ABSTRACT

Chronic obstructive pulmonary disease (COPD) is initiated by exposure to a noxious stimulus, which, in susceptible individuals, initiates an inflammatory response in the lower airways leading to emphysema and mucus hypersecretion. Numerous therapies to address different aspects of the COPD disease process—the inflammatory component as well as bronchoconstriction, mucus hypersecretion, and pulmonary hypertension—are in various stages of development. Long-acting bronchodilators are one area of current interest. The US Food and Drug Administration has recently approved tiotropium and (R,R)-formoterol is in phase 3 clinical trials. Other types of drugs under evaluation are mucolytic agents and vasodilators. Anabolic steroids are being tested to address some of the systemic effects of COPD. Current therapeutic strategies target a subset of pathogenic mechanisms, so any single treatment is only addressing a portion of the disease process. Future “rational treatment” will aim to match the appropriate drug(s) with the pathophysiological process(es). Current challenges to reaching this level of treatment include the need for better understanding of the pathophysiological processes, the need for appropriate clinical trials for COPD (particularly if exacerbations and survival are assessed), the lack of a surrogate marker for COPD to provide an expedited assessment of any treatment benefit, and the limitations of animal models of COPD. Another aspect of COPD treatment that has been under-recognized and underutilized is palliative care delivered at end-stage disease. During the last year of life, COPD patients are incapacitated by severely reduced forced expiratory volume in 1 second and performance status; multiple hospitalizations; numerous comorbidities; neuropsychiatric disorders such as depression, anxiety, and panic; insomnia; and cognitive impairment, and they typically live alone. Although it can be an uncomfortable subject, palliative care, including hospice, offers the clinician the chance to relieve the patient of pain and to reinforce the commitment of the healthcare team to care for the patient throughout the entire disease process. (Adv Stud Med. 2004;4(10A):S767-S772)

FUTURE DIRECTIONS IN COPD MANAGEMENT*

John J. Reilly, MD†

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†Associate Professor of Medicine, Harvard Medical School, Medical Director, Pulmonary Rehabilitation Program, Clinical Director, Pulmonary and Critical Care Medicine, Brigham and Women’s Hospital, Boston, Massachusetts.

Address correspondence to: John J. Reilly, MD, Clinical Director, Pulmonary and Critical Care Medicine, 75 Francis Street, PBB Clinic 3, Brigham and Women’s Hospital, Boston, MA 02115. E-mail: jreilly@partners.org.

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the lower airways characterized by airflow limitation and damage to lung tissue. It is a heterogeneous mixture of conditions including emphysema, chronic airway inflammation, and mucus hypersecretion; the contribution of each to the COPD disease state varies with each individual. COPD remains ill defined in terms of its mechanisms but a common outcome is airflow obstruction. To date, almost all clinical trials of drugs to treat COPD, therefore, use a measure of airflow (forced expiratory volume in 1 second [FEV1]) as the endpoint.

Our current understanding of COPD mechanisms indicates that COPD is initiated by exposure to a noxious stimulus. In susceptible individuals, this exposure
initiates an inflammatory response that recruits macrophages and neutrophils to the lower airways, which release proteases and oxidants leading to emphysema and mucus hypersecretion (Figure 1). The “cigarette-inflammation-protease theory” is an incomplete explanation of the inflammatory process of COPD, because inflammation continues even after smoking cessation. Nonetheless, specific therapies are in development to address different aspects of the COPD disease process—the inflammatory component as well as bronchoconstriction, mucus hypersecretion, and pulmonary hypertension.

