COPD, a multicomponent disease: implications for management

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Summary Chronic obstructive pulmonary disease (COPD) is a multicomponent disease. These components affect both the lungs and organs outside the lungs (the so-called systemic effects of COPD) and can be of either a structural (including airway remodelling, emphysema, skeletal muscle wasting) or functional nature (inflammation, apoptosis, senescence). Further, these components are interdependent in a closely linked 'vicious cycle'. Accordingly, optimal therapies should therefore aim to address more than one of these components to break such a cycle. This needs to be considered not only in the development of future treatments but also in the current clinical management of patients with COPD. In this paper, evidence that supports the concept that COPD is a multicomponent disease is presented. The effects of currently available therapeutic options, including long-acting anticholinergics and long-acting beta2-agonist/inhaled corticosteroid combination therapies, upon each of these components is reviewed. In addition, potential new avenues for drug development and improved patient care are highlighted. By developing a better understanding of how different therapies impact upon the 'vicious cycle' of COPD, treatment regimens can be optimised to provide the greatest benefits to patients.

The size of the problem

Chronic obstructive pulmonary disease (COPD) is a major health problem. The World Health Organization (WHO) has predicted that COPD will become the fifth largest disease burden and the third greatest cause of death by 2020.1 Because COPD is not usually detected until patients seek medical attention for dyspnoea or an exacerbation of the disease,2 COPD is an under-diagnosed disease and, thus, available prevalence and mortality data are likely to greatly underestimate the total burden to patients and healthcare providers. There is, therefore, a need to improve our diagnostic and therapeutic options for such a devastating disease.

COPD is a multicomponent disease

Our traditional understanding of COPD has focused on the presence of chronic airflow obstruction and,
accordingly, therapy has been mainly directed to relieve this. More recently, we have realised that this airflow limitation is associated with an abnormal inflammatory response, and that the latter appears to be responsible for specific effects on mucociliary function, some structural changes in the airways and lung parenchyma, and, as is likely, some of the effects outside the lung (the systemic effects of COPD). In this context, COPD can be considered a multicomponent disease, comprising structural and functional changes, inside and outside the lungs (Fig. 1). These multiple components are closely interdependent in what can be considered ‘the vicious cycle of COPD’ (Fig. 2).

Elements of the Disease—the vicious cycle of COPD

Mucociliary dysfunction

The exposure to initiating factors (mostly cigarette smoke) causes an enlargement of the mucous glands (hypertrophy) and an increase in the number of the mucus-secreting goblet cells. In addition, the ciliated epithelium becomes damaged, resulting in decreased mucociliary transport. The combination of mucus hypersecretion and decreased mucociliary transport, leads to an accumulation of mucus within the airways, which increases the likelihood of recurrent respiratory infections. Bacterially induced damage to the epithelium leads to further cilial loss, and may further impair mucus clearance and the epithelial defence function (reduced secretion of defensins and other antimicrobial peptides). In addition, bacterial colonisation of accumulated mucus can stimulate the inflammatory response, which, as discussed below, represents one of the core components of the vicious cycle of COPD.

Mucociliary dysfunction is not an innocent bystander and has direct clinical consequences. The Copenhagen City Heart Study Group, a large population study, demonstrated that chronic mucus secretion was associated with accelerated decline of lung function and increased hospitalizations due to COPD, suggesting that mucociliary dysfunction may contribute to the decline in forced expiratory volume (FEV1) often seen in these patients.

The inflammatory component

Exposure to initiating noxious substances (mostly tobacco smoke) stimulates a “physiological” inflammatory response, whereby the lungs are infiltrated by neutrophils, macrophages and lymphocytes. Whether the type or intensity of this inflammatory reaction is different in smokers with and without COPD is a matter of intense research. In any case, in patients with COPD these inflammatory cells can release pro-inflammatory and destructive mediators such as elastases, proteases,
interleukin-8 (IL-8), leukotriene B-4 (LTB4), matrix metalloproteinases (MMPs) and tumour necrosis factor α (TNF-α), which further damage airway tissue and sustain airway inflammation by attracting more cells to the area.11,12 This cycle of chronic inflammation leads to permanent structural changes in the airways, including fibrosis, alveolar destruction and epithelial hyperplasia, all of which contribute to chronic airflow obstruction. Finally, it is worth noting that the inflammatory cascade in the airways can also induce mucous gland hypertrophy and goblet cell metaplasia, which further aggravates the mucociliary dysfunction and mucus accumulation components of COPD discussed above.13–15

