NEW APPROACHES TO COPD THERAPY

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ABSTRACT

New treatments— together with new and more aggressive uses of existing treatments— are urgently needed to manage the growing epidemic of chronic obstructive pulmonary disease (COPD). Promising classes of agents such as the selective phosphodiesterase 4 inhibitors, which target fundamental pathophysiologic mechanisms such as inflammation and lung tissue remodeling, are now in late-stage clinical development. This article describes the expanding range of such targeted therapies for COPD and also reviews several innovative uses of existing therapies, such as long-acting or combination bronchodilators or drugs for muscle gain in high-risk underweight patients with COPD. In decades to come, the population of patients with symptomatic COPD will increase and the burden of disease on society will grow. Clinicians will have to manage this crisis by combining therapies and individualizing treatment as necessary to slow lung function decline (eg, forced expiratory volume in 1 second) and also to improve key outcomes such as exacerbation frequency, exercise ability, and quality of life. As with many other chronic diseases, a multimodal treatment approach and an infusion of new mechanism-based therapies will be required to reverse long-standing trends of increased COPD morbidity and mortality.


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There is now a greater need for new medications to treat chronic obstructive pulmonary disease (COPD). Recent statistics from the third National Health and Nutrition Examination Survey (NHANES III) and other government sources indicate that COPD now leads annually to about 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths. By 2020 the disease will leap from sixth to third worldwide as a cause of death. COPD-related direct healthcare costs will skyrocket—a product of increasing expenditures for hospitalization due to exacerbations, surgeries for lung volume reduction and lung transplantation, long-term oxygen therapy, nocturnal home ventilation, pulmonary rehabilitation, and long-term drug therapy. Indirect costs of COPD related to the burden on caregivers and to society, though harder to quantify, will add significantly to the overall burden of this disease.

Smoking cessation is clearly the most rational treatment approach to COPD. Cessation alters the natural history of the disease and, if adopted early enough, preserves lung function, diminishes the tremendous personal burden of the disease, and in the longer term may even limit the soaring societal costs of advanced COPD. However, successful smoking cessation also assumes considerable levels of personal effort and societal investment. The addictive properties of nicotine and the sociopolitical complexities related to tobacco create high barriers to public health programs aimed at smoking cessation. [Editor's Note: See Dr Rennard's article on smoking cessation in the previous issue of this COPD series in Advanced Studies in Medicine.] Even if current antismoking initiatives are successful, the aging of the population and the legacy of past smoking behavior will continue to push the COPD burden and costs higher over the next 20 years to 30 years.
Current drug therapies for COPD such as the bronchodilators, corticosteroids, and theophylline are aimed mainly at symptom relief. Vaccinations, antibiotic therapy, and rehabilitation are the other main components of current therapy employed to reduce exacerbation frequency and to treat symptoms. Oxygen is the only intervention known to increase survival. While inhaled corticosteroids may limit exacerbations to some degree, they have limited impact on the unasthma-like inflammatory processes of COPD, minimal effects on lung function decline or mortality, and a relatively undefined long-term safety record.

**SPECIFIC THERAPIES FOR A HETEROGENEOUS DISEASE**

Increased understanding of COPD pathophysiology is the basis for new pharmacologic approaches aimed at improving symptom management, slowing lung function loss, and perhaps even repairing lung tissue following the development of structural changes that characterize COPD. Processes related to inflammation, protease and oxidant activity, mucus secretion, and tissue remodeling and repair are all considered potential leverage points for improved and more disease-specific therapies. This article describes several attempts to influence the underlying pathophysiology of COPD with new therapies. Novel drug classes targeting specific aspects of the inflammatory response or tissue modeling/repair are introduced (e.g., phosphodiesterase 4 inhibitors, retinoic acid) along with modified versions or uses of existing drug classes (e.g., long-acting anticholinergics, oxandrolone).

