The Past Decade of Advances in the Pharmacological Treatment of COPD

The COPDGene® Study: Past, Present and Future

New Open Access COPD Journal Launched and Available

Engage Our Experts at the COPD Pocket Consultant Guide Community Website

Respiratory Therapists Seize the Day

COPD Management in Primary Care: The Past Ten Years

COPD Foundation’s Medical and Scientific Advisory Committee (MASAC) and Clinical Advisory Committee (CAC) Resolution

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Letter from the Managing Editor:
Katelyn Turner

There has already been so much exciting activity and news for the COPD Foundation, and it's only our second issue of the year. In this issue, we continue to feature 10-year anniversary articles that commemorate the past decade of progress for the COPD Foundation and COPD community. On behalf of the COPD Foundation, I want to thank all of our authors who make Lung Health Professional possible, and I want to thank all of you for your support. I encourage you to share COPD Foundation resources with your colleagues and patients—we are continuously receiving wonderful articles and are grateful to all who make it happen.

Feature on a Decade of Advances in the Pharmacological Treatment of COPD:

I am grateful to Dr. Kristina Bailey's contribution of our feature piece for this issue. She reviews new COPD drugs with their mechanism of action, dosage, and side affects, also summarizing the data available from clinical trials in which patients are most likely to benefit. You can find this article on page 6.

The COPDGene® Study: An Important Update:

Dr. Craig Hersh contributed this article that discusses the history of the pivotal COPDGene® Study, as well as its current status and what he sees for the future. He writes about the importance of this study and why all members of the COPD community should be excited about it. You can find his article on page 11.

New Open Access COPD Journal Launched and Available:

Cathy Carlomagno, Production Editor for the COPD Foundation's Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation, discusses its launch and inaugural issue which is accessible online at http://journal.copdfoundation.org. It features review articles that discuss progress made in COPD over the past decade, and original research articles. To read more about the Journal, please read her article on page 22.

COPD Pocket Consultant Guide Community Website:

Our Director of Education, Scott Cerreta, BS, RRT, contributed this piece that discusses the COPD Foundation Pocket Consultant Guide (PCG) for the Diagnosis and Management of COPD—designed to be a practical tool to assist practicing clinicians in managing the diagnosis and treatment of COPD patients. The PCG Online Community Website was launched in February, and allows physicians and other healthcare professionals to interact with COPD experts. You can read all about this on page 25.

COPD Management in Primary Care: The Past Ten Years

Drs. Alan G. Kaplan and Barbara Yawn contributed this important piece that discusses how primary care has made progress in the past 10 years in improving the diagnosis, management and lives of individuals living with COPD. This article is on page 31.

As always, please feel free to send me your suggestions for topics for future issues of LHP. I welcome your input.

Best,
Katelyn Turner

Please send suggestions to: kturner@copdfoundation.org

Lung Health Professional magazine is published 4 times annually and is available from the COPD Foundation free of charge. If you would like to be added as a subscriber, please email Katelyn Turner at kturner@copdfoundation.org or call the C.O.P.D. Information Line 1-866-316-COPD (2673).
Important Safety Information

PROLASTIN®-C (alpha₁-proteinase inhibitor [human]) is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to deficiency of alpha₁-proteinase inhibitor (alpha₁-antitrypsin deficiency).

The effect of augmentation therapy with any alpha₁-proteinase inhibitor (alpha₁-PI) on pulmonary exacerbations and on the progression of emphysema in alpha₁-antitrypsin deficiency has not been demonstrated in randomized, controlled clinical trials. PROLASTIN-C is not indicated as therapy for lung disease in patients in whom severe alpha₁-PI deficiency has not been established.

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PROLASTIN-C is made from human plasma. Products made from human plasma may carry a risk of transmitting infectious agents, eg, viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent.

References:
1. Data on file, PROLASTIN DIRECT program.

Please see brief summary of PROLASTIN-C (alpha₁-proteinase inhibitor [human]) full Prescribing Information on adjacent page.

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PROLASTIN®-C
Alpha1-Proteinase Inhibitor (Human)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROLASTIN®-C (Alpha1-Proteinase Inhibitor [Human]) safely and effectively. See full prescribing information for PROLASTIN-C.

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Initial U.S. Approval: 1987

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PROLASTIN-C is an alpha1-proteinase inhibitor that is indicated for chronic augmentation and maintenance therapy in adults with emphysema due to deficiency of alpha1-proteinase inhibitor (alpha1-antitrypsin deficiency). The effect of augmentation therapy with any alpha1-proteinase inhibitor (Alpha1-PI) on pulmonary exacerbations and on the progression of emphysema in alpha1-antitrypsin deficiency has not been demonstrated in randomized, controlled clinical trials. PROLASTIN-C is not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been established.

-----------CONTRAINDICATIONS-----------

IgA deficient patients with antibodies against IgA.

--------WARNINGS AND PRECAUTIONS--------

- IgA deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions.
- This product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent.

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COPD Foundation’s Medical and Scientific Advisory Committee (MASAC) and Clinical Advisory Committee (CAC) Resolution

*This article is special for the COPD Foundation’s 10-year anniversary.
The Past Decade of Advances in the Pharmacological Treatment of COPD

COPD is characterized by persistent airflow limitation due to chronic inflammation of the lower airways. The symptoms of shortness of breath, cough and sputum production can increase during exacerbations of COPD. Appropriate pharmacological therapy of COPD can reduce symptoms, the frequency and severity of exacerbations and improve exercise tolerance. Despite these advancements, there is a desperate need for new drugs to treat COPD. The available drugs do little to slow the progression of COPD. Developing new COPD drugs is often a difficult process, due to the fact that there are not good animal models and long-term studies are typically required to see differences with treatment.

In this article, we will review each new drug along with its mechanism of action, dosage, and side effects. We will also summarize the data available from clinical trials and which patients are most likely to benefit. In the last 10 years, there have been nine new drugs approved for COPD. Most represent new combinations of known drugs, or a new variation in an already available class of drugs. Only one drug represents a new class of medications, the phosphodiesterase 4 (PDE4) inhibitor, Roflumilast.

**Phosphodiesterase 4 (PDE4) inhibitor Roflumilast**

**Mechanism of action:** Roflumilast blocks PDE 4, which is expressed in macrophages, neutrophils, CD8+ T-cells, and airway smooth muscle cells. PDE4 normally degrades cAMP. By inhibiting PDE4, cAMP accumulates in the cells. The increase in cAMP is thought to diminish inflammation and provide bronchodilation.

**Dose:** 500mcg orally once a day.

**Side effects:** Nausea (5%), diarrhea (10%), loss of appetite (2%), weight loss (5-10%).

**Contraindications:** Moderate to severe hepatic impairment (Child-Pugh class B or C)

**Data from clinical trials:** In a randomized, placebo controlled study over 1 year, there was an increase in FEV1 of 48ml in the roflumilast patients compared to control. There was also a decrease in exacerbations of 17% in the roflumilast group.[1] A subsequent post-hoc analysis showed that a subset of COPD patients with chronic bronchitis were most likely to benefit independent of whether they were treated with inhaled corticosteroids.[2]

**COPD patients most likely to benefit:** Patients with GOLD stage 3-4 disease (FEV1 < 50%) with a history of exacerbations and chronic bronchitis (chronic cough and sputum production). It can be used in combination with long-acting β-agonists and inhaled corticosteroids.

**Long-acting β-agonists Indacaterol**

**Mechanism of action:** A long-acting (over 24 hours) β-agonist, with a rapid (5 min) onset of action.

**Dose:** One inhalation once daily (75mcg/inhalation) in the USA, 150-300mcg in Europe.

**Side effects:** Cough (7-24%) Headache (5%)

**Contraindications:** Hypersensitivity to indacaterol, not to be used for acute exacerbations of COPD

**Data from clinical trials:** Indacaterol improves trough FEV1 by 120-140 ml (with 75mcg) [3] and 170 ml (with 300mcg) [4] after 12-weeks of therapy compared to control. It also shows a greater increase in FEV1 compared to formoterol [5] [4] and salmeterol [6]. It was equivalent to tiotropium monotherapy [5].

