Chronic obstructive pulmonary disease • 12: New treatments for COPD

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Drugs currently available or under development for the treatment of chronic obstructive pulmonary disease (COPD) are reviewed. More research on the basic cellular and molecular mechanisms of COPD and emphysema is urgently needed to aid the logical development of new treatments for this common and important disease for which no effective preventative treatments currently exist.

There is a major need to develop new treatments for chronic obstructive pulmonary disease (COPD), as no currently available drug therapy reduces the relentless progression of the disease. In particular, there is a need to develop drugs that control the underlying inflammatory and destructive processes. There have been few therapeutic advances in the drug treatment of COPD, in contrast to the enormous advances made in asthma management which reflect a much better understanding of the underlying disease. 8,9 Although COPD is commonly treated with drugs developed for asthma, this is often inappropriate as the inflammatory processes in the two conditions differ markedly. 10 Recognition of the global importance and rising prevalence of COPD and the absence of effective treatments has now led to a concerted effort to develop new drugs for this disease. 11

Rational treatment depends on understanding the underlying disease process and there have been recent advances in understanding the cellular and molecular mechanisms that may be involved. COPD involves a chronic inflammation in the small airways and lung parenchyma with the involvement of neutrophils, macrophages, and cytotoxic (CD8+) T lymphocytes. This inflammation results in fibrosis with narrowing of the small airways (chronic obstructive bronchitis) and lung parenchymal destruction due to the action of various proteases such as neutrophil elastase and matrix metalloproteinases (emphysema). This inflammation is quite different from that seen in asthma, indicating that different treatments are likely to be needed. 12

DISCOVERING NEW DRUGS FOR COPD
There are several reasons why drug development in COPD may be difficult. Only recently has there been any research interest in the molecular and cellular biology of COPD in order to identify new therapeutic targets. 13 There are no satisfactory animal models of COPD for early drug testing, 14 and there are uncertainties about how to test drugs for COPD which may require long term studies (over 3 years) in relatively large numbers of patients. Furthermore, there is little information about surrogate markers to monitor the short term efficacy of new treatments. However, some progress is underway and several classes of drug are now in preclinical and clinical development. 15

SMOKING CESSATION
Cigarette smoking is the major cause of COPD worldwide, and smoking cessation is the only therapeutic intervention so far shown to reduce disease progression. Nicotine addiction is the major problem and treatment should be directed at dealing with this addictive state. The main approaches have involved behavioural approaches and nicotine replacement therapy, but the overall rates of quitting are small (5–15%). 16 One important advance has been the discovery that the antidepressant bupropion given as a short course (6–9 weeks) is the most effective treatment so far described, with sustained quit rates of 18% at 12 months, compared with 9% with nicotine skin patches and 6% with placebo. 17 Results in patients with COPD are similar. 18 This does not appear to be a general effect of antidepressants, although nortryptiline has some effect. 19 Bupropion is well tolerated apart from sleeplessness, but epileptic fits occur in approximately 0.1% of patients, predominantly those with previous epilepsy. 20 In the future more effective drugs may arise from a better understanding of the neurotransmitter pathways involved in nicotine addiction and advances are likely to come from research in neurosciences.

NEW BRONCHODILATORS
Since bronchodilators are the mainstay of current management, a logical approach is to improve existing bronchodilators. Once daily inhaled β2 agonists are not in clinical development, but the long acting inhaled anticholinergic tiotropium has recently become available in some countries.

Tiotropium bromide
Tiotropium bromide is a long acting anticholinergic drug that has a unique kinetic selectivity with very slow dissociation from M1 and M3 muscarinic receptors. 21 Clinical studies in COPD now indicate that inhaled tiotropium once daily is an effective bronchodilator in patients with COPD and is more effective than conventional ipratropium bromide four times daily. 22,23 Long term studies with tiotropium bromide have demonstrated significant improvement in symptoms and improvement in the quality of life, as well as
patients, indicating the potential clinical value of such neutrophil chemotactic activity of sputum from COPD may be synergistic with interleukin (IL)-8. Two subtypes of derived from alveolar macrophages as well as neutrophils and receptor for LTB4 have been described; BLT1 receptors are likely to become the bronchodilator of choice in COPD and may have additive effects with long acting β2 agonists.

