VOLUME 3 | ISSUE 7 | NOVEMBER 2013

L | E | C | O | M Point

WELCOME TO
A DRUG INFORMATION SOURCE DIRECT AND TO THE POINT

COPD awareness

Keith Sawh, PharmD Candidate; Marcus Campbell, PharmD, BC-ADM

Chronic Obstructive Pulmonary Disease (COPD) is an airway disease characterized by long term progressive airflow limitation. The most common symptoms exhibited by COPD patients include dyspnea, chronic cough with sputum production, tiredness, chest tightness, and limitations of activity. The National Heart, Lung, and Blood Institute (NHLBI) estimates that 24 million Americans suffer from COPD, and half of them remain undiagnosed.[1] COPD is the third leading cause of death in the Unites States with direct and indirect medical costs equating to approximately $50 billion annually.[1]

The goals of COPD management aim to improve symptoms, lung function, and health status and to reduce exacerbations, and mortality. With the exception of smoking cessation, there is no pharmacological treatment that has been shown to conclusively modify the rate of decline in lung function or disease progression.[2]

Treatment plans based on the updated Global Initiative for Obstructive Lung Disease (GOLD) guidelines now place patients in 1 of 4 groups (A, B, C or D) based on symptoms, degree of airflow limitations, risk of exacerbations and comorbidities.[2] This is a change from the previous guideline revision which used spirometry alone to classify disease severity. However, the approach to treatment remains relatively unchanged.

Table 1 outlines primary pharmacotherapeutic options used in the management of COPD. In an effort to improve patient compliance, different pharmacological classes of COPD medications are being combined into single inhalers that are administered once daily. Recently, several new COPD treatment options have been introduced. This November during National COPD Awareness Month, LECOM CDIR offers readers an analysis of recent advances in the COPD arena.

<Click for References>

Table 1: Primary pharmacotherapeutic options used in the management of COPD

Bronchodilators Inhaled β-2 agonists & Inhaled anti-muscarinic agents	• First line treatment option and cornerstone of pharmacologic therapy • As needed or regular basis to reduce symptoms • Long-acting formulation are preferred and more effective than short-acting formulations at producing maintained symptom relief • Combination of different pharmacological classes may improve symptoms more than increasing the dose of monotherapy • Treatment with theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable.
Inhaled corticosteroids	• Regular treatment with ICS improves symptoms, lung functions and quality of life. It reduces frequency of exacerbations for those with $FEV_1 < 60\%$ • Withdrawal may lead to exacerbations in some patients
Phosphodiesterase-4 inhibitors	• Less effective and less well tolerated than inhaled long-acting bronchodilators • Modest bronchodilator effect and some symptomatic benefit compared with placebo in stable COPD. (Low dose theophylline reduces exacerbations but does not improve post-bronchodilator lung function)

A novel COPD medication

Keith Sawh, PharmD Candidate; Marcus Campbell, PharmD, BC-ADM

Presently, no pharmacological treatment is shown to modify the rate of decline in lung function or disease progression. Patients are commonly treated with bronchodilators to improve symptoms and reduce exacerbations: long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs). LAMAs and LABAs can be used as monotherapy or in combination depending on the severity of the disease.

A growing body of evidence shows that LAMA and LABA co-administration is more effective than using either drug class alone. Co-administration has been shown to improve lung function (FEV1), symptoms, resting and dynamic hyperinflation, exercise capacity, and reduce exacerbations.[3]

Other potential benefits of co-administration include reduced need for rescue medication compared with monotherapy, and decreased risk of adverse effects compared with increasing the dose of a single bronchodilator.