Because of the extreme heterogeneity of COPD—in terms of underlying causes, genetic susceptibilities, concurrent diseases, rates of progression, symptoms, severities, and clinically relevant outcomes—a combination of new therapeutic strategies may be needed to manage this growing and diverse patient population. An expanded range of new treatments will allow clinicians to tailor COPD therapy for individual patients. On a population level, this targeted use of new therapies should slow the current inexorable growth in the worldwide COPD disease burden. Just as no single therapy for heart disease can be credited for reversing the mid-century increases in cardiovascular mortality in the United States, no single COPD therapy will emerge to reverse the current momentum in COPD deaths. Instead, as with heart disease therapies, a spectrum of COPD therapies will attack the problem mechanism by mechanism, phenotype by phenotype, and case by case. The targets will include those pathogenetic processes that contribute to the limited airflow and symptoms of COPD, including inflammation, peribronchial fibrosis, alveolar destruction, and mucus hypersecretion as well as the processes that account for the systemic aspects of COPD.

Even if the coming generation of targeted COPD therapies is not a cure, they will be critical in helping clinicians and healthcare systems manage the huge cohort of COPD morbidity that is “built-in” for the next 20 years to 40 years. Combined with a renewed emphasis on smoking cessation, this array of new therapies will prevent the lung function and symptomology of these at-risk patients from deteriorating to the point that their quality of life drops markedly and their therapy costs rise rapidly (Figure 1).

This article is not a comprehensive review of the drugs in development for COPD; this article will provide the clinician with information about the rationale and the clinical goals now driving these varied research
REVIEW

Focus on Inflammation: Targeting Pathophysiology in COPD

Excessive proteolysis due to neutrophil elastase has long been recognized as a central process in COPD pathogenesis. But the elastase:antielastase imbalance model has now expanded to include many of the other inflammatory cells and mediators that typically populate the lower respiratory tract of cigarette smokers.

In fact, the National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition states that the progressive airway limitation of COPD is “associated with an abnormal inflammatory response of the lungs to noxious particles or gases.”

The main inflammatory cells in COPD are neutrophils, macrophages, and CD+8 T lymphocytes, which differ from the inflammatory cell profile seen in asthma (predominantly CD+4 lymphocytes and eosinophils). This cell profile difference may explain why corticosteroids are not as effective in COPD as they are in asthma. As mentioned previously, corticosteroids have relatively little impact on the inflammatory processes of COPD. Researchers are now studying the signals and mechanisms that recruit COPD-related inflammatory cells to the lung and then stimulate the activity that causes damage (Table).

Cigarette smoke can incite this inflammatory cascade in a number of ways: smoke or other insults can directly recruit inflammatory cells or stimulate mediators (eg, via complement activation), or they can indirectly promote inflammation by stimulating epithelial cells or resident macrophages in the airway to release chemoattractants. Neutrophils gather in the lung within hours of smoke exposure while it takes weeks to months for macrophages to accumulate. These cells may be essential in the early inflammatory breakdown of lung tissue and in the related liberation of peptides that subsequently attract and stimulate T cells.

Opportunities for targeted COPD therapy occur at virtually every stage of inflammatory cell recruitment and activation as well as tissue disruption. Researchers are hoping to prevent lung tissue damage and scarring by blocking 1 or more of the molecular or cellular pathways mediating this process. This blockage will encourage the lung to repair or reduce the systemic effects of COPD that define the full range of this complex disease, as shown in these examples:

- Increased levels of certain matrix metalloproteases and other proteases (eg, elastase, cathepsin) are linked with the destruction of lung elastin in emphysema; specific inhibitors of these molecules are now being tested in various COPD models.
- Interferon-gamma and interleukin-13 may regulate protease and antiprotease activity and are, therefore, also seen as potential therapeutic anti-inflammatory targets. Since elevated lung levels of certain other cytokines (eg, tumor necrosis factor-alpha, interleukin-8, and monocyte chemoattractant protein-1) are associated with COPD, these important chemotactic proteins are now considered promising targets for novel therapies.
- The nuclear transcription factor κB is expressed in higher than normal quantities in the airways of patients with COPD. Since this factor regulates expression of other genes involved in inflammation (eg, genes for cytokines, chemokines, adhesion molecules, proteases), it has become a target for inhibition.