This article is special for the COPD Foundation’s 10-year anniversary.
However, indacaterol does provide additional bronchodilation when used in conjunction with tiotropium.\([8]\) It also improves dyspnea compared to control, and health-related quality of life as measured by the St. George respiratory questionnaire\([9]\).

**COPD patients most likely to benefit:**
Indacaterol can be used in COPD patients with moderate to severe disease. It has the additional benefit of once a day administration, which could benefit patients that struggle with complex regimens.

### Arformoterol

**Mechanism of action:** Arformoterol is the (R,R) enantiomer of the long acting \(\beta\)-agonist formoterol. It is administered by nebulizer.

**Dose:** 15mcg/2ml nebulized twice a day

**Side effects:** Chest pain (7%), diarrhea (6%)

**Contraindications:** Hypersensitivity to arformoterol or racemic formoterol

**Data from clinical trials:** Arformoterol has been shown to improve trough FEV1 and dyspnea in moderate to severe COPD.\([10]\) The bronchodilatory effect of arformoterol was similar to mono-therapy with tiotropium, but there was additional benefit to using both drugs together.\([11]\)

**COPD patients most likely to benefit:**
Arformoterol is useful for patients that have difficulty with using the traditional inhaled powder inhaler, or prefer nebulized medications.

### Tiotropium

**Mechanism of action:** Tiotropium is a long acting anti-cholinergic agent. It blocks primarily the M3 receptor, which is responsible for bronchodilation, over the M2 receptor, which is responsible for side effects such as tachycardia.

**Dose:** 18mcg inhaled once a day

**Side effects:** Dry mouth (5-16%), upper respiratory tract infection (41%), sinusitis (7-11%)

**Contraindications:** Hypersensitivity to tiotropium or ipratropium. Tiotropium may worsen the symptoms of narrow-angle glaucoma, myasthenia gravis and prostatic hyperplasia.

**Data from clinical trials:** Tiotropium improves FEV1 and SGRQ status to a greater extent than ipratropium \([12]\). When tiotropium is added to treatment with long acting \(\beta\)-agonists and inhaled corticosteroids, the tiotropium group maintains a higher FEV1, has improved health status and fewer exacerbations. Tiotropium may also improve dynamic hyperinflation and exercise endurance in patients with COPD \([13]\) as well as respiratory muscle strength and oxygen uptake after exercise \([13]\).

**COPD patients most likely to benefit:**
Moderate to severe COPD. The inhalation device may be easier for patients with severe COPD to use, because it has a lower resistance than tiotropium's inhaler \([12]\).

### Aclidinium bromide

**Mechanism of action:** Blockade of the M3 and M2 receptor. However, the half-life of inhibition of the M3 receptor is 6 times that of the M2 receptor.

**Dose:** One inhalation (400mcg) twice daily

**Side effects:** Headache (7%), pharyngitis (6%),

**Contraindications:** May worsen symptoms of narrow-angle glaucoma, myasthenia gravis, and prostatic hypertrophy.

**Data from clinical trials:** Aclidinium bromide induced larger increases in FEV1 than placebo \([14, 15]\), and they were comparable to those of tiotropium \([16]\).

**COPD patients most likely to benefit:**
Moderate to severe COPD. The inhalation device may be easier for patients with severe COPD to use, because it has a lower resistance than tiotropium's inhaler \([12]\).

### Inhaled combination medications

In the last 10 years, there have been 2 new inhaled corticosteroid/ long acting \(\beta\)-agonist combinations: Fluticasone/Vilanterol and Mometesone/formoterol. There has also been one combination of long acting anticholinergic and long-acting \(\beta\)-agonist, Umedclininum/vianterol.

### Fluticasone/Vilanterol

**Mechanism of action:** Fluticasone is an inhaled corticosteroid with anti-inflammatory and immunosuppressive properties. Vilanterol is a long-acting \(\beta\)-agonist (24 hrs), which relaxes bronchial smooth muscle by selective action on \(\beta\)-agonist receptors

**Dose:** Fluticasone 100 mcg and vilanterol 25
mcg one inhalation per day.

**Side effects:** Headache (7%), Nasopharyngitis (9%), upper respiratory tract infection (7%), pneumonia (6%), oral candidiasis (5%).

**Contraindications:** Hypersensitivity to fluticasone or vilanterol

**Data from clinical trials:** Fluticasone/Vilanterol improves trough FEV1 compared to placebo in a group of patients that included many current smokers.[17] It did not cause any increase in heart rate.[18] COPD patients most likely to benefit: This is a once a day preparation which may be particularly useful for patients that desire a simpler regimen.

**Mometasone/formoterol**

**Mechanism of action:** Mometasone is an inhaled corticosteroid and formoterol is a long-acting β-agonist.

**Dose:** Mometasone 100 mcg/ formoterol 5mcg per inhalation twice a day or 200 mcg/ formoterol 5mcg per inhalation twice a day

**Side effects:** Nasopharyngitis (5%), voice disorder (4% to 5%).

**Contraindications:** Hypersensitivity to mometasone, formoterol,

**Data from clinical trials:** Most clinical trials were focused on asthma, but there are studies showing improvement in FEV1 in COPD compared to control. There are also improvements in quality of life and number of exacerbations.[19]

**Umedclinium/vilanterol**

**Mechanism of action:** Umedclinium is a long acting antimuscarinic (M3) blocker. Vilanterol is a long-acting selective β-agonist.

**Dose:** Umeclidinium 62.5 mcg and vilanterol 25 mcg per inhalation once a day

**Side effects:** Pharyngitis (2%), lower respiratory tract infection (1%) Hypersensitivity to vilanterol

**Data from clinical trials:** Umedclinium/vilanterol significantly improved FEV1 compared to placebo[20] or tiotropium[21]. COPD patients most likely to benefit: Those that have made the decision that it is time to stop smoking.

**Smoking cessation aids**

**Varenicline**

**Mechanism of action:** Varenicline is a partial agonist for the β4β2 nicotinic acetylcholine receptor. In other words, varenicline binds to the receptor, and does not let nicotine bind.

**Dose:** Varenicline should be started 1 week prior to the quit date. Then start 0.5mg each day for 3 days. Then 0.5mg twice a day for 4 days, then 1mg twice a day for up to 12 weeks.

**Side effects:** Nausea (30%), Vivid or unusual dreams (13%), constipation (8%), Flatulence (6%), vomiting (5%)

**Contraindications:** Patients need to be monitored closely for neuropsychiatric symptoms, because Varenicline can increase the risk of suicidal thoughts or actions.

**Data from clinical trials:** Several randomized, controlled clinical trials have shown that varenicline is superior to placebo[22-25] and sustained-release bupropion[26] for smoking cessation.

COPD patients most likely to benefit: Those that prefer a once a day regimen.

Although our armamentarium of available drugs for COPD has increased over the past 10 years, we still have a long way to go to have good treatment options for all of our patients. Advancement in the treatment of COPD will require further understanding of the pathophysiology of COPD, so that we can determine the best ways to target the underlying inflammation of the airways.

(Continued on page 10)
References


The COPDGene® Study: Past, Present and Future

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States and the fourth leading cause worldwide. COPD is diagnosed and staged based on pulmonary function tests, specifically the forced expiratory volume in 1 second (FEV1) and the ratio of FEV1 to the forced vital capacity (FVC). Cigarette smoking is a major contributor to COPD development, but differential disease susceptibility among smokers and differential symptoms among COPD patients may be due to other factors, including genetics. COPD is a heterogeneous disease, including emphysema (lung tissue destruction) and large and small airway disease. Historically, these distinctions were made on pathological specimens; however, chest computed tomography (CT) scans can demonstrate these features in COPD patients.

The Genetic Epidemiology of COPD Study (COPDGene®) was launched in 2007 with the goal to enroll 10,000 smokers with and without COPD in order to better understand COPD and its subtypes and to discover genetic contributions to COPD. This large study population with state of the art characterization using chest CT scans and genome wide genetic analysis has contributed greatly to these efforts. Phase 2 of COPDGene® started in 2013, in which subjects will return for a 5-year follow up clinical assessment and additional genomic studies.