**MEDIATOR ANTAGONISTS**

Several inflammatory mediators are likely to be involved in COPD as many inflammatory cells and structural cells are activated and there is an ongoing inflammatory process, even in patients who have given up smoking. The profile of mediators in COPD is different from that in asthma, so different drugs are likely to be effective. Since COPD is characterised by a neutrophilic inflammation, attention has largely focused on mediators involved in recruitment and activation of neutrophils or on reactive oxygen species in view of the increased oxidative stress in COPD (box 1).

**Leukotriene B4 inhibitors**

LTB4 is a potent chemoattractant of neutrophils and is increased in the sputum of patients with COPD. It is probably derived from alveolar macrophages as well as neutrophils and may be synergistic with interleukin (IL)-8. Two subtypes of receptor for LTB4 have been described; BLT, receptors are mainly expressed on granulocytes and monocytes, whereas BLT, receptors are expressed on T lymphocytes. BLT, antagonists such as LY29311 have now been developed for the treatment of neutrophilic inflammation. LY293111 inhibits the neutrophil chemotactic activity of sputum from COPD patients, indicating the potential clinical value of such drugs. Selective LTB4 receptor antagonists are now in development, including SC-53228, CP-105696, SB201146, and BIIL284. LTB4 is synthesised by 5-lipoxygenase (5-LO), of which there are several inhibitors, although there have been problems in the clinical development of drugs in this class because of side effects.

**Chemokine inhibitors**

Several chemokines are involved in neutrophil chemotaxis and mainly belong to the CXC family, of which the most prominent member is IL-8. IL-8 levels are markedly increased in the sputum of patients with COPD and are correlated with disease severity. Blocking antibodies to IL-8 and related chemokines inhibit certain types of neutrophilic inflammation in experimental animals and reduce the chemotactic response of neutrophils to sputum from COPD patients. A human monoclonal antibody to IL-8 blocks the chemotactic response of neutrophils to IL-8 and is effective in animal models of neutrophilic inflammation. This antibody is now in clinical trials, but it may be less effective than drugs that block the common receptor for other members of the CXC chemokine family. IL-8 activates neutrophils via a specific low affinity G-protein coupled receptor (CXCR1) coupled to activation and degranulation and a high affinity receptor (CXCR2), shared by other members of the CXC family, which is important in chemotaxis. Other CXC chemokines such as growth related oncprotein-α (GRO-α) are also increased in patients with COPD, so a CXCR2 antagonist is likely to be more useful than a CXCR1 antagonist, particularly as CXCR2 are also expressed on monocytes. Small molecule inhibitors of CXCR2 such as SB225002 have now been developed and are entering clinical trials.

CC chemokines are also involved in COPD. There is increased expression of monocyte chemotactic protein 1 (MCP-1) and its receptor CCR2 in macrophages and epithelial cells from patients with COPD, and this may play a role in recruitment of blood monocytes to the lungs of these patients. This suggests that CCR2 antagonists may be of use and small molecule inhibitors are now in development.

**Tumour necrosis factor (TNF-α) inhibitors**

TNF-α levels are also raised in the sputum of COPD patients and TNF-α induces IL-8 in airway cells via activation of the transcription factor nuclear factor-κB (NF-κB). The severe wasting in some patients with advanced COPD might be caused by skeletal muscle apoptosis resulting from increased levels of circulating TNF-α. Patients with COPD with cachexia have increased release of TNF-α from circulating leucocytes. Humanised monoclonal TNF antibody (infliximab) and soluble TNF receptors (etanercept) effective in other chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease should also be effective in COPD. There may be problems with long term administration because of the development of blocking antibodies and repeated injections are inconvenient. TNF-α converting enzyme (TACE), which is required for the release of soluble TNF-α, may be a more attractive target as it is possible to discover small molecule TACE inhibitors, some of which are also MMP inhibitors. General anti-inflammatory drugs such as phosphodiesterase inhibitors and p38 MAP kinase inhibitors also potentely inhibit TNF-α expression.