In coming years, clinicians can expect to see many preliminary reports on the anti-inflammatory activity of various agents aimed at mediators such as these.

Table. Inflammation in COPD: Multiple Opportunities for Altering Disease Pathophysiology

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<th>1. Recruitment of inflammatory cells</th>
<th>2. Activation of inflammatory cells</th>
<th>3. Damage to lung tissue</th>
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Demonstration of anti-inflammatory activity in laboratory and animal models is not difficult—as our group illustrated recently by showing that even chicken soup extract can inhibit neutrophil chemotaxis in the laboratory. But as these agents progress from the laboratory stage to clinical trials, efficacy will be harder to prove. The Lung Health Study, for example, demonstrated the benefit of smoking cessation and included a population of 6000 and a timeline of 5 years, which the researchers believed were necessary to provide statistical power adequate to confirm their hypothesis. Thus, any anti-inflammatory agent developed for use in COPD will face considerable challenges in documenting efficacy.

The specific phosphodiesterase (PDE) inhibitors have already advanced to phase II and phase III clinical trials in COPD. PDEs catalyze the breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate. Because intracellular cAMP regulates pulmonary inflammatory responses, as well as bronchial smooth muscle tone and certain immune functions, inhibition of the specific types of the PDE enzyme relevant to COPD pathophysiology has emerged as a major goal. Theophylline is considered a nonspecific PDE inhibitor, although it has other pharmacologic actions as well.

PDE4 is a cAMP-specific PDE expressed in airway smooth muscle cells, accounting for its bronchodilator effects, and is present also in inflammatory cells. Inhibition of PDE4 causes an elevation of cAMP in these cells, which in turn downregulates the inflammatory response. The anti-inflammatory effects of PDE4 inhibitors have been well documented, both in vitro and in vivo in a range of animal models, and the possibility of having an effective anti-inflammatory treatment in COPD has generated considerable excitement. Cilomilast is a second-generation selective PDE4 inhibitor that potently inhibits inflammatory cytokine production (e.g., tumor necrosis factor alpha, interleukin-4) in a variety of in vitro models and is currently the PDE4 inhibitor most advanced in clinical trials. The first randomized, placebo-controlled, dose-ranging study with cilomilast included 424 patients with COPD and demonstrated significant improvement in airflow over a 6-week treatment period. At week 6, cilomilast 15 mg bid had improved forced expiratory volume in 1 second (FEV1) by a mean of 130 mL, as compared to a mean of -30 mL for the placebo group (P < .0001). There were no significant differences in serious adverse events between the groups; the most common adverse event in the cilomilast group was nausea (12% incidence in the 15-mg group versus 1% in the placebo group). Preliminary reports of reduced exacerbations, lower per-patient treatment costs, and improved health status associated with cilomilast therapy in patients with COPD are encouraging. Other PDE4 inhibitors are also in development. Of these, roflumilast is probably the most advanced. The full results of clinical trials with PDE4 inhibitors will provide a long-awaited indication of the potential of this anti-inflammatory strategy in COPD.

TISSUE REMODELING AND REPAIR

Excessive inflammation and fibroblast activity at the site of tissue damage can lead to scarring and distortion (i.e., contraction) of normal tissue. In COPD, the small airways are frequently the site of such remodeling; peribronchial fibrosis is a common pathological finding in patients with COPD. These alterations to the airways and in the lung parenchyma can produce the fixed airway obstruction seen late in a patient's life. The exact connections leading from inflammation to tissue remodeling in COPD are not known, but it is likely that distinct forms of treatment will be required to target these 2 processes separately. Agents such as inhaled corticosteroids, long-acting beta agonists, and leukotriene receptor antagonists have been tested for their ability to halt the tissue remodeling associated with asthma and COPD. The ability of these agents to do so and the clinical impact of their use must be adequately tested. Inhaled glucocorticoids have not been found to alter the rate at which airflow declines in 4 separate placebo-controlled clinical trials. Cyclic AMP helps regulate fibroblast chemotaxis and fibrosis-related tissue contraction, the specific PDE4 inhibitors are thought to have potential in blocking cAMP degradation and thereby in altering fibroblast-mediated repair processes. In vitro tests show that 2 selective PDE4 inhibitors (rolipram and cilomilast) suppress both fibroblast chemotaxis and fibroblast-mediated collagen-gel contraction in a concentration-dependent manner (Figure 2). This activity indicates that certain PDE4 inhibitors may alter not only inflammatory processes but also the subse-
quent tissue-remodeling process and progressive fibrosis seen in COPD.