The systemic component

The systemic component of COPD is an important part of the vicious cycle, and should always be considered in the clinical management of patients with COPD. It is thought that extrapulmonary inflammation is pivotal in the pathogenesis of the systemic component of COPD. Not only can the elevated levels of inflammatory mediators such as IL-8 and TNF-α in the lungs escape to the peripheral circulation, but they are also likely to be involved in priming of circulating inflammatory cells. Other potential contributors to the systemic effects of COPD include, among others, tissue hypoxia, oxidative stress, sedentarism and other metabolic abnormalities. The systemic effects more commonly associated with COPD include skeletal muscle dysfunction, nutritional abnormalities and weight loss, cardiovascular and nervous system abnormalities, and osteoskeletal effects such as osteoporosis.16,17 In particular, skeletal muscle dysfunction significantly limits the exercise capacity of patients with COPD. It is thought that muscle dysfunction in patients with COPD is due to both a reduction in muscle mass, and malfunction of the remaining muscle resulting, in part, from the abnormalities of pulmonary gas exchange that characterise COPD.17 The reduction in muscle mass and severe weight loss of patients with COPD may also be related to the increased levels of circulating TNF-α, which can lead to skeletal muscle apoptosis.18 The extent to which systemic effects contribute to the overall pathology of COPD varies from patient to patient, and will depend on other factors such as genetic predisposition, confounding conditions such as heart disease and diabetes, as well as whether or not the patient continues to smoke.

In summary, COPD has to be considered a multi-component disease, with both pulmonary and extrapulmonary consequences. Accordingly, an optimal therapy for COPD should treat the multi-component nature of the disease. The goals of effective COPD management (as defined by the Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines) include a reduction in symptoms, complications and exacerbations, improved exercise tolerance, improved health status and reduced mortality.2 Ideally, any form of treatment should also have an impact on disease progression. Some current and future therapies have the potential to achieve these goals.

Breaking the COPD vicious cycle—current therapies

Several currently available agents act on different aspects of the disease, as depicted in Fig. 3.

Bronchodilators

Bronchodilator therapy plays an important role in the treatment of COPD. Despite the fact that airflow limitation is generally poorly reversible in COPD patients due to fixed, structural abnormalities within the lungs, there is often a reversible component. In a study of 660 patients meeting European Respiratory Society (ERS) diagnostic criteria for irreversible COPD, 38.2% of patients were found to change their responder status, as measured using spirometric parameters, between visits. When American Thoracic Society (ATS) criteria for bronchodilator responsiveness were used, 52.1% of patients changed status between visits.19 Further, it is possible that the measure of the forced expiratory volume in 1 s (FEV1) may not be the optimal method to assess the response to bronchodilator therapy in these patients. Other measures, such as changes in lung volume (inspiratory capacity) may prove more sensitive to the effects of these drugs (the so-called ‘pharmacological volume reduction’). Commonly used bronchodilatory drugs for COPD include anticholinergics, beta2-agonists and methylxanthines.20,21

Anticholinergics

A number of anticholinergic drugs are currently used for the treatment of COPD, including ipratropium bromide, oxitropium and tiotropium. Ipratropium bromide and oxitropium have a relatively short duration of action (4–6 h) and therefore require multiple daily administration.22,23 In contrast, the newer anticholinergic agent tiotropium, has a prolonged duration of action of more than 24 h and can therefore be taken once daily.
Tiotropium has additional advantages over older anticholinergics, in that it has a 10-times greater affinity for the $M_1$ and $M_3$ muscarinic receptor subtypes, compared with ipratropium. The human lung has five subtypes of muscarinic receptors, of which $M_1$ and $M_3$ are the most important in mediation of bronchoconstriction. Two 1-year studies have shown that in patients with COPD, tiotropium (18 mcg once daily) is associated with improvements in bronchodilation, dyspnoea, and quality of life, as well as reduced exacerbations (20% vs. placebo, $P = 0.045$; and 24% vs. ipratropium, $P = 0.006$) compared with placebo and ipratropium.24,25 Dry mouth may limit compliance in some patients.26,27 A 6-month study comparing tiotropium with the long-acting beta2-agonist salmeterol, and placebo, found that tiotropium and salmeterol were both significantly superior to placebo in the treatment of COPD, in terms of trough FEV$_1$, peak FEV$_1$, and average FEV$_1$ (0–12 h), with tiotropium statistically significantly superior to salmeterol in terms of mean FEV$_1$.28