Study Design and Enrollment

Phase 1

The COPDGene® study was funded in 2007 by the National Heart Lung and Blood Institute (NHLBI) of the U.S. National Institutes of Health (NIH). The goals of the study at that time were to look for genetic associations to COPD in smokers and identify subtypes of disease based on clinical characteristics and CT imaging. A team of investigators at twenty one medical centers were part of the initial application and collaborated on the study design and data collection for the first phase of the study. Regular investigator meetings twice yearly have kept the study moving forward and encouraged the investigators to pursue additional projects and ancillary studies associated with COPDGene®. There have been nearly 80 papers published from the study to date and many more that are in preparation. Clinical, imaging, and genetic data from Phase 1 have been uploaded to the NIH database of genotypes and phenotypes (dbGaP, http://www.ncbi.nlm.nih.gov/gap) making the data available to researchers worldwide.

The focus of the initial phase of COPDGene® was to obtain a cross-sectional view of smokers who had at least 10 pack years of smoking (1 pack-year = 1 pack of cigarettes smoked daily for 1 year). The initial plan was to enroll 10,000 smokers across the range of COPD severity, with over-sampling in African Americans to comprise one-third of the cohort. In order to maximize the power in the genetics study, specific racial groups must be targeted, and COPDGene® focused on non-Hispanic Whites and African Americans. High resolution chest CT scans were a critical tool to look for subtypes of disease. Although the genetic association studies were initially planned for only a subset of the cohort, by the time the DNA was tested, it had become feasible to perform genome wide genetic studies on all subjects.

In order to develop a broad understand of COPD, the major

This article is special for the COPD Foundation’s 10-year anniversary.

The COPDGene® Study is supported by U.S. National Institutes of Health grants R01HL089856 and R01HL089897. COPDGene® is also supported by the COPD Foundation through contributions made to an Industry Advisory Board comprised of AstraZeneca, Pfizer, Novartis, Boehringer-Ingelheim, GlaxoSmithKline, and Sunovion.
exclusion was another lung disease other than COPD, including pulmonary fibrosis, diffuse bronchiectasis, sarcoidosis, cystic fibrosis, and lung cancer. Subjects who had had a recent respiratory exacerbation were asked to wait one month to allow the subject’s lung and general health to return to their usual state. A history of asthma was discussed extensively because of the complex relationship of asthma and COPD, but ultimately it was not an exclusion from COPDGene®.

The subjects were initially to be recruited based on the GOLD classification of COPD, which was based on the results post-bronchodilator spirometry.[1] Within a short time period it was noted that a significant number of smokers who otherwise met the enrollment criteria did not fit into the category of normal spirometry but also did not show a clear obstructive pattern that would fit into the GOLD classification. We postulated that these subjects might represent an important subtype of smoking-related lung disease. Therefore, the study protocol was modified to include these smokers who were initially named GOLD Unclassified and now have been described as Preserved Ratio Impaired Spirometry (PRISm) subjects. The cohort that was finally recruited totaled 10,300 subjects, including 108 never-smokers.

Comprehensive data were collected regarding the subjects’ respiratory symptoms, including cough, sputum, dyspnea, wheezing and respiratory exacerbations. Unlike population based studies that may have only a few individuals with a particular disease, the COPDGene® study is able to focus on the impact of smoking on the lung and the whole person. Information has been collected about quality of life using both a generic instrument, the Medical Outcomes Study SF-36 and the respiratory specific St George’s Respiratory Questionnaire. Information about other medical conditions and medications were recorded, and a six minute walk test was done to determine exercise capacity. The study questionnaires and protocols are available on the study website (www.copdgene.org).

Longitudinal Follow-Up and Phase 2

Shortly after the study start it was clear to the investigators that it was important to maintain contact with the subjects to track their health, particularly respiratory exacerbations. With such a large cohort and no defined funding for maintaining follow-up, an innovative method was tested. Subjects were contacted by automatic phone calls or emails from a remote server (or by a coordinator call if the subject preferred) every six months and answered questions about exacerbations, new medical conditions, oxygen use and general health.[2] More than 80% of the subjects participated in the longitudinal follow-up program providing additional information about COPD and its impacts.

In 2012 the NHLBI renewed the COPDGene® Study grant for an additional five years. With Phase 2 COPDGene® became a longitudinal cohort. Understanding the progression of the disease over time became a priority and determining genetic factors that associated with progression was a new goal. Efforts were expanded to collect detailed information about environmental exposures. The study also had to track subjects who were deceased and obtain information about cause of death. As of late February 2014, over 450 subjects have returned for the Phase 2 visit.

Study Results

Previous articles in this magazine have described results from COPDGene®.[3,4] Here we will present the most recent publications.

Chest CT Imaging in COPDGene®

The COPDGene® Study has collected inspiratory and expiratory chest CT scans on almost 10,000 subjects. Visual review and computerized analysis of these scans have provided novel insight into both the pulmonary and systemic manifestations of smoking. Assessments of the lung tissue, airways, vasculature, pulmonary artery, bones, and skeletal muscle are helping us understand the heterogeneity of disease that may lead to improved therapies.

Perhaps one of the most utilized CT tools in the study of COPD involves densitometric measures of the lung tissue. Using a density threshold the lung can be dichotomized into low attenuating tissue thought to represent emphysema and higher attenuating normal lung. Such an approach to the quantitative assessment of lung disease has been possible for 30 years, and precise measures of the amount of emphysema can be generated for clinical, epidemiologic, and genetic investigation. A limitation to this analysis is
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that it does not adequately discriminate between the types of emphysema (such as centrilobular or panlobular) that may have unique genetic determinants and clinical implications. In an effort to address this, COPDGene® investigators developed a tool to recognize different patterns of emphysema based upon subtle variations in the density patterns of the lung at a regional level.\cite{5} Termed “local histogram”, this method was applied to the full set of COPDGene® CT scans and demonstrated that the type of emphysema present on CT scan provides additional information about the clinical manifestations of COPD, beyond the total amount of emphysema (Figure 1). Further work to determine the genetic associations of these radiologic patterns is ongoing.


Enlargement of the pulmonary artery on chest CT scan may be another non-invasive marker of pulmonary hypertension (Figure 3). In COPDGene®, dilation of the main pulmonary}


![Figure 3. Ratio of the diameter of the pulmonary artery (PA) to aorta (A) < 1 is normal (left). Ratio of the PA/A > 1 may indicate pulmonary hypertension and is a predictor of COPD exacerbations (right). Image created by Dr. George R. Washko](image3)
artery (PA) so that is larger in diameter than the aorta (A) was a strong predictor of COPD exacerbations, suggesting that a significant proportion of these respiratory events involve the pulmonary vasculature.[7]

Muscle wasting or cachexia is a dreaded complication in COPD, especially severe disease, which is associated with a poor prognosis. The area of the pectoralis muscle can be directly measured on standard chest CT scans (Figure 4). Reduced pectoralis muscle area tracked with reduced lung function, reduced exercise capacity and increased symptoms.[6] Further work is needed to expand this effort to other muscle groups and regions of subcutaneous fat seen on CT, but the results suggest that chest imaging may provide new insights into the systemic manifestations of COPD.

Many COPD patients have been previously diagnosed with asthma, but it is not clear whether this represents a misdiagnosis or a true overlap between these related lung diseases. Almost 13% of COPDGene® subjects were diagnosed with asthma before the age of 40, an age when COPD would be unlikely.[11] These subjects had smoked less but had similar reduction in lung function, with less emphysema and more airway disease on CT scans compared to those with COPD alone. Genetic factors may be partially responsible for this COPD-asthma overlap.

In addition to these clinical distinctions among types of COPD patients, statistical methods can be used to define disease subtypes. A clustering analysis in COPDGene® found four subgroups: (1) resistant smokers with normal or near normal lung function and minimal emphysema on chest CT scans, (2) mild upper lobe predominant emphysema, (3) airway disease and (4) severe emphysema.[12] Genetic associations were found for these subtypes as well.