**Targeting COPD Inflammation**

As shown in Figure 2, there are numerous potential therapeutic targets in the inflammatory component of COPD alone. Current research is focusing on drugs that interfere at 4 steps: chemokines and cytokines that control the inflammatory response, intracellular signal transduction pathways that are activated during COPD inflammation, mediators that promote tissue damage, and cellular response to inflammation that causes tissue damage. The current drugs under evaluation and their targets are summarized in the Table. Almost all are in the very early stages of development. Two exceptions are the phosphodiesterase (PDE)-4 inhibitors and retinoids. PDE4 activates the intracellular pathways of CD8+ T cells, neutrophils, and macrophages in COPD inflammation; it also increases airway smooth muscle tone. PDE4 inhibitors, therefore, reduce COPD inflammation and relax airway smooth muscle tone. Cilomilast and roflumilast are the 2 PDE4 inhibitors that have been studied most extensively (ie, in phase 3 clinical trials). Although roflumilast has a higher PDE4 binding affinity than cilomilast, cilomilast has been under investigation longer. Cilomilast has shown a small but significant benefit in FEV1 compared with placebo. Early data with roflumilast show important benefits in FEV1 as well as a dose-dependent reduction in exacerbations. Retinoids are key molecules in wound repair, regulating cell proliferation, cell differentiation, and morphogenesis. In dermatology, they are used for reversing or preventing cutaneous signs of aging. The majority of COPD-related research with retinoids has been in preclinical studies, but the Feasibility of Retinoic Acid Treatment in Emphysema (FORTE) trial is a large study \((n = \sim 300)\) in emphysema patients that has been under way for the last several years.

![Figure 1. COPD Pathogenesis](image1)

![Figure 2. Treatment Targets in COPD Pathogenesis](image2)
**TARGETING BRONCHOCONSTRICTION, MUCUS SECRETION, AND PULMONARY HYPERTENSION**

Long-acting bronchodilators are also under investigation. Tiotropium, an anticholinergic agent delivered via aerosol, has recently approved by the US Food and Drug Administration as maintenance therapy for COPD. (R,R)-formoterol (afomterol) is an isomer of formoterol, which has historically been administered as a racemic mixture of the R and S isomers; the latter is associated with toxicity and bronchoconstriction. (R,R)-formoterol is a long-acting beta agonist that has the potential for once-daily administration. It is now in phase 3 clinical trials.

Vasodilators are under investigation, particularly to relieve the pulmonary hypertension and cor pulmonale found during the end stages of COPD. In theory, vasodilation may also help ventilation/perfusion mismatch, often found in COPD, and thus improve gas exchange and oxygen levels. Inhaled nitrous oxide is under investigation in COPD patients (phase 3 clinical trials) and the early results are promising, with significant improvements in FEV1 and pulmonary hypertension.8 However, as with the other compounds

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**Table. Drugs Under Evaluation for COPD Inflammation**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Agent</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemokines and cytokines</td>
<td>NF-κB inhibitor</td>
<td>NF-κB regulates expression of chemokines known to activate neutrophils</td>
</tr>
<tr>
<td></td>
<td>Adhesion molecule inhibitors</td>
<td>Recruitment of neutrophils, monocytes, and T cells during an inflammatory response is dependent on expression of adhesion molecules of these cells and on endothelial cells in the bronchial and pulmonary circulation</td>
</tr>
<tr>
<td></td>
<td>IL-10 inhibitors</td>
<td>IL-10 inhibits the secretion of cytokines from macrophages but also affects the protease-antiprotease imbalance in favor of antiproteases</td>
</tr>
<tr>
<td>Signal transduction pathways</td>
<td>PDE4 inhibitors</td>
<td>PDE4 activates the intracellular pathways of CD8+ T cells, neutrophils, and macrophages in COPD inflammation; it also increases airway smooth muscle tone</td>
</tr>
<tr>
<td></td>
<td>MAP kinase inhibitors</td>
<td>Some MAP kinases are involved in expression of inflammatory cytokines</td>
</tr>
<tr>
<td></td>
<td>Pt-3K inhibitors</td>
<td>Pt-3Ks are enzymes that promote intracellular “second messenger” pathways, which help to recruit and activate neutrophils</td>
</tr>
<tr>
<td>Mediators released during COPD</td>
<td>LTB4 inhibitors</td>
<td>LTB4 is a strong chemoktractant of neutrophils</td>
</tr>
<tr>
<td>inflammation (proteases and oxidants)</td>
<td>IL-8 human monoclonal antibody</td>
<td>IL-8 is heavily involved in neutrophil chemotaxis</td>
</tr>
<tr>
<td></td>
<td>TNF-alpha inhibitor</td>
<td>TNF-alpha induces IL-8 via NF-κB</td>
</tr>
<tr>
<td></td>
<td>iNOS inhibitor</td>
<td>iNOS is involved in the formation of peroxynitrite, a potent radical that can alter protein function via nitration</td>
</tr>
<tr>
<td>Inflammatory cellular responses</td>
<td>Retinoids</td>
<td>Retinoids are important in wound repair, regulating cell proliferation, cell differentiation, and morphogenesis. In dermatology, they are used for reversing or preventing aging</td>
</tr>
<tr>
<td>(oxidative damage, mucociliary clearance)</td>
<td>Protease inhibitors</td>
<td>Proteases can destroy lung tissue</td>
</tr>
<tr>
<td></td>
<td>Antioxidants (N-acetylcytysteine, NAC)</td>
<td>Provides cysteine for increased production of glutathione and has antioxidant activity</td>
</tr>
</tbody>
</table>