**Antioxidants**

Oxidative stress is increased in patients with COPD, particularly during exacerbations, and reactive oxygen species contribute to its pathophysiology. This suggests that antioxidants may be of use in the treatment of COPD. N-acetyl cysteine (NAC) provides cysteine for enhanced production of glutathione (GSH) and has antioxidant effects in vitro and in vivo. Recent systematic reviews of studies with oral NAC in COPD suggest small but significant reductions in exacerbations. More effective antioxidants, including stable glutathione compounds, analogues of superoxide dismutase and selenium based drugs, are now in development for clinical use.

**iNOS inhibitors**

Oxidative stress and increased nitric oxide release from expression of inducible nitric oxide synthase (iNOS) may result in the formation of peroxynitrite which is a potent radical and may nitrate proteins, resulting in altered function. 3-Nitrotyrosine may indicate peroxynitrite formation and is markedly increased in sputum macrophages of patients with COPD. Selective inhibitors of iNOS are now in development, one of which—N-(1-imminoethyl)lysine (L-NIL)—causes a profound and long lasting reduction in exhaled nitric oxide.

**NEW ANTI-INFLAMMATORY TREATMENTS**

COPD is characterised by chronic inflammation of the respiratory tract, even in ex-smokers, with increased numbers of macrophages, neutrophils and cytotoxic (CD8+) T lymphocytes in airways and lung parenchyma. This suggests...
that anti-inflammatory treatments may be of value and there are several possible approaches (fig 1).

**Resistance to corticosteroids**

Because there is chronic inflammation in COPD airways, it was argued that inhaled corticosteroids might prevent the progression of the disease. However, four large 3 year controlled trials of inhaled corticosteroids have shown no reduction in disease progression. This might be predicted by the demonstration that neither inhaled nor oral corticosteroids have any significant effect on neutrophil counts, granule proteins, inflammatory or proteases in induced sputum. Inhaled corticosteroids do not inhibit neutrophilic inflammation induced by ozone in humans, and this may reflect the finding that corticosteroids prolong neutrophil survival. There may also be an active resistance to corticosteroids due to an inhibitory effect of cigarette smoke on histone deacetylation which is required for corticosteroids to switch off inflammatory genes. The disappointing action of corticosteroids in COPD suggests that new types of non-steroidal anti-inflammatory treatment may be needed. Alternatively, therapeutic strategies that unlock the molecular mechanism of resistance might be possible. For example, drugs that increase histone deacetylase activity may re-sensitise cells to the effects of corticosteroids. There are several new approaches to anti-inflammatory treatment in COPD (box 2).

**Phosphodiesterase-4 (PDE4) inhibitors**

PDE4 is the predominant PDE expressed in neutrophils, CD8+ cells, and macrophages, suggesting that PDE4 inhibitors might be effective in controlling inflammation in COPD. Selective PDE4 inhibitors such as cilomilast and rolflumilast are active in animal models of neutrophil inflammation. Cilomilast has some beneficial clinical effect in patients with COPD, and larger studies are currently underway. Rolflumilast appears to be well tolerated at doses that significantly inhibit TNF-α release from peripheral blood monocytes. PDE4 inhibitors are limited by side effects, particularly nausea and other gastrointestinal effects, but it might be possible to develop isoenzyme subtype selective inhibitors in the future which are less likely to be dose limited by adverse effects.

**NF-κB inhibitors**

NF-κB regulates the expression of IL-8 and other chemokines, TNF-α, and some matrix metalloproteinases. There are several possible approaches to inhibition of NF-κB, including gene transfer of the inhibitor of NF-κB (IκB), a search for inhibitors of IκB kinases (IKK), NF-κB inducing kinase (NIK) and IκB ubiquitin ligase which regulate the activity of NF-κB, and the development of drugs that inhibit the degradation of IκB. The most promising approach may be the inhibition of IKKβ by small molecule inhibitors which are now in development. An apparently selective IKK inhibitor, hypoestoxide, is a component of African folk remedy for inflammatory diseases. One concern about long term inhibition of NF-κB is that effective inhibitors may result in immune suppression and impair host defences, since mice which lack NF-κB genes succumb to septicaemia. However, there are alternative pathways of NF-κB activation that might be more important in inflammatory disease. Adhesion molecule inhibitors