Genetic Studies

Decades of research have shown that COPD runs in families, which may suggest a genetic influence. However, cigarette smoking also runs in families. In fact, over 80% of COPDGene® subjects had parents who smoked.[13] Family history was a risk factor for COPD and was associated with more severe disease. Using advanced statistical methods and genomewide genetic data, investigators showed that genetic factors were responsible for a higher fraction of variation in lung function and COPD diagnosis than CT emphysema and gas trapping measurements.[14]

A genomewide association study (GWAS) evaluates hundreds of thousands of genetic markers across the human chromosomes on a single microchip. The GWAS from

Co-morbidities and Subtypes

There is a high prevalence of other diseases in COPD patients, due to their age and smoking history. Some of these illnesses directly influence COPD and vice versa. Thirteen percent of COPDGene® subjects reported a diagnosis of diabetes, and these subjects had lower lung function, reduced exercise capacity and poorer quality of life.[5] Cardiovascular disease is more frequent in COPD patients than in smokers without COPD, showing the connection is more than just the common risk factor of cigarette smoking.[10] Subjects with both cardiovascular disease and COPD also had a higher risk of exacerbations, reduced exercise capacity and lower quality of life.
COPDGene® has been combined with results from three other large COPD genetics studies (ECLIPSE, GenKOLS from Norway, and National Emphysema Treatment Trial/Normative Aging Study). Data from the first 1000 COPDGene® subjects were used to replicate the association with the gene FAM13A on chromosome 4[15] and to find a new COPD susceptibility region of chromosome 19q13.[16] The GWAS results from the entire COPDGene® Study were combined with these other populations in a meta-analysis which confirmed known COPD genes FAM13A, HHIP and IREB2, and found novel associations with RN3, TGFβ3 and MMP12, the latter two more specific for severe COPD.[17] Genetic studies of other important COPD-related outcomes are in progress.

A study evaluating RNA gene expression, as opposed to genetic variation in DNA, in white blood cells from a subset of COPDGene® subjects uncovered potential pathways involved in COPD such as immunity, inflammation and lipid metabolism.[18]

**Future Directions**

The combination of the clinical, imaging and genetic data collected in the first phase of the COPDGene® Study has provided valuable insight into COPD epidemiology, co-morbidities, subtypes and biologic mechanisms. The second phase of the study will show how these aspects change over time and how they interact to affect the progression of COPD. The important aim of using the clinical, imaging and molecular information to identify subtypes of COPD is a necessary first step towards the ultimate goal of personalized medicine for COPD patients. Continued collaborations with other COPD investigators, the NHLBI, the COPD Foundation, and the pharmaceutical industry will be essential to reach these objectives.
Attendees of the COPD9 USA conference will explore improving outcomes in the management of COPD through scientific presentations and unique networking opportunities.

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New Open Access COPD Journal Launched and Available

This May, in conjunction with its 10th anniversary commemoration, the COPD Foundation launched its new, open access, online journal—Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation.

The inaugural issue of the journal is accessible online at http://journal.copdfoundation.org and features:

• Eight review articles which discuss progress made in COPD over the past decade including discussions on COPD imaging, genetics, defining comorbidities, COPD treatments in the pipeline, the clinical characteristics of biomass smoke-associated COPD around the world and research and education provided by the Foundation and the National Heart, Blood, and Lung Institute.

• Six original research articles covering volume-controlled multi-detector CT repeatability; CT findings in nonobstructed spirometric smokers; comorbidities impact on clinical outcomes; dietary intake and COPD phenotypes; centrilobular and panlobular emphysema differences; and the effect of exercise intervention on gait in COPD.

• An update on the COPD Foundation Pocket Consultant Guide

The journal accepts original research articles, basic and clinical review articles, perspectives/short communications, practice guidelines related to COPD and letters to the editor. The journal publishes quarterly; however, articles are published online rapidly following peer review and editorial acceptance. Details of publication guidelines are outlined below.

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Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation publishes original papers on any aspect of chronic obstructive pulmonary disease including human clinical studies. All submissions must be in English. Manuscripts should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org).

The Journal is published in electronic format.

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  - Clinical
  - Basic
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  - Practice Guidelines Related to COPD
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To submit your manuscript, send it by email to COPD@njhealth.org. Manuscripts that do not conform to guidelines will be delayed or returned. All questions related to manuscripts should be addressed to:

Tina Watson, Editorial Assistant
Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation

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By virtue of submitting a manuscript to Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation, the authors certify that (a) the material is original, has not been published except in abstract form, and is not being considered for publication elsewhere, including publicly accessible websites or e-print servers, (b) all authors have read the manuscript and approve its submission, and (c) all clinical trials have been registered in a public trial registry.

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- A list of keywords that best represent the key topics of the article
- A statement of funding support for the article’s research and work including but not limited to grant funding, support sources, provision of equipment and supplies and role of the sponsor.

Abstract. A concise abstract of no more than 250 words is required.

Text. The body of the article should include an introduction and methods, results and discussion sections.

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Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation will not consider manuscripts that are funded in any part by tobacco companies.

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COPD Foundation Educational Resources

Pocket Consultant Guide

The COPD Foundation Pocket Consultant Guide is available in hard copy and as a smartphone App. We also encourage you to join the Pocket Consultant Guide Community and submit your questions and comments. We will use your input to create the next version of the Pocket Consultant Guide.

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Engage Our Experts at the COPD Pocket Consultant Guide Community Website

The COPD Foundation Pocket Consultant Guide (PCG) for the Diagnosis and Management of COPD was designed to be a practical tool to assist practicing clinicians in managing the diagnosis and treatment of COPD patients. The Guide is designed to aid in identifying patients for whom spirometry should be performed, how patients should be classified based on spirometry, what additional assessments should be performed and when and how these diagnostic evaluations should influence therapy.

“The PCG pocket cards and app address time constraints for providers, and that some of the more complex issues related to the illness cannot be discussed at length with the patient,” Walsh adds. “The Guide will evolve to help facilitate the best possible care for COPD patients.”

The associated PCG Online Community was launched on February 11, 2014. It allows physicians and other healthcare professionals to interact with our COPD experts and one another. Submit your questions and comments that will help inform future updates of the PCG card and app. This is your one-stop-shop for all things related to the PCG. Including access to order FREE pocket cards and a COPD Foundation prepared PowerPoint presentation slide deck for you to deliver a Grand Rounds presentations at your institution.

This community is led by well recognized thought leaders in COPD including Dr. Byron Thomashow, Dr. David Mannino, Dr. Stephen Rennard, Dr. Andrew McIvor, Dr. James Crapo, Dr. MeiLan Han, Dr. Neil Schachter, Dr. Barbara Yawn and many more. All members of the healthcare community are invited to become an active part of the discussions, so we can promote better COPD diagnosis and treatment through the PCG. We encourage you to join the FREE community at: http://pocketconsultantguide.copdfoundation.org

With the PCG app, healthcare professionals fill in a symptoms assessment, spirometry results and exacerbation history for each patient in order to access a therapy chart. The chart becomes smart and highlights further testing and/or therapy, based on the inputted patient information. The chart also stresses the importance of smoking cessation, vaccinations, exercise, testing for Alpha-1 and evaluating co-morbid conditions. The app has been updated in April 2014 to include the two new medication categories, three new medications and a toggle feature to switch between generic name drugs and trade name drugs. A free android version of the PCG app will be released in the summer of 2014.

“Healthcare providers face three significant challenges: identify those who remain undiagnosed; ensure that those who are already diagnosed are correctly diagnosed; and make sure that those with the correct diagnosis are getting the appropriate treatment,” says John W. Walsh, president and co-founder, COPDF. “While existing guidelines for COPD management are excellent, they are much too long for busy clinicians to use on a day-to-day basis.”

Come join the discussions with our COPD experts and learn how you can share this Guide with your colleagues for the betterment of your community!
Respiratory Therapists Seize the Day
Growing Awareness + Health Care Reform = Opportunities to do More for Those With COPD

Respiratory therapists (RTs) have long played an important role in the care of COPD patients. And perhaps just as long, they have lamented the fact that so many of these patients are diagnosed with the condition so late in the disease process that early interventions are out of the question and repeated hospitalizations are the norm.

