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Updates and Future Perspectives in the Management of Stable Chronic Obstructive Pulmonary Disease

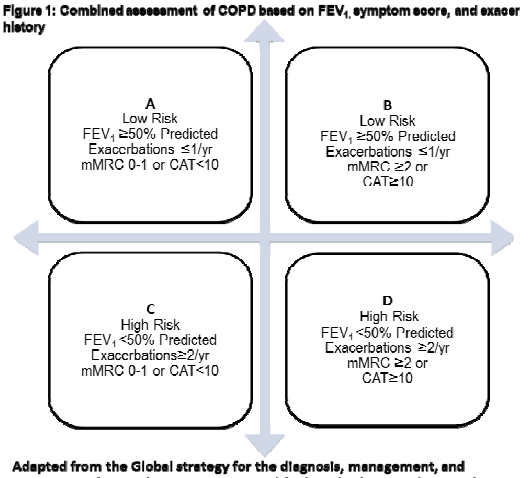
By Amy Higginson and Kathy Nguyen, PharmD. Candidates 2013, Megan Herink, Pharm.D. and Harleen Singh, Pharm.D., BCPS, all from Oregon State University College of Pharmacy

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterized by loss of lung function over time. The World Health Organization estimates that by 2030, COPD will be the third leading cause of death worldwide.[1] Cigarette smoking is the major risk factor for COPD; other risk factors include genetic, air pollution and occupational exposures. Bronchodilators such as beta agonists and long acting anticholinergic agents constitute the mainstay of therapy. Inhaled corticosteroids are used in combination with bronchodilators depending on the frequency of exacerbations and severity of COPD. New evidence and development of novel agents have resulted in significant changes in the management of COPD. As a result, The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines were revised in late 2011 and updated in 2013.[2,3] This review will highlight pertinent GOLD guideline revisions and evaluate the evidence behind the addition of new treatment options.

2011 Revision-2103 Updates

The definition of COPD is no longer limited to chronic bronchitis or emphysema; it is a mixture of airflow obstruction, alveolar destruction and chronic inflammation. Previous GOLD guidelines categorized COPD severity by post-bronchodilator FEV_1 alone.

Figure 1: Combined assessment of COPD based on FEV_1, symptom score, and exacerbation history



Adapted from the Global strategy for the diagnosis, management, and prevention of COPD.[3] mMRC score = modified Medical Research Council symptom score. CAT = COPD assessment test.

The updated guidelines grade severity (A-D) of COPD based upon a combination of clinical symptoms, in particular dyspnea, and staging of spirometry (Figure 1). Patients assigned to group D have more options, including more approved agents.

Recently, an epidemiological study compared the 2007 staging classification1-4 versus the 2011 staging classification A-D in predicting exacerbations, morbidity and mortality among patients with COPD.[4] The new COPD stratification was able to identify a higher percentage of patients at risk of exacerbations. Another finding was that patients presenting with dyspnea in the group B category (low risk and more symptoms) had higher 3-year mortality rates than patients in group C (high risk and less symptoms) despite minimally reduced FEV1 (10.6% vs. 8.2%, respectively; P=0.02). Patients in subgroups B and C also had a higher prevalence of cardiovascular (CV) disease and cancer, with reduced survival. Since dyspnea is commonly reported by patients with CV disease as well as patients with COPD, screening for comorbidities is essential in the assessment and treatment of COPD.[4] Short-acting beta agonists (SABA) and short acting anticholinergics are recommended as first-line as-needed therapy, followed by long-acting drugs for more ongoing control.[3] These are followed by recommendations for combination drugs. Inhaled corticosteroids with a long-acting beta agonist (LABA) is more effective than the individual components alone in reducing exacerbations, improving lung function, and enhancing health status (Evidence A in severe COPD; Evidence B in moderate COPD). There is evidence to support that long acting anticholinergics are superior to LABAs, however; the guidelines note that the difference is small and give each agent the same level of evidence.[2,5]

New Therapeutic Options

Appropriate medical management of stable COPD can reduce symptoms, reduce the frequency of exacerbations, and improve overall health status of the patient. Despite recent improvements, existing medications have not been shown to consistently modify the long-term decline in lung function.

Indacaterol (Arcapta®) was the first new bronchodilator approved and added to the 2011 update of the GOLD guidelines.[2,7] Indacaterol is a once daily LABA therapy with a faster onset of action than salmeterol. It has shown to reduce days of poor control and need for rescue medication, reduce symptoms and exacerbations and improve health status.[2,3] While the FDA approved the 75 mcg dose, the two dose strengths (150 and 300 mcg) that were most commonly studied in the original efficacy studies were not FDA approved due to a lack of evidence of increased efficacy with dose escalation. The most recent guidelines state that the bronchodilator effect of indacaterol is significantly greater than that of formoterol and salmeterol, and similar to tiotropium (Evidence A).[3] A meta-analysis evaluated the efficacy of indacaterol, tiotropium, salmeterol, and formoterol in COPD.[8] A total of 22 publications were included in the analysis and found that indacaterol resulted in a comparable FEV_1 at 12 weeks to tiotropium and salmeterol, and higher FEV_1 versus formoterol (0.05 L difference; 95% CI 0.01-0.09).[8] Indacaterol has an acceptable safety profile, however; cough occurring after inhalation of indacaterol has been observed in up to 24% of patients.[3] Similar to other LABA's, indacaterol contains a black box warning of an increase in the risk of asthma-related death and is contraindicated in patients with asthma without the use of a long-term asthma control medication.[7]