Stimulation of the nerves via muscarinic receptors causes bronchoconstriction and mucus secretion.22 Therefore anticholinergic bronchodilators, which block the muscarinic receptors, may also reduce mucus secretion, thus targeting two important elements of the vicious cycle of COPD (Fig. 3). However, this latter effect is difficult to demonstrate in vivo. Indeed, a recent, randomized, double-blind, controlled trial could not find evidence of retardation of mucus clearance from the lungs in COPD patients treated with tiotropium.29

**Beta$_2$-agonists**

Beta$_2$-agonists mediate their bronchodilatory effects by stimulating the beta$_2$-adrenoreceptors found throughout bronchial smooth muscle. Stimulation of these receptors results in relaxation of the airway smooth muscle, thus relieving airflow limitation.26,30

Short-acting beta$_2$-agonists have been used in the treatment of COPD for many years, and provide effective short-term relief from bronchoconstriction. Although this is useful on an as-required basis and provides immediate relief, bronchoconstriction is not the only cause of airflow limitation. Furthermore, these agents are often considered inconvenient to use for regular maintenance therapy, as their short duration of action means that they have to be taken at multiple intervals throughout the day, which may influence patient compliance.

Long-acting beta$_2$-agonists (LABAs), such as salmeterol and formoterol, are available for the treatment of COPD, and are more convenient than short-acting beta$_2$-agonists for regular maintenance therapy, due to their extended period of action and twice-daily dosing. The longer duration of action of salmeterol may be due to an ability to interact with the beta$_2$-receptor through a second binding site, whereas the prolonged action of formoterol may be related to its partitioning within the cell membrane.27

Short-term (12-week), randomised, placebo-controlled trials in patients with COPD have shown that treatment with salmeterol (bid) results in
significantly greater sustained bronchodilation over 12 h, and greater time-to-first COPD exacerbation, when compared with either placebo or ipratropium bromide. This treatment difference reflects the longer duration of action of salmeterol, as peak responses were generally similar to those seen with ipratropium bromide. The effects of salmeterol have been shown to be maintained in a long-term (12-month) trial where salmeterol induced a 20% reduction in exacerbation rate compared with placebo. Beneficial effects on lung function have similarly been reported with formoterol where it has been shown to provide significantly greater improvements in lung function and reduced symptoms compared with placebo and ipratropium bromide. One long-term (12-month) study reported that treatment with formoterol was more effective and better tolerated than slow-release theophylline. However, another study found no significant difference in exacerbation rate with formoterol compared with placebo, over a 1-year period.

In addition to their bronchodilatory effects, salmeterol and formoterol have both been shown to improve mucociliary dysfunction by increasing mucus clearance. A study in healthy subjects revealed that salmeterol led to greater improvements in mucociliary transport compared with placebo, and formoterol was shown to provide increased mucociliary clearance compared with placebo in patients with bronchitis. The mucociliary effects of LABAs may be due to an increase in ciliary beat frequency, as demonstrated in studies on the effects of salmeterol in human bronchial epithelial cells. Salmeterol has also been shown to decrease bacterially induced tissue damage in vitro, which is thought to account for the reduced incidence of respiratory tract infection associated with its use. There is also evidence of anti-inflammatory effects with LABAs. Studies have shown that LABAs have multiple effects on neutrophil activity, by acting on beta2-adrenoreceptors found on neutrophils. Salmeterol has been shown to inhibit neutrophil adhesion to human airway epithelial cells, and both salmeterol and formoterol have been shown to inhibit neutrophil adhesion to the vascular endothelium in experimental animal models.