Advances in care and treatment over the past decade, however, plus the new emphasis on lowering costs of care brought about by health care reform, have opened the door to a new way of thinking about this chronic respiratory condition and RTs have been among the first to walk through it. Working alongside patient advocates in the public arena they are helping to ensure more patients are diagnosed before it’s too late to impact the disease course. By teaming up with their colleagues in medicine and nursing they’re also carving out disease management programs aimed at equipping patients at any stage of the disease with the education and services they need to stay out of the revolving door of hospital admissions.

DRIVE4COPD

Launched in 2010, the national DRIVE4COPD campaign proved to be the perfect fit for RTs who wanted to reach more COPD patients while there was still time for lifestyle changes to make a big difference in prognosis. Largely through a partnership between the campaign and their professional organization, the American Association for Respiratory Care, they played a major role in the distribution of a simple, five question risk screener used to identify people who may have the disease but not know it.

The health expos and other events where DRIVE set up shop gave therapists the opportunity to offer one-on-one education on COPD to people considered at risk. By explaining the need for these individuals to visit their primary care physicians for more testing and reassuring them that there was much that could be done to slow the progression of the disease, they helped to create a growing population of COPD patients — one carrying the “early stage” label rather than the “end stage” label. Along the way they also got to visit with people who had already been diagnosed with the condition and educate them on the proper use of their inhalers and other respiratory medication devices.

Last year alone, RTs staffed more than 160 events in every state except Montana, reaching over 14,600 people. Since the inception of DRIVE4COPD in 2010, the campaign has screened more than 2.5 million people, with well over 60,000 of those screens credited to respiratory therapists.

Evolving Role

The evolving role for the respiratory therapist in the disease management arena has its roots firmly entrenched in the home care services and pulmonary rehabilitation programs RTs have staffed since the 1970s or even before. Going into patients’ homes on a regular basis, and working with them to regain lost abilities through pulmonary rehab, taught therapists that the conventional wisdom about COPD — that it was a progressive disease with no real hope of slowing — was not only wrong but self-defeating. When hospitals finally realized that something had to be done to reign in out of control costs for COPD exacerbations the time was right to pull the knowledge and experienced gained in the home care and pulmonary rehab settings into the hospital to create new services that would help patients better deal with their condition.

A study published in the January 2010 edition of the American Journal of Respiratory and Critical Care Medicine outlined the positive outcomes seen in a program established at five VA hospitals around the country. Investigators used registered respiratory therapists (RRTs) to provide 1.5 hour, one-on-one education sessions on COPD to veterans with COPD.

This article is special for the COPD Foundation’s 10-year anniversary.

(Continued on page 28)
How Can Grain Berry® Slow Digestion and New Plan Help Manage Your Weight?

Follow this easy 2-2-2™ Grain Berry Eating Regimen.

Simple carbs and concentrated sugars many of us consume in cakes, candy, sodas and many cereals and snacks speed up the digestive process and create sugar “spikes” in our blood. The recent article in The New York Times, titled, “Always Hungry? Here’s Why” suggests that it’s the simple carbs and added sugars that store fat in our tissues - not fats and calories per se.

In that regard, Grain Berry whole grain, sorghum bran antioxidant cereals, pasta and mixes along with fresh or frozen multi-colored vegetables and fruits digest slower in our bodies and prevent spikes in sugar content in our blood (lower glycemic index). Plus Grain Berry Cereals contain fewer added sugars than many other brands to begin with.

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2 Servings
Whole fruits and berries each day.
Also add to cereal.

2 Servings
Green and other color vegetables each day.
Results of the research, which was conducted among 743 patients with either a hospital admission or ED visit for COPD, chronic home oxygen use, or course of systemic corticosteroids for COPD in the past year, showed the educational intervention plus telephone follow up reduced COPD hospitalizations and emergency department visits by 41%, cardiac or other pulmonary hospitalizations by 49%, hospitalizations for all causes by 28%, and ED visits for all causes by 27%. A significant improvement in self-reported respiratory health status was seen as well.

Co-author Michael Caldwell, RRT, RN, played a key role in identifying RTs as the right clinicians to carry out the program. “When the protocol was being developed for the study we discussed what skill sets the case managers should possess,” said the VA manager of cardiopulmonary services. “Myself being a registered nurse and registered respiratory therapist allowed us to verify that a registered nurse possesses a general knowledge of lung disease, whereas respiratory therapists are specifically trained in the pathophysiology and treatment of lung disease, as well as work specifically with those patients every day.”

For example, the group noted that RRTs already have the knowledge to understand and interpret pulmonary function tests, a key measure used to identify the severity of a patient’s condition. “Registered nurses as a whole do not possess this knowledge,” said Caldwell. “We felt that it would take less time to train the respiratory therapists as opposed to registered nurses.”

ROAD to success

RTs are also playing a key role in the COPD disease management component of the Reversible Obstructive Airway Disease (ROAD) Center at the University of California, Davis, in Sacramento. The program begins while the patient is still in the hospital recovering from an acute exacerbation. The RRT case managers typically see patients over a four day period to provide education in nine key areas and they also refer patients to other services when appropriate, including smoking cessation, pulmonary rehabilitation, and pulmonary function testing.

Follow up calls go out to patients three to five days after discharge and then again every six to eight weeks thereafter to ensure patients have made follow up appointments with their primary care physicians and are complying with the medication plans established during the hospital visits. Every patient in the program leaves the hospital with an Action Plan to prevent exacerbations and a Rescue Plan to implement if he/she feels an exacerbation is imminent. Patients also receive a pager number they can call at any time between 7 a.m. and 8 p.m. for immediate assistance with questions or concerns.

The program was implemented in 2012 and outcomes over the first four months of operation showed COPD readmissions within 30 days of discharge dropped dramatically from 11-16% of cases to just 2.4%. Michelle Young, RRT, who serves as one of the COPD case managers, says these outcomes reflect the customized care patients receive in the program. “The most important service we provide is attention to the person, not just the disease,” she said. “We look at medications, assess effectiveness, and make changes based on the subjective information given by the patient.”

Stepping out of the hospital

At Indiana University Health in Indianapolis, respiratory therapists are taking COPD disease management out of the hospital altogether. Working through the health system’s Ambulatory Pulmonary Care Program, RTs travel to 20 separate locations operated by two affiliated medical groups, where they work under “treat, provide, order” protocols approved by the physicians that allow them to start and stop medications without going back to the doctor for approval. The goal is to help prevent the progression of the disease, relieve symptoms, improve exercise tolerance, improve health status and quality of life, reduce ED visits and
hospitalizations, and promote smoking cessation.

Visits range from comprehensive 90 minute sessions to shorter 30 minute rechecks and 60 minute smoking cessation counseling sessions. Emergency room utilization dropped to 2% per month after implementation of the program, representing an average yearly cost avoidance of $466,000, and compliance with COPD/spirometry testing reached the 90th percentile on HEDIS. “According to our physician survey, 100% of our physicians are satisfied with our services,” noted Debbie Koehl, MS, RRT-NPS, FAARC, who oversees pulmonary rehabilitation at the facility. “Our patient satisfaction survey indicates that patients feel their symptoms are better controlled, their quality of life has improved, and they now have the knowledge and tools they need to manage their condition.”

Up in Pennsylvania, the DASH program developed by Klingensmith HealthCare in Ford City uses RTs to assess, treat, and educate COPD patients in their homes. The initiative has reduced readmission rates from a historical range of 20-30% to 3% for patients who complete all three visits by day 30. Brian Carlin, MD, FAARC, helped to develop the program and believes these outcomes more than make up for the cost of running it. “In many instances reimbursement for performance of such services by a respiratory therapist are either unrecognized or uncovered or both,” said the physician. “Taking into account the ‘overall costs’ associated with a rehospitalization, the costs of having such a therapist available in such a program are truly minor.”

