with COPD and taking statins have reduced hospitalization for COPD exacerbations, lower mortality from COPD exacerbations and lower cardiovascular mortality compared with those not taking statins [Mortensen *et al.* 2009; Blamoun *et al.* 2008; van Gestel *et al.* 2008; Soyseth *et al.* 2007]. Statins may also reduce decline in lung function with the size of the beneficial effect modified by smoking status [Alexeeff *et al.* 2007]. Statins may also reduce the risk of lung cancer [Khurana *et al.* 2007] and extrapulmonary cancer mortality in patients with COPD [van Gestel *et al.* 2009]. Data also suggest that statins have a beneficial effect on other comorbidities such as diabetes and osteoporosis [Paraskevas *et al.* 2007]. A recent meta-analysis [Brugts *et al.* 2009] including 70,388 participants without established cardiovascular disease but with cardiovascular risk factors randomized to statin therapy or placebo demonstrated that statin therapy was associated with a significant risk reduction in all-cause mortality of 12%, in major coronary events of 30%, and in major cerebrovascular events of 19%. No significant differences in treatment effect of statins were observed when subgroup analysis was performed for diabetic status. There is also evidence that the use of statins is associated with an increase in bone mass density and reduction in fracture risk [Tang *et al.* 2008] suggesting a role in osteoporosis.

A randomized, double-blind study [Lee *et al.* 2008] showed a 54% increase in exercise tolerance in COPD patients treated with pravastatin compared with placebo. This was associated with a decrease in high sensitivity CRP suggesting that a reduction in systemic inflammation may be related to this benefit. Clearly, this data indicate a need for well-designed prospective randomized controlled trials to determine the effect of statins on COPD and its comorbidities.

When statins have been used in combination with ACE inhibitors or angiotensin receptor blockers (ARBs), retrospective studies have suggested a reduction in COPD hospitalization and total mortality [Mancini *et al.* 2006]. Furthermore, this drug combination is associated with reduced myocardial infarction in the COPD cohort with high cardiovascular risk. Whether this provides an additive benefit needs to be determined.

ACE inhibitors. As indicated above, ACE inhibitors in combination with statins may have a beneficial effect. Patients with COPD are at greater risk of developing heart failure and diabetes, for which ACE inhibitors are widely used. Polymorphisms of the ACE gene have been associated with increased susceptibility to COPD [Busquets *et al.* 2007]. Randomized controlled trials are now needed to confirm any impact of ACE inhibitors on COPD mortality and comorbidities.

PPAR agonists. PPARs are a family of ligand-activated transcription factors belonging to the nuclear hormone receptor family [Belvisi and Mitchell, 2009]. Three subtypes are recognized; PPAR α (also known as NR1C3), PPAR γ (NR1C1) and PPAR δ (also known as PPAR β or NR1C2) and are widely expressed, having a range of effects on metabolism, cellular proliferation and immune responses [Berger *et al.* 2005; Kota *et al.* 2005]. PPARs have been implicated in several systemic manifestations of COPD, including cachexia, skeletal muscle weakness and systemic inflammation [Remels *et al.* 2008].

PPAR γ and PPAR α have been demonstrated in lung tissue [Belvisi and Hele, 2008]. Synthetic ligands of the two receptor isotypes, the thiazolidinediones and fibrates, are clinically used to treat type 2 diabetes and dyslipidaemia, respectively. As discussed above, both diabetes and CVD are found more commonly amongst patients with COPD. Studies in animal models

of human lung inflammatory diseases have provided evidence of the beneficial effects of PPAR γ and PPAR α . In mice with deletion of the PPAR γ gene specifically within conducting airway epithelial cells, there is persistent enlargement of the airspaces resulting from insufficient postnatal lung maturation. The increase in airspace size is accompanied by changes in lung physiology and suggest that airway epithelial cell PPAR γ is necessary for normal lung structure and function [Simon *et al.* 2006]. Birrell and colleagues showed that in the mouse model of airway inflammation the PPAR γ agonist, rosiglitazone, inhibited LPS-induced neutrophilia and associated chemoattractants/survival factors [Birrell *et al.* 2004]. This suggests that this class of drug may be beneficial in conditions where neutrophil mediated inflammation plays a role, such as in COPD.

In a mouse model of asthma, treatment with a PPAR γ agonist, ciglitazone, significantly reduced lung inflammation and mucus production [Mueller *et al.* 2003]. T cells from these ciglitazone-treated mice also produced less interferon (IFN) γ , IL-4 and IL-2 upon allergen challenge *in vitro*. Genovese and colleagues demonstrated that two PPAR γ agonists significantly reduced bleomycin-induced lung injury in mice [Genovese *et al.* 2005]. These studies give further evidence for targeting PPAR γ in inflammatory diseases of the lung.