In addition, a study in healthy subjects found that therapeutic doses of inhaled salmeterol resulted in an increase in respiratory muscle activity. As such, salmeterol may potentially have an effect on the systemic component of COPD by improving skeletal muscle function, although further research to confirm this is required. Because of their many effects on respiratory function, LABAs are capable of addressing multiple components of the vicious cycle of COPD.

**Methyloxanthines**

For many years, theophylline, a non-selective phosphodiesterase (PDE) inhibitor, has been the cornerstone of COPD therapy—it was the only therapy known to induce bronchodilation and improve FEV1 in patients with COPD. However, its narrow therapeutic range, frequency of undesired adverse events and potential to interact with other drugs limits its current use in clinical practice. Selective PDE inhibitors may overcome these limitations and prove to be more effective treatments for COPD, as discussed below.

On the other hand, recent data has shown that theophylline may have some anti-inflammatory effects on top of its bronchodilator effects. Hence, low-dose theophylline treatment has been shown to reduce neutrophil numbers in induced sputum by 22%, and to inhibit neutrophil chemotaxis by 28% in patients with COPD. The exact mechanism by which theophylline may exert this anti-inflammatory action is not well understood, but it seems to be unrelated to PDE inhibition because at low doses the degree of PDE inhibition is small. Other plausible molecular mechanisms may include adenosine receptor antagonism, IL-10 release, effects on transcription control (through its effects upon histone acetylation) and apoptosis. The effects of theophylline on histone acetylation may be potentially useful to enhance the anti-inflammatory effects of steroids in COPD.

**Inhaled steroids**

As airway inflammation represents one of the critical components of the vicious cycle of COPD, inhaled corticosteroids (ICSs), such as fluticasone propionate and budesonide, which have anti-inflammatory properties, have the potential to play an important part in the treatment of COPD. ICSs have been shown to decrease the number of neutrophils present in the lung, and to prevent the release of pro-inflammatory mediators such as IL-8, which would usually amplify the inflammatory state by recruiting further inflammatory cells to the area. A recent study in patients with COPD revealed that fluticasone propionate inhibited macrophage-derived cytokine release (IL-8 and TNF-α) compared with placebo. Fluticasone propionate has also been shown to decrease the ratio of CD8:CD4 cells in the epithelium and the numbers of subepithelial mast cells in bronchial biopsies of
treated patients, compared with patients receiving placebo. In terms of effect on COPD, significant improvements in pre-dose FEV1 have been observed with fluticasone propionate vs. placebo in COPD patients over 1 year. In addition, short-term studies in COPD patients with budesonide have shown improvements in mean FEV1, and a reduced need for rescue medication, compared with placebo. A number of randomised, placebo-controlled trials have been performed to assess the long-term effect of ICS therapy in COPD. Although these studies did not reveal any significant effect of ICSs over placebo in terms of the rate of lung function decline over 3 years, some important benefits were seen. In the European Respiratory Society study on Chronic Obstructive Pulmonary disease (EURO-SCOP) trial in patients with mild COPD who continued smoking, a significant benefit with budesonide over placebo in FEV1 was seen initially, although this effect disappeared with long-term treatment. In a further study in COPD patients, inhaled triamcinolone did not slow the rate of decline in lung function compared with placebo, but improvements in airway reactivity and respiratory symptoms were noted. In the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, treatment with fluticasone propionate was shown to result in a 25% reduction in exacerbations, a reduced need for oral corticosteroids, and a slower decline in health status, compared with placebo. Furthermore, mean post-treatment FEV1 was significantly higher in fluticasone propionate-treated patients compared with placebo-treated patients at endpoint. Therefore, despite the lack of effect on disease progression in these trials (although a modest effect on the rate of lung-function decline has been shown in a recent meta-analysis of randomised controlled trials), ICS therapy is recommended for regular treatment in some patients (those with frequent exacerbations), and abrupt withdrawal has been associated with increased likelihood of exacerbations.

Oral corticosteroids (OCSs) have been associated with a reduction in bone mineral density (BMD) and an increased risk of osteoporosis and fractures. However, several studies in patients with COPD have found that there is no significant increase in fracture incidence due to ICS treatment compared with placebo. The Lung Health Study II, which looked at the safety and efficacy of inhaled triamcinolone acetonide (600 mcg bid) over 3 years, reported a 2% reduction in BMD in the femoral neck with triamcinolone compared with placebo, but the clinical relevance of this change is unclear. In addition, epidemiological investigations suggest that the excess risk observed with ICS treatment in COPD is related to the underlying disease rather than to this therapy, and as such, is a factor that should be considered in all patients, regardless of treatment.