**More positive outcomes**

St. Luke’s Episcopal Hospital in Houston, TX, has developed an advanced role for the registered respiratory therapist called the “respiratory care specialist” or “RCS.” Likened to a “traffic cop,” the RCS is charged with monitoring inpatient care, providing specific education/training, and facilitating discharge for COPD patients who are treated in the hospital’s special care unit for people with the condition.

“The RCS also provides aftercare, with follow up phone calls to discharged patients to ensure patients have received home equipment and/or remember how medications should be taken,” said RT Manager Joy Hargett, BS, RRT. “Providing patients with a COPD Action Plan, a tool used to identify actions to improve lung health, is an excellent way to keep patients on track.” Referral to a pulmonary rehabilitation program is often made as well, and the RCS also encourages patients to follow up with their primary care physician post discharge and serves as the hospital contact person for patients once they are home.

Outcomes collected in 2009 and 2010 reported an improvement in net margin and length of stay for patients who were treated in the special care unit and received the services of the RCS.2,3

Becky Anderson, RRT, oversees a COPD disease management program at Sanford Medical Center in Fargo, ND, where respiratory therapists facilitate the work of the interdisciplinary team by providing care management and patient education services. They work with staff therapists to ensure protocols are initiated appropriately and the patient receives the aggressive treatment needed to bring an exacerbation under control as quickly as possible.

“The RT disease managers also partner with the patient to identify and resolve barriers to a successful transition from the hospital and then provide follow up after discharge,” she said. The program launched in 2008 and the impact on readmissions was significant. All cause readmissions went from 33% to just 6% in the first two years of operation and the delivery of recommended care in the inpatient setting climbed from 57% to more than 90%. The bottom line improved remarkably as well, going from a financial loss of about $650 per patient to a net profit of around $1000 per patient stay.

The five facility Wellstar Health System in Georgia has seen similar results from a disease management program led by RTs.
“Our respiratory therapists here at Wellstar really are the key folks that start out the Breathing Easier Program,” said RT Clinical Specialist Karen Sicard, RRT. “When the patient is admitted, they will actually identify those patients on admission diagnosis.” Therapists run patients through a pulmonary questionnaire to assess their knowledge of COPD and they also ask them what they do at home to care for themselves in an attempt to identify gaps in knowledge. A “Breathing Easier” booklet developed by the team assists with the education.

After implementation of the program, the health system’s COPD to COPD readmission rate went from 6.0 to 3.8 and their all cause readmission rate dropped from 20% to 18%.

Exponential growth

Clearly, the past decade has been one of exponential growth for the respiratory therapist involved in COPD. Thanks to the DRIVE4COPD campaign, they’ve been able to reach thousands of people with information and early screening, and the new roles they are taking on in the disease management arena are helping patients develop the self-management skills they need to stay healthy and out of the hospital. Hospitals and health systems are saving money as a result, and therapists themselves are finally fulfilling a mission they’ve had for decades — making sure more people with this chronic lung disease continue leading rewarding lives despite their COPD.

References
COPD Management in Primary Care: The Past Ten Years

Introduction

In the past 10 years COPD has become the third leading cause of death in the United States (https://www.nhlbi.nih.gov/health/health-topics/topics/copd/) and the fourth leading cause of adult deaths in the world (http://www.internationalcopd.org/materials/patients/learn/facts.aspx)

Each year since 2000, more US women than men have died from COPD (http://www.lung.org/lung-disease/disparities-reports/risе-of-copd-in-women/). But not all the news is bad. A major new class of bronchodilators, long acting anti-muscarincs, has been approved by the FDA, as well as a new class of drugs for exacerbations in people with chronic bronchitis, the PDE-4 inhibitors, Medicare has agreed to cover pulmonary rehabilitation services, the Behavioral Risk Factor Survey (BFRSS) has included questions about COPD on its annual survey, the American Lung Association (ALA) released a first ever report on COPD in women (http://www.lung.org/lung-disease/disparities-reports/risе-of-copd-in-women/), practice guidelines for COPD have been released by the ATS/ERS, IPAG, GOLD and the COPD Foundation recognizing the importance of not just lung function but the patient’s symptom burden and risk of exacerbations in selecting therapy and new tools are available for rapid assessment of lung function and practice tools are available for supporting COPD management. The last ten years have brought us a clear concise approach to the management of COPD, from diagnosis to end of life care.

But have these new resources made their way from bench to the bedside and the community? For many years we have recognized that the majority of COPD patients are seen in primary care practices. We also know that many patients with unrecognized and untreated or undertreated COPD receive their care in primary care practices. The reasons that those patients remain unrecognized and undertreated have been studied and in part are due to failure to incorporate the advances listed above into daily practice. However, primary care has made some progress in improving the diagnosis, the management and the lives of people with COPD.

Diagnosis

The diagnosis of COPD is considered in a patient with risk factors and symptoms, an appropriate medical examination and confirmed with spirometry. No longer does a patient have to be referred from primary care to a lung function laboratory for this test since an increasing number of physician’s offices have incorporated the less expensive, more user friendly version of the spirometer. Many of the newer spirometry devices also have the ability to communicate directly to an electronic medical record (EMR) making data collection and use easier. Discussions around spirometry results may even assist in smoking cessation discussions. Like all diagnostic testing, the results and interpretation of results requires vigorous standards to assure accurate assessment and medical evaluation. In a few sites, collaborative oversight projects between primary care physicians and pulmonologists have been developed to facilitate appropriate use and interpretation of spirometry testing. Many additional opportunities for such collaboration exist.

The diagnostic value for COPD has long been a post bronchodilator FEV1/FVC ratio of <70% in the appropriate patient. During the past 10 years, there has been a move supported by several primary care and specialty physicians towards a post broncho-dilator FEV1/FVC ratio of...
less than lower limit of normal instead to prevent the over diagnosis of COPD in our elderly population whose lungs are stiffening due to age and not disease.

**COPD screening and case finding**

While spirometry is a central tool in assessing and diagnosing COPD, primary care physicians and other clinicians must still decide on whom to order spirometry. Sometimes labelled as case finding, tools have been developed to identify those appropriate for spirometry assessment. Several validated tools including the COPD Foundation Screener (www.copdfoundation.org), the Canada Lung Health test http://www.lung.ca/diseases-maladies/copd-mpoc/signs-signes/COPDQuiz-MPOCQuiz_e.php (called by similar names in other countries) encourage the use of spirometry in patients who are smokers or ex-smokers over the age of 40 with any symptom of cough, wheeze, sputum, dyspnea or frequent respiratory tract infections. The new COPD Foundation guidelines would add smokers and ex-smokers with marked premature wrinkles to those risk factors. But how to identify those patients with the risk factors remains less widely accepted.

In some settings assessing who is a candidate for spirometry to evaluate for COPD is called screening and over the past 10 years several COPD screening studies have been completed using a variety of screening instruments. Screening tools are intended to be used in the entire population making it unnecessary to pre-identify those with risk factors since the tools include the most common risk factors. The screening process can identify new cases of COPD and result in further evaluation.

Whether case identification or screening impacts outcomes remains controversial and will continue to be a priority for study in the next few years. Currently 2 of 3 patients with COPD are not recognized until they have lost over 50% of their lung function. Earlier diagnosis might improve outcomes, especially improving symptoms and reducing exacerbation recurrence. Smoking cessation could prevent lung function loss. It would seem that common sense supports screening or case identification but then common sense has failed the evidence-based test previously.

**Subtypes or phenotypes of COPD**

Primary care physicians have recognized the wide range of risk factors, disease expression and progression of patients with COPD. These variations have been labelled as the phenotypes of COPD including the recently described frequent exacerbators. This is the main phenotypical group that has been incorporated into several of the COPD guidelines with recommendations for immediate use of exacerbation prevention therapy.

Recently a newer category has been created and discussed in both international asthma and COPD guidelines, the Asthma-COPD Overlap Syndrome. The recognition that patients can have components of both are beyond the scope of this article, but these patients are clearly more complicated and require aspects of therapy both common to each illness as well as separating out the differences.