In emphysema, outright destruction of the alveoli and the lung parenchyma is the characteristic pathology. These permanent changes are thought to result from an imbalance of proteases and antiproteases, perhaps as a result of the genetic factors or the inflammatory mediators described earlier. Other imbalances, such as between oxidants and antioxidants, may have similar effects.

Until recently, the possibility of stimulating growth of new alveoli was considered remote; however, animal studies have now shown that treatment with retinoic acid can reverse elastase-induced emphysema damage. Human studies are currently in progress. This exciting line of pharmacologic research is one of the few to pursue the goal of improving COPD, rather than merely maintaining the disease status quo or slowing the functional deterioration.

BRONCHODILATOR THERAPY:
STILL ROOM FOR IMPROVEMENT

Even if researchers find a biologic therapy that targets COPD pathophysiology and slows progression of the disease, the near-term and medium-term needs for existing COPD therapies will not disappear. Because the patient population is large and no single treatment will be capable of fully preventing or reversing lung deterioration, a combination of new and existing therapies will likely be required in coming decades. All of which reinforces the need for ongoing research to improve the efficacy, safety, and convenience of the current first-line therapies for COPD: the bronchodilators.

In this context, several recent improvements in bronchodilator treatment are worthy of mention. The fixed combination of ipratropium and albuterol, for example, provides a more powerful bronchodilator effect and a longer duration of action than either agent alone. A variety of other combinations has been tested, and it is likely that bronchodilator agents of different classes will generally be more effective in combination with each other and with inhaled corticosteroids. Patients will likely benefit from the convenience of fixed combinations; in addition, the possibility of synergistic or additive effects plus reduced toxicity (due to reduced doses of each individual component) may also account for their growing popularity.

In terms of monotherapy, the longer-acting beta agonists such as salmeterol and formoterol have also been shown to improve lung function over a 12-hour period, thus allowing a twice-a-day dosing regimen instead of the more frequent dosing needed for ipratropium or short-acting beta agonists. Tiotropium is a long-acting anticholinergic; the bronchodilating effects of a single dose last for up to 32 hours, and gradual accumulation of the drug eventually produces a larger peak effect and greater bronchodilation with dosing over several days. The long-acting beta agonists also exert other beneficial effects in addition to bronchodilation, although the clinical importance of these effects in COPD remains to be determined. Alternative effects of long-acting beta agonists currently under investigation include inhibition of airway smooth muscle cell proliferation and inflammatory mediator release, stimulation of mucociliary transport, cytoprotection of respiratory mucosa, attenuation of neutrophil recruitment and activation, and reduction of edema.

Whatever bronchodilator is prescribed, clinicians must remember that rehabilitation is needed if patients are to benefit from the use of bronchodilators.

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**Figure 2. Effects of Selective PDE4 Inhibitor (Cilomilast) on Fibroblast Activity**

PDE4 = type 4 phosphodiesterase; PGE2 = prostaglandin E2.

Without concomitant exercise training, the patients' perceptions of dyspnea and their exercise performance will not show as much improvement as do their lung function tests. While hardly surprising, such findings underline the need for researchers to focus on COPD clinical study endpoints in addition to the traditional FEV₁. Alternative outcomes such as health status (quality of life), exercise performance, and survival will become increasingly important as new COPD therapies are tested in the future.