A number of retrospective studies have been performed to assess the potential role of ICSs in COPD mortality. A retrospective study in 22,620 elderly patients with COPD demonstrated that during a 1-year follow-up period, ICS therapy was associated with a relative risk reduction for all-cause mortality of 29%, compared with those who did not receive ICS therapy. Further cohort analysis based on patients from the UK General Practice Research database showed that use of ICSs was associated with a significant reduction in death compared with short-acting bronchodilators in COPD patients (16%). However, it should be recognised that there are limitations to such studies as they are based on retrospective patient records. Therefore, randomised controlled trials are needed to confirm these reported effects. Very recently, Sin and coworkers have shown that ICS can influence the level of systemic inflammation, highlighting a potential beneficial effect of these drugs on another important component of COPD.

Combination therapies

LABA/ICS combination therapy

Given that LABAs and ICSs have complementary mechanisms of action, targeting different arms of the vicious cycle of COPD, a combination of the two types of drug has the potential to address several major components of COPD, including airflow limitation, mucociliary dysfunction, and airway inflammation. In the 52-week, double-blind TRial of Inhaled STeroids AND long-acting beta2 agonists (TRISTAN) study, a combination of salmeterol and fluticasone propionate was shown to result in significantly greater improvements in FEV1 than placebo, or either salmeterol or fluticasone propionate alone in patients with COPD. The number of exacerbations per patient per year was reduced by 25% with combination therapy, 20% with salmeterol and 20% with fluticasone propionate compared with placebo. In addition, combination salmeterol/fluticasone propionate treatment produced a clinically significant improvement in health-status questionnaire score, and the greatest reductions in daily symptoms. The safety profile of the combination treatment was comparable to those of the individual agents. Two 24-week studies have also investigated combined salmeterol...
and fluticasone propionate at two doses (50 mcg/250 mcg and 50 mcg/500 mcg) and revealed significant improvements in pre-dose FEV1, vs. salmeterol alone or placebo, and in post-dose FEV1, vs. fluticasone propionate alone or placebo. Greater improvements in the Transition Dyspnoea Index were seen versus placebo for the 50 mcg/250 mcg dose, and versus placebo and individual treatments alone for the 50 mcg/500 mcg dose.72,73

Likewise, two 12-month, double-blind studies in adults with COPD have shown that a combination of formoterol and budesonide can give clinically meaningful benefits for patients with COPD.37,74 These studies have shown that therapy with formoterol/budesonide reduces the need for reliever beta2-agonists, improves health-related quality of life, reduces daily symptoms, and significantly improves FEV1.37,74 In addition both studies found that combination therapy significantly reduced the mean number of exacerbations per patient per year, compared to placebo and formoterol, but not budesonide alone.37,74

Importantly, an observational cohort study has revealed that the combination of a LABA and an ICS can offer increased survival; 3-year survival rates were numerically higher in patients receiving salmeterol and fluticasone propionate prescribed concurrently, compared with those receiving either agent alone.75 Furthermore, survival rates in all of these patient groups were higher than those seen in a reference group of patients who used bronchodilators other than LABAs or ICSs.75 The results of this observational cohort study require confirmation in a randomized controlled setting. The ongoing 3-year TORCH study comparing combination therapy with salmeterol plus fluticasone propionate, with each agent as monotherapy and placebo, is one such trial which will evaluate all-cause mortality as a primary efficacy endpoint.76 Over 6000 patients have been randomised, and the results should help answer many questions about long term effects of LABAs and ICSs in patients with COPD.