The role of PPAR α has been studied using both PPAR α -deficient mice and mice treated with a PPAR α agonist, fenofibrate [Delayre-Orthez *et al.* 2005]. PPAR α -deficient mice exhibit greater neutrophil and macrophage numbers in BALF, as well as increased levels of TNF α and other chemoattractants, following intranasal exposure to LPS. Fenofibrate has been shown to reduce the increase in neutrophil and macrophage number induced by LPS in wild-type mice in a dose-dependent manner. PPAR α -deficient mice did not show a reduction in airway inflammation with fenofibrate, demonstrating that PPAR α is responsible for mediating the anti-inflammatory effect of fenofibrate. Again, this suggests that PPAR α may play an important role in inflammatory diseases of the lung.

There is reduced expression of PPAR α and PPAR γ in skeletal muscle of COPD patients who have cachexia [Remels *et al.* 2007]. PPAR agonists may therefore have benefit in treating

this systemic aspect of COPD. Unfortunately, there has been an increased incidence of myocardial infarction and heart failure in diabetic patients treated with the PPAR γ agonist, rosiglitazone [Singh *et al.* 2007]. On the other hand, pioglitazone is associated with a significantly lower risk of death and myocardial infarction amongst diabetic patients [Lincoff *et al.* 2007], suggesting that the cardiovascular risk seen with rosiglitazone may not be a class effect. Cardiovascular risk may also be avoided if these drugs were to be given to COPD patients via the inhaled route although this may reduce any efficacy related to the systemic comorbidities unless the 'overspill' hypothesis is valid.

Newer anti-inflammatory treatments

Corticosteroids, while effective in treating asthma, have more limited efficacy in the treatment of COPD. There is therefore a need for novel anti-inflammatory treatments, but systemic treatments may be associated with adverse effects due to widespread distribution, and agents given by the inhaled route may avoid this. Whereas systemic anti-inflammatory treatment may have direct beneficial effects in many organs, novel inhaled treatments for COPD may also confer indirect benefit to comorbidities by reducing an 'overspill' inflammation from the lungs to the systemic circulation.

PDE4 inhibitors. There are more than 11 members of the PDE superfamily and PDE4 is the predominant isoenzyme in most inflammatory cells thought to have a role in the pathogenesis of COPD [de Boer *et al.* 2007]. In an early 6-week randomized dose-ranging human study of cilomilast, a selective PDE4 inhibitor, an improvement in lung function was seen [Compton *et al.* 2001]. Cilomilast has also been shown in a randomized study to reduce the number of inflammatory cells in bronchial biopsies [Gamble *et al.* 2003]. Another PDE4 inhibitor, roflumilast, has been shown to inhibit lung inflammation and emphysema in mice exposed to cigarette smoke [Martorana *et al.* 2005]. In a human crossover study [Grootendorst *et al.* 2007], roflumilast has been shown to significantly reduce the number of neutrophils and eosinophils in sputum compared with placebo. Further, levels of soluble IL-8 and neutrophil elastase in sputum and the release of TNF α from blood cells were significantly reduced by roflumilast. An improvement in postbronchodilator FEV₁ was also observed in the roflumilast

group which may relate to these anti-inflammatory effects.

In two double-blind multicentre studies [Fabbri *et al.* 2009] of patients with moderate-to-severe COPD, roflumilast was shown to improve lung function even in patients treated with salmeterol or tiotropium. Roflumilast has also been shown to reduce moderate-to-severe exacerbations [Calverley *et al.* 2009]. However, patient withdrawal in studies has been a problem due to adverse effects such as nausea, diarrhoea, weight loss, and headache when the drug is given systemically. A phase II trial of a novel inhaled PDE4 inhibitor [Vestbo *et al.* 2009] showed no effect of treatment on spirometric measures and symptom scores in patients with moderate-to-severe COPD, therefore raising doubts as to the benefit or clinical use of this class of drug especially by the inhaled route.

The PDE4 family comprises four genes (PDE4 A, B, C, D). PDE4D inhibition is thought to be the cause of the side effects of the orally delivered compounds, while PDE4B is a therapeutically relevant target [de Boer *et al.* 2007]. Therefore, systemic treatment with PDE4 subtype inhibitors may be better tolerated and deserve further consideration especially in view of the positive effects of roflumilast.

Rolipram, a PDE4 inhibitor, has been shown to prevent bone loss and increase skeletal muscle mass in ovariectomized rats [Yao *et al.* 2007]. This may have implications for treating COPD comorbidities such as skeletal muscle dysfunction and osteoporosis. Any effects on CVD have yet to be studied although preliminary studies suggest roflumilast may have a positive benefit on glucose control [Waddleton *et al.* 2008]. Clearly this class of drug needs further development and study in COPD and its comorbidities.