Recently, an FDA committee voted to recommend approval of a new combination product containing a LAMA (umeclidinium) and a LABA (vilanterol). The committee determined that the efficacy and safety data provided substantial evidence to support approval of umeclidinium/vilanterol (UMEC/VI, 62.5/25 mcg dose) for the long-acting, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.[4] Anoro Ellipta is the proprietary name for UMEC/VI, administered using the Ellipta inhaler. GlaxoSmithKline and Theravance, Inc. will be marketing this novel product.[4]

Phase 3 studies of UMEC/VI in patients with chronic COPD included two 24-week efficacy studies that compared the combination, its components and placebo as well as two 24-week active comparator studies that compared the combination to tiotropium for the maintenance treatment of COPD. For all 4 studies, the primary outcome was trough FEV1 at the end of 24 weeks, and inclusion criteria consisted of post bronchodilator FEV1/FVC ration <0.70, post bronchodilator FEV1 ≤70% predicted, and modified Medical Research Council (mMRC) dyspnea scores ≥2. Two doses of UMEC/VI, 62.5/25 and 125/25 mcg were evaluated, and both doses were found to be similar with regard to efficacy and safety in the overall Phase 3 study population.

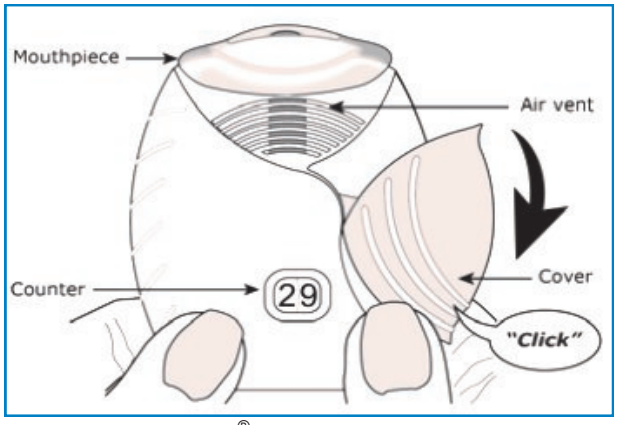


Figure 1: The Ellipta® dry powder inhaler

These UMEC/VI clinical trials involved over 4500 COPD patients. The most frequently reported adverse events across all treatment arms (including placebo) were headache, nasopharyngitis, cough, upper respiratory tract infection, and back pain. COPD exacerbation was the most common serious adverse event reported.

While Anoro Ellipta is not yet approved, it is the first product that delivers dual long-acting bronchodilators (LAMA AND LABA) via single inhaler device administered once daily. If the FDA follows the recommendation of their advisory committee and the product gains approval, it may offer a simplified therapeutic option for patients that require dual long-acting bronchodilator therapy for control of their COPD.

<Click for References>

Duration of systemic glucocorticoid therapy for acute COPD exacerbations

Camille Zambrana, PharmD Candidate; Marcus Campbell, PharmD, BC-ADM

Patients with COPD experience exacerbations approximately 1 to 2 times per year; those with frequent episodes are reported to have a more rapid decline in overall lung function. Exacerbations are triggered by a number of factors (i.e., exposure to pollutants and interruption of maintenance therapy), but the majority of episodes are caused by bacterial and viral respiratory tract infections.[1]

Standard therapy for the treatment of COPD exacerbations is directed towards minimizing the impact of the current episode and preventing future occurrences. The Global Initiative for Obstructive Lung Disease (GOLD) treatment guidelines recommend a 10-14 day course of systemic glucocorticoid therapy, a recommendation which is based on a trial published In 1999. In recent years, experts have questioned whether 10-14 days increases risk of side effects and mortality, while failing to provide additional therapeutic benefit.[2,3]

The REDUCE Trial was designed to investigate whether a 5-day course was non-inferior to a 14-day course of systemic glucocorticoids for the treatment of COPD exacerbations. A total of 314 patients, presenting to the emergency department with an exacerbation, were randomized to either a conventional therapy group or a short-term therapy group. The inclusion criteria were defined as at least 2 of the following: 1) change in

(Continued on page 4)

Effectiveness of vilanterol/fluticasone furoate as once daily dosing in COPD patients

Wycliffe Mugoya, PharmD Candidate; Marcus Campbell, PharmD, BC-ADM, Ryan Wargo, PharmD, BCACP