Several mechanisms have been proposed to explain the additive effects seen with the LABA/ICS propionate combination, such as glucocorticoid-mediated upregulation of beta2-receptor levels, beta2-agonist induced nuclear translocation of glucocorticoid receptors (GRs), and beta2-agonist transcription factor modulation of the GR signalling pathway.77 However, the mechanism by which this combination therapy provides improved efficacy needs further exploration. The positive effects of LABAs on enhancing the anti-inflammatory effects of ICSs may be particularly relevant in COPD patients with a reduced anti-inflammatory response—so-called ‘steroid resistance’. It has been hypothesised that steroid resistance is a result of cigarette smoke-induced damage to the histone deacetylase 2 (HDAC2) enzyme, which is involved in GR-induced downregulation of proinflammatory genes.51 However, a recent study in asthmatic patients revealed that those patients who were steroid-resistant also showed a failure in GR translocation to the nucleus.78 Thus, if steroid resistance is in fact due to a reduction in GR translocation to the nucleus, the addition of a LABA which increases nuclear localisation of the GR, may overcome steroid resistance resulting in improved anti-inflammatory effects. There is also the possibility of combining LABAs, ICSs and long-acting anticholinergics. This sort of combined therapy could potentially target the major components of the vicious cycle of COPD, and the therapeutic benefits of the various combinations will need to be studied in the future.

Anticholinergic/beta2-agonist combinations
A combination of bronchodilatory agents with different mechanisms of action can potentially provide a greater clinical effect than administration of the single agents alone. In particular, the combination of beta2-agonists and anticholinergic agents provides the potential to target multiple components underlying COPD, through their complementary modes of action. Evidence for the effectiveness of such combination treatments in COPD can be seen in a 12-week, randomised, parallel-group study in COPD patients treated with the short-acting beta2-agonist, salbutamol, the anticholinergic, ipratropium bromide, or a combination of both. This found that the combination treatment was significantly superior to either agent alone, in terms of peak FEV1, mean FEV1 (0–4 h), and total area under the curve of the FEV1 response.79 Similar improvements in FEV1 response were also seen when a combination of the LABA, salmeterol, and ipratropium bromide was used.80 There are no data currently available on the role and potential benefits derived from the combination of LABAs and the new long-acting anticholinergics (such as tiotropium) in COPD. Given the superiority of tiotropium over ipratropium bromide, a LABA/tiotropium combination is likely to have improved efficacy over the results seen with salmeterol and ipratropium bromide.

Other available treatments
A number of other pharmacological therapies are used in the treatment of COPD, including antioxidants, antibiotics and vaccinations. Reactive
oxygen species, produced either endogenously by inflammatory cells, or from cigarette smoke, are believed to contribute to the pathophysiology of COPD. Elevated levels of lipid peroxidation, degraded proteins, and an increase in exhaled nitric oxide and hydrogen peroxide, particularly during exacerbations, all point to oxidative stress in patients with COPD. Oxidative stress may induce damage to lung tissue, increase mucus production and have pro-inflammatory effects via up-regulation of IL-8 and inducible NO synthase (iNOS). The antioxidant N-acetylcysteine (NAC) has been shown in clinical trials to improve respiratory symptoms and reduce the rate and duration of exacerbations in patients with COPD. In animal models, NAC has also been shown to inhibit thickening of the airway epithelium and secretory cell hyperplasia induced by cigarette smoke. The Bronchus trial is a multicenter, randomised controlled study investigating the potential therapeutic effect of NAC in patients with COPD. Its preliminary results were reported at the European Respiratory Society meeting held in Vienna in September 2003. Despite an apparent lack of effect of NAC upon the rate of decline of FEV1, some potentially beneficial effects upon lung hyperinflation were reported.

Elderly patients with COPD are particularly at risk from influenza infections during colder months of the year, and annual influenza vaccinations in the winter and/or autumn are recommended in this patient group. Pneumococcus vaccines may also be of benefit to some COPD patients. Prophylactic use of antibiotics is not recommended in COPD patients but short-term antibiotic therapy plays an important role in the treatment of COPD exacerbations.

To date, there are no specific treatments available that target the pathophysiology of the systemic component of COPD. Several non-pharmacological therapies, such as domiciliary oxygen therapy, pulmonary rehabilitation and nutritional support, have shown positive effects, but there remains a considerable unmet need for specific therapies for the systemic component of COPD. It is hoped that in the future, therapies will be developed to address this need.