NF- κ B inhibitors. Many of the pro-inflammatory chemokines, cytokines, adhesion molecules, growth and angiogenic factors relevant to COPD are induced via the NF- κ B family of transcription factors [Edwards *et al.* 2009]. Increased markers of NF- κ B pathway activity have been demonstrated in the airways of COPD patients, including sputum macrophages during exacerbations [Caramori *et al.* 2003] and in bronchial biopsies of stable patients [Di Stefano *et al.* 2002]. NF- κ B activation is also implicated in mediating systemic inflammation and may be

involved in skeletal muscle dysfunction in COPD patients [Agusti *et al.* 2004]. NF- κ B activation has also been associated with several of the other comorbidities of COPD, including CVD, lung cancer, osteoporosis and diabetes [Karin *et al.* 2004]. NF- κ B inhibitors may therefore target the inflammation of COPD and some of the associated comorbidities. However, targeting NF- κ B may also affect host response to infection as mice lacking NF- κ B genes die of septicaemia [de Boer *et al.* 2007]. Clearly further studies and consideration of the benefit-to-risk ratio are required.

p38 MAPK inhibitors. p38 MAPK is involved in many processes thought to be important in inflammatory responses and tissue remodelling in the lower airways and recent *in vitro* and *in vivo* results suggest a therapeutic opportunity in this area in COPD [Lee *et al.* 2000]. There are four members of the p38 MAPK family (α , β , γ and δ) [Adcock *et al.* 2006]. Each inhibitor has its own specificity towards one of more of these isozymes, leading to differential effects. An inhibitor of the α isoform inhibits TNF α release from human lung macrophages *in vitro* [Smith *et al.* 2006b] and exerts pulmonary anti-inflammatory effects in a smoking mouse model when corticosteroids have been ineffective [Medicherla *et al.* 2008]. SB-239063, a second-generation p38 MAPK inhibitor selective for α and β , reduces neutrophil infiltration and the concentrations of IL-6 and matrix metalloproteinase (MMP)-9 in BALF of rats after endotoxin inhalation, suggesting its potential as an anti-inflammatory agent in COPD [Underwood *et al.* 2000].

A recent randomized placebo-controlled study looked at the effects of a p38 MAPK inhibitor, SB-681323, on blood biomarkers of inflammation in COPD patients [Singh *et al.* 2010]. It was shown that SB-681323 inhibits the p38 MAPK pathway to a greater degree than prednisolone, and inhibits TNF α production. Therefore SB-681323 may potentially suppress inflammation in COPD and could have a role in treating the comorbidities of COPD where TNF α appears to be a key inflammatory mediator. Use of this new class of anti-inflammatory drugs may however be limited by liver toxicity and safety in long-term studies remains to be established. The limiting side effects may possibly be overcome by targeting downstream substrates or administering the drug by inhalation.

Conclusion

Comorbidities in COPD are often underdiagnosed and undertreated, and contribute to increased morbidity and mortality. It is therefore imperative to consider their coexistence when managing these patients. Likewise, pulmonary function testing should be considered in patients with other chronic diseases such as CVD and diabetes in order to identify those with coexisting COPD that may require treatment in its own right. Many clinical guidelines do not take account of the fact that patients with a particular chronic disease are likely to have other comorbidities. Increased awareness of the presence of comorbidities in chronic disease amongst physicians and general practitioners is of paramount importance and a multi-system approach should be adopted for these patients, with strong emphasis on the importance of smoking cessation.

It is clear that more effective treatments are needed for COPD inflammation and associated comorbidities. Pharmacological treatments are often developed for a specific disease but may favourably affect other conditions, such as statins and ACE inhibitors which have shown benefits in COPD patients. Newer systemic anti-inflammatory treatments may have direct beneficial effects in many organs, whereas inhaled treatments may confer indirect benefits to comorbidities by reducing an 'overspill' inflammation from the lungs to the systemic circulation. However, use of some systemic anti-inflammatory treatments may be limited by adverse effects due to their wide distribution.

Until effective, novel anti-inflammatory treatments become available, the main goals of COPD management remain early and accurate diagnosis, emphasis on smoking cessation and reducing the frequency of acute exacerbations using currently available effective pharmacological and non-pharmacological treatments.

Clearly, further research is needed into the treatment of COPD and its comorbidities, as well as a better understanding of the cellular, molecular and genetic abnormalities found in COPD. Future studies will need to address optimal methods of administration, dosage and duration of therapy, as well as including relevant outcome measures.

Conflict of interest statement

R.A. Stockley has been on the steering committee for INSPIRE and served on advisory boards for GSK, Boehringer, Astra Zeneca, Schering Plough and Nycomed.

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