Recently, FDA approved GlaxoSmithKline's Breo Ellipta; an inhaled corticosteroid and long-acting beta agonist (ICS/LABA) combination product for long-term maintenance therapy in COPD patients. Breo Ellipta contains 100 mcg of fluticasone furoate and 25 mcg of vilanterol, which is administered via dry powder inhaler once daily. Prior to Breo Ellipta, the only ICS/LABA combination products (Advair® and Symbicort®) required twice daily dosing; this prompted research for a once daily alternative to reduce patient burden and improve compliance. Approval of the new product was based on several dose-ranging trials and four confirmatory trials in subjects with COPD.[3] Including two, 24-week, randomized, double-blind, placebo-controlled trials designed to evaluate the effects on lung function of fluticasone furoate and vilanterol (FF/VI) combination in comparison to single ingredient fluticasone fuoroate, vilanterol, and placebo were conducted (Table 1).

In addition two, randomized, double-blind, 52-week trials designed to evaluate the effect of FF/VI on the rate of moderate and severe COPD exacerbations were conducted. After completing a run-in phase, patients were assigned to take FF/VI 100/25 mcg, FF/VI 200/25 mcg, FF/VI 50/25 mcg, or vilanterol 25 mcg. The primary endpoint for both trials was annual rate of moderate or severe exacerbations of COPD. Exacerbations were considered moderate if treatment with systemic corticosteroids and/or antibiotics was required and were considered to be severe if hospitalization was required. In both trials patients with FF/VI 100/25 mcg had a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol alone.[3] The safety and efficacy of Breo Ellipta has been evaluated in 7,700 subjects with COPD.[3]

November is National COPD Awareness Month!

A major barrier to effective COPD management is patient compliance making the arrival of a once-daily treatment an attractive option for healthcare providers. The most common adverse effects associated with Breo Ellipta include nasopharyngitis, upper respiratory tract infections, headache, and oral candidiasis.[3] Serious adverse events include pneumonia and reduction in bone mineral density.[3] Breo Ellipta carries the same black box warning as other long-acting beta agonists regarding an increase in the risk for asthma related deaths. As a result, Breo Ellipta is not indicated for the treatment of asthma.

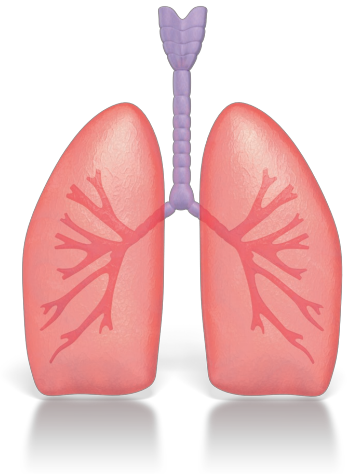
The addition of a once-daily ICS/LABA combination inhaler is a positive advancement in the treatment of COPD. It offers an alternative to existing twice-daily products that are currently first line agents for treatment of patients at high risk for COPD exacerbation based on current GOLD guidelines.[1]

< Click here for references>

Table 1: Trials designed to evaluate the effects of FF/VI on lung function[3]

Treatment	N	Weighted Mean FEV1 (0-4h) (mL) Difference from Placebo (95% CI)	Weighted Mean FEV1 (0-4h) (mL) Difference from FF 100 mcg (95% CI)	Weighted Mean FEV1 (0-4h) (mL) Difference from FF 200 mcg (95% CI)	Trough FEV1 (mL) Difference from Placebo (95% CI)	Trough FEV1 (mL) Difference from Vilanterol 25 mcg (95% CI)
Trial 1						
FF/VI 100 mcg/25 mcg	204	214 (161, 266)	168 (116, 220)	—	144 (91, 197)	45 (-8, 97)
FF/VI 200 mcg/25 mcg	205	209 (157, 261)	—	168 (117, 219)	131 (80, 183)	32 (-19, 83)
Trial 2						
FF/VI 100 mcg/25 mcg	206	173 (123, 224)	120 (70, 170)	—	115 (60, 169)	48 (-6, 102)

FEV1-forced expiratory volume in 1 second; FF-fluticasone furoate; VI-vilanterol ; CI-confidence interval; COPD-chronic obstructive pulmonary disorder