Breaking the COPD vicious cycle—future therapies

A number of new therapies are currently being developed for COPD, including selective PDE4 inhibitors, protease inhibitors, retinoic acid, p38 MAP kinase inhibitors, TNF-α inhibitors, new antioxidants and CXCR2 antagonists. Many of these therapies would be potentially combinable with existing therapies that target airway inflammation and/or mucociliary dysfunction in order to address the multicomponent nature of COPD. In addition TNF-α inhibitors and antioxidants may potentially also address the systemic component of the vicious cycle of COPD.

Selective PDE4 inhibitors

Phosphodiesterase is a key enzyme in the cyclic AMP (cAMP) signalling pathway. Because it is present in inflammatory cells, PDE inhibitors may also have anti-inflammatory properties. These may be useful in the long-term treatment of COPD. A major PDE type found in inflammatory cells is PDE4. A number of preclinical studies have demonstrated the anti-inflammatory properties of two selective PDE4 inhibitors in development, cilomilast and roflumilast. Cilomilast was shown to inhibit TNF-α and IL-4 secretion in vivo in guinea pigs, and roflumilast mediated responses against neutrophils, eosinophils, monocytes, macrophages, dendritic cells and T cells in vitro. Cilomilast treatment appears to reduce the number of CD68+ and CD8+ cells in the bronchial biopsies of patients with COPD. A preliminary randomised, dose-ranging trial in patients with COPD demonstrated improved lung function with cilomilast, compared with placebo, after 6 weeks of therapy. In a further study in COPD, roflumilast improved FEV1, forced vital capacity (FVC), and peak expiratory flow rate (PEFR) after 4 weeks to a greater degree than placebo. Ongoing clinical trials will further assess the therapeutic potential of these PDE4 inhibitors.

Protease inhibitors

An imbalance between proteases and anti-proteases in patients with COPD may lead to excess protease activity in pulmonary tissues and tissue damage. Neutrophil activation and migration into the lungs is believed to be one of the major features of the inflammatory component of COPD, and represents a novel therapeutic target. Several small molecule inhibitors of neutrophil elastase are currently in clinical development, and have been shown to protect against neutrophil elastase-induced lung injury in experimental animals. Proteolytic enzymes other than neutrophil elastase have been implicated in inflammation-associated damage to lung tissue in COPD. The therapeutic potential of inhibitors of cathepsin G
and proteinase 3 (produced by neutrophils), macro-
phage-derived cathepsins B, L and S, is also being
investigated. Administration of endogenous anti-
proteases, such as secretory leukoprotease inhibi-
tor, α1-antitrypsin or tissue inhibitors of MMPs
(TIMPS), is another potential strategy for redressing
antiprotease deficiencies in the lung.

**Retinoic acid**

Emphysema, a key component of COPD, results
from progressive destruction of alveolar septae.
Retinoids are known to activate genes involved in
lung development and promote alveolar separation
and growth, and have, therefore, the potential to
address this structural component of COPD. A study
in a rat model of emphysema revealed that
administration of all-trans-retinoic acid (ATRA)
resulted in the reversal of the structural changes
associated with emphysema. A pilot study in 20
patients with severe emphysema did not provide
evidence of increased alveolarisation in the short
term, but it showed that ATRA was well-tolerated
and warrants further clinical investigation. In any
case, the realisation that there is potential for lung
regeneration opens a whole new area of investiga-
tion which may eventually lead to the “holy grail”
of COPD treatment, this is, the restoration of a
normal lung structure and function. Eventually, the
use of pluripotent stem cells may contribute to this
goal.

**p38 mitogen activated protein kinase inhibitors**

Mitogen activated protein (MAP) kinases play a key
role in chronic inflammation, and one, p38 MAP
kinase, is involved in the expression of IL-8, TNF-α
and MMPs, the levels of which are increased in
COPD. Non-peptide p38 MAP kinase inhibitors have
been shown to have a wide range of anti-inflam-
matory activities in rats, although such a broad-
based activity may lead to some toxicity issues.