Aclidinium bromide (Tudorza Pressair®) is a new inhaled long-acting anticholinergic drug that is administered twice daily.[9] Until recently; tiotropium was the only available long acting inhaled anticholinergic. The ATTAIN and ACCORD COPD I studies were phase III trials evaluating the approved 400 mcg twice daily dose of aclidinium versus placebo.[9] Both found that treatment of moderate to severe COPD patients with twice-daily aclidinium was associated with significant improvements in bronchodilation, health status, and COPD symptoms. A minimum clinically important difference for FEV1 has not been defined in COPD, although improvement of around 100 to 140ml has been suggested as a benchmark.[10] The treatment effect of aclidinium 400 ug ranged from 61 ml to 124 ml across the studies at week 12. In comparison, tiotropium has been shown to increase FEV1 by around 140ml compared to placebo. There remains insufficient evidence to determine aclidinium's effects on mortality and other patient-centered outcomes, including exacerbations.[9] In clinical trials, serious adverse event rates were low with aclidinium. However, the CV risks are not well defined and need to be studied in larger clinical trials. Although aclidinium was added to the 2013 GOLD guidelines as a therapeutic option, tiotropium has level A evidence to support its use in reducing exacerbations, reducing hospitalizations, and improving symptoms and health status.[3]

Agents have also been developed that target specific inflammatory processes, including inhibition of phosphodiesterase-4 (PDE4). However, theophylline is a nonselective phosphodiesterase inhibitor and is associated with potentially life-threatening and difficult to treat adverse effects.[13] Roflumilast (Daliresp®) is the first oral selective PDE4 inhibitor approved as 500 mcg daily to reduce the risk of exacerbations in patients with severe COPD (FEV1 <50% predicted) associated with chronic bronchitis and a history of exacerbations.[14] Roflumilast is supported in the 2011 and 2013 GOLD guidelines with level A evidence for its proven efficacy in reducing moderate and severe exacerbations requiring treatment with corticosteroids by 15-20% in patients with severe COPD.[2,3] It is recommended based on level B evidence in appropriate patients who are not adequately controlled

with long-acting bronchodilators; it should always be used in combination with bronchodilator therapy. The most frequent adverse effects being nausea, reduced appetite, abdominal pain, diarrhea, sleep disturbance, and headache. Psychiatric adverse events are also a concern with the use of roflumilast.

Recently, the combination of fluticasone furoate, an inhaled corticosteroid, and vilanterol inhalation powder (Breo Ellipta®), a LABA, was approved for the long-term, once-daily, maintenance treatment in patients with COPD, as well as for reducing exacerbations in patients with a history of exacerbations.[15] This is the first approval of vilanterol for any indication and is a once daily alternative to Advair (fluticasone/salmeterol) and Symbicort (budesonide/formoterol), which are both dosed twice daily. This therapy was approved in May of 2013 and has not yet been evaluated for inclusion in treatment guidelines. Clinical trials showed improved lung function compared to placebo with an improved FEV1 of 173ml and 209 ml compared to placebo.[15,16] In the exacerbation trials, treatment with fluticasone/vilanterol demonstrated a statistically significant 31% reduction in moderate and severe exacerbations in one trial, and a non-significant 15% reduction in a second trial.[17] An increase in the incidence of pneumonia was observed in subjects receiving fluticasone/vilanterol in clinical trials (6%), including pneumonias resulting in hospitalizations.[15,16] Treatment with inhaled corticosteroids or combination therapy is associated with a further increased risk of pneumonia in patients with COPD. In patients who develop repeated episodes of pneumonia, the guidelines recommend that inhaled corticosteroids be discontinued and evaluated as a causative factor, however; they take no stance on which agents are implicated more frequency in the development of pneumonia. A Cochrane systematic review found an increased rate of pneumonia in patients on ICS therapy versus placebo (11% vs. 7.6% respectively, OR 1.56; 95% CI 1.30-1.86).[18]

New Delivery Devices

In addition to novel COPD treatments, new devices and formulation strategies are being developed to improve drug delivery. Inhaled medications are delivered by MDI, dry-powder inhaler (DPI), or nebulizer. A new delivery option is the soft mist inhaler (SMI). Combivent® is the ipratropium and albuterol combination previously available as a metered dose inhaler (MDI), which has recently been replaced by a SMI formulation called Combivent Respimat®; the only SMI available for clinical use. The ipratropium/albuterol MDI is being phased out because of government restrictions on the use of chlorofluorocarbons (CFCs), which were contained within the inhaler. The ipratropium/albuterol Respimat will be the only formulation available after January 1, 2014. Main differences between the products include its general appearance, dosing, and the Respimat inhaler does not contain soy lecithin and therefore is not contraindicated in patients with soybean or peanut allergy.[19] The ipratropium/albuterol Respimat dose is one puff four times daily compared to the previous inhaler, which is two puffs four times daily.[19] A systematic review was conducted to evaluate the effectiveness of the Respimat inhaler and demonstrated no difference in risk of exacerbations (RR 1.20, 95% CI 0.95 to 1.51; p=0.12).[19] Currently, no evidence suggests that the Respimat inhaler device provides any additional clinical benefit to that provided by other devices. Because of differences between the delivery devices, patients will require education on use when converting to the new product. The 2013 GOLD guideline update discourages the use of tiotropium delivered via the Respimat SMI until additional studies comparing delivery devices and doses are completed.[3] A systematic review and meta-analysis of randomized controlled trials found tiotropium delivered via the Respimat soft mist inhaler to be associated with a significant increase in mortality (RR 1.52; 95% CI 1.06 to 2.5; p=0.02) compared to placebo substantiating safety concerns regarding the use of this agent.[20]

Conclusion

The new GOLD guidelines classification is an important update, because it highlights the importance of both symptom severity and exacerbations in better understanding the disease course and tailoring therapy. Furthermore, when symptoms improvement is minimal, it prompts to search for comorbidities that could potentially mimic COPD symptoms.

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