(Continued from page 2)

baseline dyspnea, cough or sputum quantity or purulence 2) age > 40, or 3) smoking history of ≥ 20 pack years. Patients with a history of asthma, FEV_1/FEV > 70% prior to randomization, and presence of pneumonia were excluded from the study. Eligible patients were stratified based on age, previous glucocorticoids use, severity of disease and trial site.[3]

Patients in the short-term group received corticosteroids for 5 days and a placebo for the remaining 9 days, whereas the conventional group received a full 14-day course of therapy. The first dose was given IV (40 mg methylprednisolone) to facilitate administration to patients in distress; subsequent doses were given orally (40 mg prednisone). All patients also received a broad-spectrum antibiotic for 7 days and nebulized short-acting bronchodilators 4-6 times/day while hospitalized.

The primary end point was time to re-exacerbation within 180 days of treatment. Secondary outcomes included all-cause mortality, length of hospital stay, and change in FEV_1. Glucocorticoid-associated adverse effects, such as new or worsening hyperglycemia, hypertension, and/or infection were recorded. End points and adverse effects were assessed daily during hospitalization then again on days 6, 15, 30, 90, and 180.[3]

Results indicated that the primary endpoint was reached by 35.9% of patients in the short-term group as compared to 36.8% in the conventional group (p=0.006). In terms of secondary outcomes, no significant difference in mortality was observed among the two groups.

A significant improvement in FEV_1 from baseline was seen with both treatment groups (p<0.001) and remained stable throughout the follow up period. Those in the short-term treatment group had shorter hospital stays (p=0.04) as compared to the conventional group. While the short-term group displayed a slightly more favorable glucocorticoid-associated adverse effect profile, the difference in cases of new or worsening hyperglycemia, hypertension, and infection were statistically insignificant (p>0.99).[3]

A 5-day course of glucocorticoids was found to be non-inferior to a 14-day course in treating patients requiring hospitalization for acute COPD exacerbations. The study design aimed to limit the risk of confounding by administering antibiotics to all patients as well as nebulized short-acting bronchodilators 4-6 times per day while hospitalized. However, it is difficult to determine the influence these medications had on the final results.[3]

The results of this particular trial, which implemented sound non-inferiority criteria and utilized appropriate dosing, support the decision by practitioners to opt for a shorter duration of systemic steroid therapy when treating acute COPD exacerbations. The practice could limit cumulative exposure to glucocorticoids and the numerous adverse effects related to their long-term use.

<Click here for references>

World COPD Day 2013

November 20, 2013

Remember to submit your drug information questions to the CDIR

Consistent with LECOM's core value of creating student-centered education, the **LECOM** School of Pharmacy offers two distinct learning pathways for the Doctor of Pharmacy (PharmD) degree providing students the option of choosing a pathway most suited to their learning needs. In Erie, PA, an accelerated three-year pathway is offered enabling students to complete the PharmD degree in three calendar years; in Bradenton, FL, a traditional four-year pathway is offered. Both curricula offer the same spectrum of didactic courses, credit hours, and experiential education and experiences. The full array of supporting services and state-of-the-art physical facilities exist at both campuses.

Managing Editor & Director CDIR: Marcus W. Campbell, PharmD, BC-ADM

Drug Info Team: Ryan Wargo, PharmD, BCACP; Danielle Debias, PharmD; Justin Scholl, PharmD; Kathryn Samai, PharmD, BCPS; Mitchelle Rodriguez, PharmD; Michael Mueller, Ph.D.; Katherine Tromp, PharmD; Abbey Powers, PharmD; Antonia Vilella, PharmD, BCPS; Stephanie Peshek, PharmD; Julie Wilkinson, PharmD, BCPS; Alejandro Vazquez, PharmD; Shalyn Quigley, PharmD

LECOM Bradenton
5000 Lakewood Ranch Blvd.

941-756-0690 Phone
941-782-5721 Fax

LECOM SCHOOL OF PHARMACY
CENTER FOR DRUG INFORMATION AND RESEARCH

LECOM Erie
1858 West Grandview Blvd.

814-866-6641 Phone
814-866-8123 Fax