**Antioxidant therapy**

The full potential of antioxidant therapy has yet to
be explored in COPD. The benefits of NAC in COPD
have not yet been fully clarified, as discussed
above. Newer, more potent antioxidants currently
in development, such as the spin-trap antioxidant α-phenyl-N-tert-butyl nitrone, may prove to be
effective treatments for COPD. Spin-trap anti-
oxidants form stable adducts with reactive oxygen
species, preventing them from oxidising lipids and
proteins, therefore potentially protecting cells
from injury. The increased levels of oxidants in
the circulation of patients with COPD will inevitably
reduce their antioxidant capacity. Although there is
epidemiological evidence linking poor dietary in-
take of vitamins C and E with COPD, there have
been no controlled trials of these antioxidant vitamins in the treatment of COPD. Oxidative
stress is thought to be one of the prime factors
contributing to the systemic components of COPD.
Therefore, newer antioxidant therapy may play a
significant role in targeting both the inflammatory
and systemic components of the vicious cycle of
COPD in the future.

**Tumour necrosis factor-α inhibitors**

Another treatment with the potential to target
multiple components of COPD, is anti-TNF-α ther-
apy. TNF-α levels have been found to be elevated in
BAL and sputum samples of patients with
COPD. In addition to its pro-inflammatory
effects within the lungs, TNF-α may also be
implicated in the systemic component of COPD.
Increased production of TNF-α by cells in the
inflamed lung may contribute to priming of circu-
lating inflammatory cells; indeed, studies have
shown that patients with COPD have increased
levels of circulating soluble TNF-α in the peripheral
circulation. This increase in circulating TNF-α
may be responsible for the severe muscle wasting
seen in patients with COPD, due to TNF-α-induced
skeletal muscle apoptosis. As such, anti-inflam-
matory drugs targeted against TNF-α such as
humanised anti-TNF-α antibodies, or recombinant,
soluble TNF-α receptor may be suitable treatments
for COPD.

**CXCR2 antagonists**

Recruitment and activation of inflammatory cells in
the lung significantly contributes to the pathophy-
siology of COPD. Its control may therefore be an
attractive strategy for therapeutic interventions.
The concentration of IL-8 is increased in the
bronchoalveolar lavage of COPD patients. IL-8
activates neutrophils via a low affinity G-protein
coupled receptor (CXCR1), and a high affinity
receptor (CXCR2). It has been shown that inhibition
of CXCR2 is sufficient to abolish IL-8 induced
chemotaxis of human neutrophils, and lipopoly-
saccharide-induced lung neutrophil infiltration in
rabbits. Small molecule antagonists of the IL-8
receptors (e.g., SB225002, SB265610) have now
been identified and may be eventually tested in patients with COPD.

Angiotensin converting enzyme (ACE) inhibitors

As our understanding of the pathophysiology of COPD deepens, we may find that pharmacological agents originally developed for other indications have beneficial effects on COPD. One example of this may be the use of angiotensin converting enzyme (ACE)-inhibitors for the treatment of muscle wasting in patients with COPD. To date, there is no data to support this potential indication, but the efficacy of ACE inhibitors to this end has been demonstrated in patients with chronic heart failure, who also develop skeletal muscle dysfunction.111

Conclusion and summary

Chronic obstructive pulmonary disease is a multi-component disease, comprising a number of processes that interact with each other in a 'COPD vicious cycle'. To treat the disease adequately, therapeutic intervention should aim to break this cycle. To date, only smoking cessation has been shown to unequivocally affect the decline in FEV₁. Monotherapy with short-acting bronchodilators targets elements of airflow limitation, but may not address other components of the disease. LABAs can affect mucus transport and reduce bacterial damage, and may also have positive effects on the inflammatory component of the vicious cycle of COPD. Anticholinergics may reduce mucus hypersecretion. ICSs target the airway inflammation and structural changes components of the vicious cycle by reducing the release of inflammatory mediators and the numbers of inflammatory cells in the lungs. Combination therapy offers the potential to target several of these components at once, and there is also evidence that combining LABAs and ICSs has improved efficacy over treatment with the individual agents alone. Future combination strategies may prove to be even more effective in the treatment of COPD. Compounds currently in development, such as newer antioxidants and type 4 PDE inhibitors, may also provide more effective treatments in the future due to their potential multiple modes of action. Finally, the extrapulmonary, systemic component of COPD has yet to be properly addressed in terms of possible pharmacologic intervention. More research is required to tackle this important, but poorly understood component of the vicious cycle of COPD.

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COPD, a multicomponent disease: implications for management