Recruitment of neutrophils, monocytes, and cytotoxic T cells into the lungs and respiratory tract is dependent on adhesion molecules expressed on these cells and on endothelial cells in the pulmonary and bronchial circulations. Several adhesion

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molecules can now be inhibited pharmacologically. For example, E-selectin on endothelial cells interacts with sialyl-Lewis α on neutrophils. A mimic of sialyl-Lewis α, TBC1269, blocks selectins and inhibits granulocyte adhesion, with preferential effects on neutrophils. However, there are concerns about this therapeutic approach for a chronic disease, as an impaired neutrophilic response may increase the susceptibility to infection. The expression of Mac-1 (CD11b/CD18) is increased on neutrophils of patients with COPD, suggesting that targeting this adhesion molecule, which is also expressed on monocytes and macrophages, might be beneficial.

Interleukin-10

IL-10 is a cytokine with a wide spectrum of anti-inflammatory actions. It inhibits the secretion of TNF-α and IL-8 from macrophages, but tips the balance in favour of anti-inflammatory cytokines including IL-8, TNF-α and IL-6 are induced. IL-10 concentrations are reduced in induced sputum from patients with COPD, so this may be a mechanism for increasing lung inflammation. IL-10 is currently in clinical trials for other chronic inflammatory diseases (inflammatory bowel disease, rheumatoid arthritis and psoriasis), including patients with steroid resistance, but it may cause haematological side effects. IL-10 may have therapeutic potential in COPD, especially if a selective activator of IL-10 receptors or unique signal transduction pathways can be developed in the future.

p38 mitogen activated protein (MAP) kinase inhibitors

Mitogen activated protein (MAP) kinases play a key role in chronic inflammation and several complex enzyme cascades have now been defined. One of these, the p38 MAP kinase pathway, is involved in the expression of inflammatory cytokines including IL-8, TNF-α, and matrix metalloproteinases (MMPs). Non-peptide inhibitors of p38 MAP kinase, such as SB 203580, SB 239063 and RWJ 67657, have now been developed and these drugs have a broad range of anti-inflammatory effects. SB 239063 reduces neutrophil infiltration after inhaled endotoxin and the concentrations of IL-6 and MMP-9 in bronchoalveolar lavage fluid of rats, indicating its potential as an anti-inflammatory agent in COPD. It is likely that such a broad spectrum anti-inflammatory drug will have some toxicity, but inhalation may be a feasible therapeutic approach.

Phosphoinositide-3 kinase (PI-3K) inhibitors

PI-3Ks are a family of enzymes which promote the generation of lipid second messengers that regulate a number of cellular events. A particular isoform, PI-3Kγ, is involved in neutrophil recruitment and activation. Knock-out of the PI-3Kγ gene results in inhibition of neutrophil migration and activation, as well as impaired T lymphocyte and macrophage function. This suggests that selective PI-3Kγ inhibitors may have relevant anti-inflammatory activity in COPD.

REMODELLING AGENTS

Since a major mechanism of airway obstruction in COPD is the loss of elastic recoil resulting from proteolytic destruction of lung parenchyma, it seems unlikely that this could be reversible by drug treatment although it might be possible to reduce the rate of progression by preventing the inflammatory and enzymatic disease process. Retinoic acid increases the number of alveoli in developing rats and, remarkably, reverses the histological and physiological changes induced by elastase treatment of adult rats. Retinoic acid activates retinoic acid receptors which act as transcription factors to regulate the expression of many genes involved in growth and differentiation. The molecular mechanisms involved have not been identified, and it is not yet known whether this can be extrapolated to humans. Several retinoic acid receptor subtype agonists have been developed that may have a greater selectivity for this effect and therefore a lower risk of side effects. A short term trial of all-trans-retinoic acid in patients with emphysema who did not show any improvement in clinical parameters is currently underway.