**Treatment of people with COPD**

The goals of therapy for COPD have advanced considerably over the last ten years. From a condition that was reviewed with a nihilistic view of a condition that was progressive and untreatable, to one that is preventable and treatable with multiple new advances. See figure A for the goals of therapy.

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Goals of Management of COPD

- Prevent disease progression
- Alleviate breathlessness and other respiratory symptoms
- Improve exercise tolerance and daily activity
- Reduce frequency and severity of exacerbations
- Treat exacerbations and complications of the disease
- Improve health status
- Reduce mortality

The goals of therapy for COPD have advanced considerably over the last ten years. From a condition that was reviewed with a nihilistic view of a condition that was progressive and untreatable, to one that is preventable and treatable with multiple new advances. See figure A for the goals of therapy.
Pharmacological therapy

The most common symptom in COPD is that of dyspnea. As such, our first goal is to improve dyspnea. A huge advantage has been the movement from the use of short acting bronchodilator to the use of Long Acting Bronchodilators.\(^\text{29}\) The last few years have granted us a plethora of choices including LABAs, LAMAs and more recently combination LABA/LAMAs.\(^\text{30}\) These allow us to attempt to maximize bronchodilation, improve obstruction and relieve air trapping. Keeping the lungs open allows better quality of life and even decrease exacerbations.

From current control, we move to the concept of ‘future risk’\(^\text{31}\) and as such we are attempting to prevent exacerbations of COPD with the safest combination of medications possible, preventing the future risk of an exacerbation as well as any future risk of side effects of medications. Two anti-inflammatory medication classes are used to reduce exacerbations as part of the pharmacologic prevention strategy. Inhaled corticosteroids (in combination with LABAs) have been shown to reduce as many as 25% of exacerbations per year.\(^\text{32-34}\)

The studies for these medications usually included patients with frequent exacerbations and an FEV\(_1\) less than 60%. Another, less commonly used anti-inflammatory is Roflumilast, a PDE-4 inhibitor. This drug can decrease exacerbations by 25% on top of LABAs\(^\text{35}\) in those COPD patients with the phenotype of chronic bronchitis; i.e., cough and sputum continuously for 3 months or longer in two consecutive years. Other studies have shown recently that use of daily Azithromycin can also prevent exacerbations but at the risk of potentially more antibiotic resistance or even some hearing loss.\(^\text{36}\) It is not clear what happens after the one year of therapy studied.\(^\text{37}\)

Non-pharmacologic therapies

Smoking cessation support, pulmonary rehabilitation, immunizations and the recognition and management of co-morbidities have become central to COPD management. Smoking cessation strategies include not only addressing smoking at each visit (the 5A’s of asking, advising, assessing, assist, and arrange follow up [http://www.publichealth.va.gov/smoking/clinicaltopics.asp] but also referring to formal smoking cessation programs and prescribing adjunct support such as nicotine replacement therapy, buproprion and varenicline. Newer replacement devices such as E cigarettes are promising for replacement of cigarettes but require significant study before they will be ready for a place in usual care of those who are nicotine addicted [http://guardianlv.com/2014/03/smoking-cessation-may-not-be-linked-to-e-cigarettes/?nb=1]

Pulmonary rehabilitation has been shown to be more effective than anything else we have to offer to improve exercise tolerance and quality of life. Pulmonary rehabilitation can also prevent hospital admissions and lower readmissions.\(^\text{38}\) While widely recommended for those at all stages of COPD requiring daily medication therapy, pulmonary rehabilitation is often not available. It was hoped that Medicare reimbursement for pulmonary rehabilitation would improve access but cuts in the funding levels have made the service a financial liability for many organizations and many programs have actually closed in the recent past. Community and home based programs are currently being developed to augment the programs in health care facilities with the hope that pulmonary rehabilitation with its support of education, exercise program and nutritional education will become a standard.

Annual influenza immunization (University of Michigan Health System. Chronic Obstructive Pulmonary Disease available at www.med.umich.edu/1info/FHP/practiceguidelines/copd/copd.pdf) has shown to reduce both exacerbations and pneumonia in individuals with COPD. The impact of the older pneumococcal vaccine, Pneumovax 23 has been less clear. Newer immunization schedules with additional boosting doses of the newer varieties of conjugated vaccine are being studied.\(^\text{39}\) Preliminary results of a study in Netherlands\(^\text{40}\) of almost 85000 community dwelling patients over 65 showed reduced pneumonia in those vaccinated but did not include any specific results for people with COPD.
Exacerbation risk management and treatment

Exacerbation prevention is recommended for those with greater than 40 to 50% loss of lung function and for those with a history of 2 or more exacerbations or a COPD hospitalization in the previous year. Smoking cessation and immunization are non-pharmacological mainstays of exacerbation prevention. Inhaled steroids (in combination with LABAs) are the primary therapy recommended for exacerbation prevention. While having shown efficacy in exacerbation prevention, ICS also have side effects both local and systematic that must be considered. Local side effects are often easily treated and include thrush, dysphonia, pharyngitis and secondary bronchospasm. Systemic side effects include increase risk of glaucoma and cataracts. Tuberculosis, osteoporosis, and even new onset diabetes mellitus. Other potential systemic side effects include increased risk of pneumonia that may rival the benefit of ICS in preventing COPD hospitalizations. Other potential systemic side effects include increased risk of pneumonia. Currently the concerns appear to have had limited impact in primary care physicians’ decisions to use ICS with many individuals without risk factors for exacerbations also being prescribed ICS. Continued study and practice support for informed decision making are required to identify a way to incorporate the risk benefit decision into selection of exacerbation risk reduction therapy, as we are currently seeing an overtreatment with ICS in patients with COPD.

Roflumilast is the first PDE-4 inhibitor to be approved for COPD therapy. Its use is limited to individuals with chronic bronchitis and high risk of exacerbation. Use in primary care practices is modest due to lack of familiarity with the drug and the frequency of GI side effects including diarrhea and nausea. While these symptoms may be transient, they are disturbing to the patient. The risk benefit of exacerbation reduction and management of common side effects may limit use of this drug to primarily specialty practices.

Treatment of exacerbations has become more straightforward with the likelihood of bacterial infection and thus antibiotic efficacy is higher in those with all three of the ‘Anthonissen criteria’ which include increased sputum, coloured sputum and dyspnea. Oral steroids in the treatment of exacerbations for those with FEV1 under 60% have been shown to increase time to the next exacerbation and improve recovery. A recent study suggests a regimen of 30 mg po daily x 5 days to be not inferior to any other. Antibiotic choice can be based on risk of antibiotic resistance which can be ascertained by recent antibiotic use, comorbidities, and the degree of lung function. Five days of antibiotics are likely plenty for this superficial infection, but longer use would be needed for actual pneumonia.

The multi morbidity of COPD patients

A significant factor in patients with COPD is the systemic inflammation that occurs and likely is responsible for part or most of the common comorbidities in these patients. Cardiovascular disease, nutritional issues, peripheral vascular disease, osteoporosis, mood and anxiety all need to be cared for to optimize our patients’ outcomes. Studies have clearly shown an improved outcome in treating patients with COPD with statins as a significant cause of mortality in COPD patients is related to the cardiovascular system.

Practice tools

In primary care, physicians and the medical home team must deal with dozens of chronic conditions each week. Trying to remember how to assess each condition and to quantify patients’ progress is often facilitated by practice tools that can be given to patients early in the visit to facilitate discussions with the patient and their families and provide longitudinal data on disease progression. New scales to help us in following our patients also allow us to speak a similar language to each other. The MRC scale allows us to define by the level of disability. The CAT score (http://www.catestonline.org/) allows a numerical score to help assess visit to visit changes in the patient. This eight part score includes four questions regarding symptoms and four questions regarding quality of life metrics. The Clinical COPD Questionnaire (CCQ) is preferred by others.
Conclusions

We have the ability to make a diagnosis, and to actually change the course of the disease by assisting in smoking cessation, maximize bronchodilation to reduce symptoms and use a myriad of techniques to attempt to reduce exacerbations. The last ten years have given us many lessons in COPD; this is no longer a hopeless condition. In those with hypoxemia, the use of Oxygen can be life prolonging. And in those who have reached the end of the line, palliative advanced directive planning can be used to improve quality of life up until the end. The last ten years have shown us that we can make a difference.