NF-κB = nuclear factor kappa B; IL = interleukin; PDE4 = phosphodiesterase-4; COPD = chronic obstructive pulmonary disease; MAP = mitogen-activated protein; PI-3K = phosphoinositide-3 kinase; LTB4 = leukotreine B4; TNF = tumor necrosis factor; iNOS = inducible nitric oxide synthase.

Data from Barnes.
described, larger studies with clinically meaningful endpoints beyond FEV<sub>1</sub> are necessary.

Mucus secretion is a very common complaint in COPD patients. Mucolytics increase expectoration of sputum by reducing the viscosity or hypersecretion of mucus. An analysis of 23 studies of mucolytic agents for COPD found that they offer important reductions in COPD exacerbations and days with disability, but they appear to have no effect on lung function. Their use in COPD is not recommended in the Global Initiative for Chronic Obstructive Lung Disease guidelines. The American Thoracic Society guidelines indicate that there is little evidence of any effect by mucolytic agents on lung function, although they cite a Cochrane review that supports a role for these drugs in reducing the number of exacerbations of chronic bronchitis,10,11 Most recently, a large multicenter trial conducted in Europe (BRONCUS) failed to find any benefit from the regular use of N-acetylcysteine (a mucolytic and antioxidant).12

TARGETING THE SYSTEMIC EFFECTS OF COPD

Muscle deconditioning, loss of muscle mass, weight loss, and poor sleep quality are some of the most disabling systemic effects of long-term COPD. Traditionally, low body weight and muscle mass have been treated with improvements in diet. Anabolic steroids are under investigation to increase body mass (eg, oral oxandrolone) or stimulate appetite (megestrol). Single studies of both drugs have shown positive results.13,14 Megestrol increased appetite and body weight, stimulated ventilation, and improved body image in underweight COPD patients, but did not improve respiratory muscle function or exercise tolerance.14

Noninvasive positive pressure ventilation (NPPV) is useful for COPD patients undergoing acute hypercapnic (ie, excess of carbon dioxide in the blood) respiratory failure during an acute exacerbation. It should be used early in the course of acute hypercapnic respiratory failure to reduce the likelihood of endotracheal intubation, treatment failure, and mortality.15 Reviews of clinical trials also suggest that NPPV may be useful in patients with severe stable COPD who suffer from substantial daytime hypercapnia and superimposed nocturnal hypoventilation. The data suggest that NPPV improves daytime and nocturnal gas exchange, increases sleep duration, improves quality of life, and possibly reduces the need for hospitalization.14

ONGOING PHARMACOTHERAPY CHALLENGES

Although we have made and continue to make important advances in COPD treatment, a “glass half empty” view has the perspective that none of the approved therapies for COPD alters disease progression or affects mortality; they only address symptoms. COPD offers other clinically meaningful treatment goals, however, that are now under evaluation (eg, reduction in exacerbation frequency and intensity, improvement in health-related quality of life, and exercise performance).5 Our current challenges to improve COPD therapy are numerous. For example, the heterogeneity of COPD pathophysiological mechanisms means that any single treatment is only addressing a subset of the disease processes. Future “rational treatment” will aim to match the drug(s) with the pathophysiological process(es). However, we need better understanding of these processes in order to achieve this next level of treatment. Clinical trials for COPD treatments are also difficult because they need to be long term (ie, years, not months), particularly if decline in lung function and survival are the primary endpoints. There is no surrogate marker for COPD to provide a rapid assessment of benefit with a treatment. Animal models replicate some aspects of COPD, but there is currently no single animal model that reproduces all aspects of the human disease.