DRUG DELIVERY

Bronchodilators are currently given as metered dose inhalers or dry powder inhalers that have been optimised to deliver drugs to the respiratory tract in asthma. However, in emphysema the inflammatory and destructive process takes place in the lung parenchyma and in chronic obstructive bronchitis the predominant irreversible changes are in the small airways. This implies that, if a drug is to be delivered by inhalation, it should have a lower mass median diameter so that there is preferential deposition in the lung periphery. It may be more appropriate to give drug treatment parenterally as it will reach the lung parenchyma via the pulmonary circulation, but parenteral administration may increase the risk of systemic side effects. One way of limiting toxicity is the targeted delivery of drugs to particular cell types. For example, alveolar macrophages may be targeted by molecules that are endogenous antiproteases

One approach is to give endogenous antiproteases (α-antitrypsin, secretory leukoprotease inhibitor, elafin, tissue inhibitors of MMP), either in recombinant form or by viral vector gene delivery. These approaches are unlikely to be cost effective as large amounts of protein have to be delivered and gene therapy is unlikely to provide sufficient protein.

Protease inhibitors

A more promising approach is to develop small molecule inhibitors of proteinases, particularly those that have elastolytic activity. Small molecule inhibitors such as ONO-5046 and FR901277 have been developed which have high potency. These drugs inhibit neutrophil elastase-induced lung injury in experimental animals, whether given by inhalation or systemically, and also inhibit the other serine proteinases released from the neutrophils cathepsin G and proteinase-3. Small molecule inhibitors of neutrophil elastase are not entering clinical trials, but there is concern that neutrophil elastase may not play a critical role in emphysema and that other proteinases are more important in elastolysis. Inhibitors of elastolytic cysteine proteinases such as cathepsins K, S and L that are released from macrophages are also in development. Matrix metalloproteinases with elastolytic activity (such as MMP-9) may also be a target for drug development, although non-selective MMP inhibitors such as marimastat appear to have considerable side effects. It is possible that side effects could be reduced by increasing selectivity for specific MMPs or by targeting delivery to the lung parenchyma. MMP-9 is markedly overexpressed by alveolar macrophages in patients with COPD, so a selective inhibitor might be useful in the treatment of emphysema.
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packaged to be phagocytosed by these cells. Another important concept is the idea of disease activation of drugs—
for example, in COPD active drugs that are released from inactive prodrugs by elastases might be considered. This
would concentrate the active drug at the site of disease activity and reduce systemic exposure.

FUTURE DIRECTIONS

New drugs for the treatment of COPD are needed. While preventing and quitting smoking is the obvious preferred
approach, this has proved to be very difficult in most patients and, even with supplementation, only about 15% of patients are sus-
ained quitters. In addition, it is likely that the inflammatory process initiated by cigarette smoking may continue even
when smoking has ceased. Furthermore, COPD may be caused by other environmental factors—such as cooking
fumes, pollutants, passive smoking, or other inhaled toxins—or by developmental changes in the lungs.

Identification of novel therapeutic targets

It is important to identify the genetic factors that determine why only 10–20% of smokers develop COPD. Identification of
genomes that predispose to the development of COPD in smokers may identify novel therapeutic targets. Powerful
techniques such as high density DNA arrays (gene chips) are able to identify multiple polymorphisms; differential display
may identify the expression of novel genes and the proteomics of novel proteins expressed.

Surrogate markers

It will be difficult to demonstrate the efficacy of novel treatments as determination of the effect of any drug on the
rate of decline in lung function will require large studies over at least 2 years. There is a need to develop surrogate
markers—such as analysis of sputum parameters (cells, mediators, enzymes) or exhaled condensates (lipid mediators,
reactive protein species, cytokines)—that may predict the clinical usefulness of such drugs. More research on the basic
molecular and cellular mechanisms of COPD and emphysema is urgently needed to aid the logical development of new
molecules for this important and common disease for which no effective preventative treatments currently exist. It may
also be important to define more accurately the presence of emphysema versus small airway obstruction using improved
imaging techniques, as some drugs may be more useful for preventing emphysema while others may be more effective
against the small airway inflammatory fibrosis process.

REFERENCES