References


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The COPD Foundation is the national not for profit organization solely dedicated to representing individuals with COPD in the United States. The COPD Foundation’s Medical and Scientific Advisory Council (MASAC) and Clinical Advisory Committee (CAC) members include leading COPD clinicians and researchers in the world.

Whereas the community of individuals with Chronic Obstructive Pulmonary Disease (COPD) depend on respiratory pharmacologics for the treatment of their destructive lung disease, and

Whereas physician choice and patient choice and access to appropriate medical care are rights of patients and central to patient-physician interaction, and

Whereas similar respiratory pharmacologics have been determined by the U.S. Food and Drug Administration to be distinct from one another, even if they primarily contain a similar active ingredients in the same class of respiratory pharmacologics and

Whereas it is our accumulated clinical experience that there are individuals with COPD with adverse experiences caused by an alternative product in the same class of respiratory pharmacologics who require a different product or who prefer one of the available products over others after long experience and achievement of disease stabilization with a particular product, and

Whereas it has come to our attention that some payers and employers have decided to provide only a single product in the same class of respiratory pharmacologics for the treatment of COPD and others have made it substantially difficult to continue on a particular preferred product by offering economic incentives to the payer who implements restrictions, and

Whereas there is considerable disruption of the clinical care of individuals who are forced to switch product as well as considerable emotional distress that denies patients access to potentially effective treatment,

the COPD Foundation’s MASAC and CAC hereby resolves that it is unacceptable to limit access of respiratory pharmacologics in any way and especially to a single product in that class when several options are available, or require that individuals provide documentation of failure or adverse experience with a particular product in order to receive or continue receiving their drug of choice.
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INDICATION FOR GLASSIA

GLASSIA is an Alpha₁-Proteinase Inhibitor (Human) (Alpha₁-PI) indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of Alpha₁-PI (alpha₁-antitrypsin deficiency). GLASSIA increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha₁-PI. The effect of augmentation therapy with any Alpha₁-PI, including GLASSIA, on pulmonary exacerbations and on the progression of emphysema in alpha₁-antitrypsin deficiency has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available.

GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha₁-PI deficiency has not been established.

DETAILED IMPORTANT RISK INFORMATION FOR GLASSIA

HYPERSENSITIVITY

- GLASSIA is contraindicated in immunoglobulin A (IgA) deficient patients with antibodies against IgA or individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha₁-PI products.
- Hypersensitivity reactions have been reported in patients following administration. Patients should be closely followed and vital signs monitored continuously. Discontinue the infusion if hypersensitivity symptoms occur and administer appropriate emergency treatment.

TRANSMISSION OF INFECTIOUS AGENTS

- GLASSIA is derived from pooled human plasma and may carry a risk of transmitting infectious agents such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. Despite manufacturing steps designed to minimize the risk of viral transmission, such products may still potentially transmit human pathogenic agents.

USE DURING PREGNANCY

- GLASSIA should not be given to pregnant women unless clearly needed, as reproduction studies have not been done in animals or humans.

ADVERSE REACTIONS

- The serious adverse reaction observed during clinical trials was exacerbation of chronic obstructive pulmonary disease (COPD). The most common adverse reactions occurring in >0.5% of infusions in clinical trials were headache and upper respiratory infection.

Please see GLASSIA Brief Summary of Full Prescribing Information on the adjacent page.

GLASSIA [Alpha1-Proteinase Inhibitor (Human)]

Injection Solution - For Intravenous Use Only

Brief Summary of Prescribing Information. Please see package insert for full prescribing information.

INDICATIONS AND USAGE

GLASSIA is an Alpha1-Proteinase Inhibitor (Human) (Alpha1-PI) indicated for chronic augmentation and maintenance therapy in adults with clinically evident emphysema due to severe congenital deficiency of Alpha1-PI (alpha-antitrypsin deficiency). GLASSIA increases antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid levels of Alpha1-PI.

- The effect of augmentation therapy with any Alpha1-PI product, including GLASSIA, on the progression of chronic obstructive pulmonary disease (COPD) has not been conclusively demonstrated in randomized, controlled clinical trials.
- Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals with GLASSIA are not available.
- GLASSIA is not indicated as therapy for lung disease in patients in whom severe Alpha1-PI deficiency has not been conclusively established.

DOSE AND ADMINISTRATION

- For Intravenous Use Only.
  - Use aseptic technique for all preparation and administration steps.
  - Dose = 60 mg/kg body weight intravenously once weekly.
  - Administer at a rate not to exceed 0.2 mL/kg body weight per minute, depending on patient response and comfort.
  - Dose ranging studies using efficacy endpoints have not been performed.

CONTRAINDICATIONS

GLASSIA is contraindicated in immunoglobulin A (IgA) deficient patients with antibodies against IgA or in individuals with a history of severe immediate hypersensitivity reactions, including anaphylaxis, to Alpha1-PI products.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions

GLASSIA may contain trace amounts of IgA. Patients with selective or severe IgA deficiency and/or known antibodies to IgA have a greater risk of developing severe hypersensitivity and anaphylactotic reactions. Monitor vital signs continuously and observe the patient carefully throughout the infusion. Discontinue the infusion if hypersensitivity symptoms occur and administer appropriate emergency treatment. Have epinephrine and other appropriate supportive therapy available for the treatment of any acute anaphylactic or anaphylactoid reaction.

Transmissible Infectious Agents

Because this product is made from human plasma, it may carry a risk of transmitting infectious agents, such as viruses, the variant Creutzfeldt-Jakob disease (vCJD), and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. The risk of transmitting an infectious agent has been minimized by screening plasma donors, by testing the product and removing certain viruses during the manufacturing process (see Description [11] in full prescribing information for viral reduction measures). Despite these measures, such products may still potentially transmit human pathogenic agents.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Kamada Ltd. at 1-866-GLASSIA or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

- No seroconversions for hepatitis B or C (HBV or HCV) or human immunodeficiency virus (HIV) or any other known infectious agent were reported with the use of GLASSIA during the clinical trials.

ADVERSE REACTIONS

The serious adverse reaction observed during clinical trials with GLASSIA was exacerbation of chronic obstructive pulmonary disease (COPD).

The most common adverse reactions (>0.5% of infusions) in clinical trials were headache (6 of 960 infusions or 0.6%) and upper respiratory infection (8 of 960 infusions or 0.8%).

An adverse reaction is any adverse event which met any of the following criteria: (a) an adverse event that began within 72 hours following the end of product infusion, or (b) an adverse event considered by either the investigator or sponsor to be at least possibly related to product administration, or (c) an adverse event for which causality assessment was missing or indeterminate.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of GLASSIA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea
- Gastrointestinal Disorders: Nausea
- General Disorders and Administration Site Conditions: Fatigue

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with GLASSIA. It is also not known whether GLASSIA can cause fetal harm when administered to pregnant women or can affect reproductive capacity. GLASSIA should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether Alpha1-PI is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GLASSIA is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Clinical trials of GLASSIA included 11 subjects of 65 years of age or older. This number of subjects was not sufficient to determine whether they respond differently from younger subjects. As for all patients, dosing for geriatric patients should be appropriate to their overall situation. Safety and effectiveness in patients over 65 years of age have not been established.

PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions, including hives, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis. Advise patients to discontinue use of the product and contact their physician and/or seek immediate emergency care, depending on the severity of the reaction, if these symptoms occur.
- Inform patients that GLASSIA is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the risk of GLASSIA transmitting an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing (see Warnings and Precautions). Symptoms of a possible virus infection include headache, fever, nausea, vomiting, weakness, malaise, diarrhea, or, in the case of hepatitis, jaundice.
- Inform patients that administration of GLASSIA has been demonstrated to raise the plasma level of Alpha1-PI, but that the effect of this augmentation on the frequency of pulmonary exacerbations and on the rate of progression of emphysema has not been established by clinical trials.

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