**Other Approaches**

The search for novel COPD therapeutic approaches has expanded to include a broadened definition of desired outcomes. These new outcomes and COPD treatment goals are relevant to clinicians as well as to researchers. Clinicians not only want their patients to display improved lung function but also to cough less, become more active and more social, have less depression, and feel stronger. Surprisingly, the level of such COPD symptoms does not always correlate with FEV₁, the current criterion standard for COPD clinical trial endpoints. The failure to correlate has resulted in pharmacological and surgical treatments being developed specifically to alter the symptomology of COPD rather than the lung function test results.

The classic systemic COPD trait of low body mass serves as an example of an endpoint other than FEV₁ now specifically targeted for therapy. Weakness is a marker for poor health and worse outcomes in COPD. One study, for instance, showed no correlation between the FEV₁ and the 12-minute walking test but did reveal a strong positive association between fat-free body mass and the walking test. The same researchers showed in a retrospective study of 400 patients with stable COPD that low body weight was a significant independent predictor of increased overall mortality (P<0.001), which is a confirmation of the common clinical impression that "being skinny" is bad in COPD. In a prospective arm of this same study, reversal of low body weight (with anabolic steroids or nutrition therapy) was associated with better survival.

Based on such intriguing results, anabolic agents and other therapies are now being tested to increase body mass in COPD. In patients with moderate-to-severe COPD (mean FEV₁ 34%) and low body mass index (BMI) (mean BMI 17.8), oral oxandrolone at 10 mg bid led to a mean increase of 6.0 pounds in 46 patients after 4 months. Nine other patients did not respond with weight gain. Bioelectric impedance analysis showed that the weight gain was primarily lean tissue (ie, muscle mass). Notably, nearly half of the patients in this open-label study had to withdraw due to adverse effects. Megestrol acetate, an appetite stimulant commonly used in patients with acquired immune deficiency syndrome and cancer, has also been shown to induce weight gain in patients with COPD. In a prospective double-blind placebo-controlled study with this progestational agent, body weight increased by 3.2 kilograms after 8 weeks (P<0.001 versus placebo), but there were no improvements in respiratory muscle function or exercise tolerance.

Whether a simple drug-induced bulking of muscle mass will improve COPD patient survival or health status is unknown. Moreover, the substantial adverse-effect profiles of anabolic steroids also need to be fully evaluated in this population. But even as researchers seek answers to these important questions, other investigations into the pathophysiology of COPD-related weakness are hinting at more targeted strategies for increasing weight in these patients. In patients with COPD with low body weight, for example, immune staining of muscle biopsies showed clear evidence of apoptotic nuclei in skeletal muscle cells. These patients also had a lower exercise tolerance than patients with COPD who had a higher body weight, despite similar lung function. Both healthy patients and patients with COPD who had normal BMIs had no signs of skeletal muscle apoptosis. Findings of a 10-fold increase in serum levels of tumor necrosis factor alpha in underweight patients with COPD points to yet another contributor to the complex clinical picture of COPD—and thus another potential target for COPD therapy.

**Summary**

The need for new therapeutic options for COPD is reaching a critical point. A large generational cohort of cigarette smokers is maturing into a large generation of patients with COPD. Researchers have developed an array of pharmacologic agents aimed at the pathophysiologic underpinnings of the disease. The selective PDE4 inhibitors may soon be available, for example, to attack both the inflammation and tissue remodeling that contribute to COPD. In the longer term, agents to stimulate lung tissue regrowth may also be developed. These are exciting avenues of research that warrant attention. Over the next decade, however,
clinicians will be seriously challenged to rethink how they manage COPD with existing therapies. They will need to (1) combine effective therapies, surgical as well as pharmacological; (2) individualize treatment based on patient phenotypes; (3) effectively integrate rehabilitation programs; and (4) learn to be more aggressive in managing hallmark symptoms of the disease. Just as the renal anemia of chronic kidney disease often merits aggressive therapy with erythropoietin, the inflammatory exacerbations, weight loss, exercise intolerance, and coughing associated with COPD merit targeted interventions with 1 or more of our current therapies. COPD is not curable, but it is treatable— and the range of treatment options is expanding.

REFERENCES