ADVANCES IN DRUG DELIVERY AND SURGICAL DEVICES

Advances have also been made in nonpharmacologic therapies to treat severe (end-stage) COPD. Flutter valves are now available to aid in mucus clearance before bronchodilator therapy use (Flutter and Acapella). The recent results of the National Emphysema Treatment Trial demonstrates that selected patients can experience substantial improvements in health-related quality of life, lung function, and exercise performance by undergoing lung volume reduction surgery (LVRS).16 A small subset of patients also experienced a substantial reduction in mortality. Current research in the area includes several different approaches to performing LVRS via an endobronchial approach. Approaches under evaluation include endobronchial valves, tissue engineering with instillation of hydrogel, and bronchial fenestration.17,19 Due to environmental concerns about the effects of propellant compounds on the atmosphere, drugs for delivery by
inhalation are now being developed as dry powder inhalers. Substantial work has been done on the development of a variety of medication delivery systems that use dry powder inhalation.

Palliative Care in COPD

Although much of the effort in COPD is devoted to prevention through efforts to reduce cigarette smoking or to help current smokers quit prior to developing symptomatic disease and to the development of more effective treatments, advances in medicine also include a better understanding and delivery of palliative care. Severe COPD is often a progressive and fatal disease. Our goal is to delay mortality and reduce morbidity from COPD as much as possible. During the last year of life with COPD, patients are incapacitated by severely reduced FEV1 and performance status, multiple hospitalizations, and numerous comorbidities (requiring their own treatments). End-stage COPD patients often live alone and suffer from neuropsychiatric disorders such as depression, anxiety, panic, insomnia, and cognitive impairment.

Palliative care is defined as treatment that “enhances comfort and improves the quality of an individual’s life during the last phase of life.” Palliative care emerges from an agreement among the individual, physician(s), primary caregiver, and the hospice team that the expected outcome is death and any treatment should focus on relief from distressing symptoms, the easing of pain, and/or enhancing the quality of life. It focuses on symptom relief, counseling, and coordination of care in the shadow of death. For COPD, palliative care includes an honest prognosis, encouragement of planning for death, managing dyspnea and psychologic distress, and promoting hospice care. Although it is an uncomfortable subject for both physician and patient, palliative care offers the physician the chance to relieve any pain the patient may be experiencing and reassures the patient and family that the healthcare team is not abandoning them.

Palliative care should be approached with an attitude of “hope for the best, but prepare for the worst.” While COPD patients understand that COPD reduces their lifespan, the way in which the physician frames the prognosis can determine the patient’s receptiveness to palliative care and the decisions that need to be made as part of this process. For example, the physician may say to an advanced-stage COPD patient “Some people with your condition live 2 years or more. However, your lung reserve is so reduced now that you might die at any time from a complication of your disease. Preparing for this helps me to provide you with the best treatment options in any situation.”

Hospice care is important for COPD patients, because they have one of the longest survival rates after enrollment in hospice (Figure 3). Consider hospice when the patient’s functional reserve is so limited that the patient might die at any time (life expectancy of weeks to months); if the patient can be expected to benefit from the specialized services offered by a hospice, and the patient understands that death may be near and does not want to suffer needlessly. A medical advance directive is also extremely important and should be agreed upon by the patient, a selected family member, and the physician.

Figure 3. Survival Rates After Enrollment in Hospice

CONCLUSION

COPD is chronic pulmonary disease that occurs in some, but not all, people who regularly smoke cigarettes. Currently available therapy improves the chances of successful smoking cessation, lung function, and health-related quality of life, and reduces exacerbations. As yet, however, no pharmacotherapy other than oxygen has been shown to affect the natural history of the disease. Other recent advances include the development of nonpharmacologic therapies for COPD. In addition, there is an emerging recognition of the importance of thoughtful and compassionate palliative care in patients with advanced disease.

The future for COPD treatment looks bright. In addition to our currently available treatments, researchers are focusing on the many known pathways involved in COPD pathology. These multifaceted treatments will offer more comprehensive and perhaps more targeted treatments, as we better understand the molecular mechanisms of COPD. There appears to be no single ideal therapy for COPD. Standard of care in the future may eventually consist of multiple therapies covering inflammation, mucus secretion, and emphysema, taking into consideration individual biochemical differences.

REFERENCES