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Update on the management of chronic obstructive pulmonary disease

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Abstract

Chronic obstructive pulmonary disease is a highly prevalent, underdiagnosed, and undertreated chronic lung disease. Early and appropriate treatment may help modify the course of the disease with respect to exacerbation timing and frequency, quality of life, and mortality. Steady progress continues to be made in understanding the disease pathogenesis and treatment modalities, and there is some evidence that outcomes are improving.

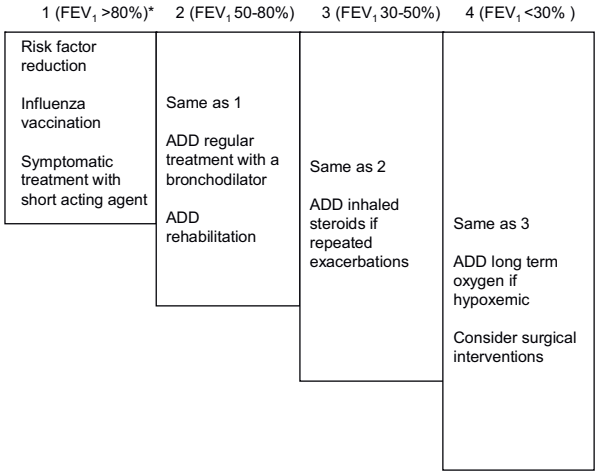
Introduction and context

Chronic obstructive pulmonary disease (COPD) is a chronic progressive systemic inflammatory disease that is generally a response to noxious particles and gases (most often, tobacco smoke) in susceptible individuals, although second-hand smoke, aging, other pollutants, and HIV may also be associated with COPD. This disease is expected to be the third leading cause of mortality worldwide by 2020 [1]. It causes 2.7 million deaths worldwide per year [2,3] and is associated with up to a twofold-higher risk of cardiovascular mortality [4-6]. Classically, COPD is a heterogeneous condition characterized by incompletely reversible airflow obstruction, including emphysema, chronic bronchitis, and bronchial hyperreactivity, often in combination. Phenotypes of COPD may be further classified on the basis of radiographic findings (i.e, the presence or absence of emphysema and/or bronchial wall thickening) or genetic polymorphisms. The main pathways studied in association with COPD development are the inflammatory, protease-antiprotease, and antioxidant pathways, but unfortunately many studies looking at genetic polymorphisms either have shown no association with COPD or had conflicting results, possibly related to the choice of study population [7,8].

In 2001, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) was formed to improve the investigation and management of this complex disease, and treatment strategies have been recommended on the basis of GOLD staging (Figure 1) [9]. Patients with respiratory symptoms but no airflow obstruction are also at increased risk for respiratory and cardiovascular morbidity and mortality [10]. Recent research has focused on identifying and modifying comorbidities associated with COPD and therapies to improve the significant individual and global morbidity and mortality associated with this disease.

Spirometry provides the single best method of diagnosing and staging COPD. The severity of COPD is staged according to the forced expiratory volume in 1 second (FEV_1), which is the most reproducible parameter of spirometric testing and the most significant predictor of prognosis in COPD [11,12]. In healthy individuals, FEV_1 declines by 20-30 mL per year, but this decline is accelerated in patients with COPD [13]. Pharmacologic therapies for COPD have been assessed by measuring lung function decline, number and timing of exacerbations, and effect on mortality counterbalanced by the side effect profile. Exacerbation endpoints have been of particular

Figure 1. Chronic obstructive pulmonary disease (COPD) stages and treatment recommendations from the guidelines of the Global Initiative on Obstructive Lung Disease [9]



*In all categories, FEV_1/FVC is less than 70% of predicted following administration of an inhaled bronchodilator

FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity.

interest given that exacerbations have been associated with increased risk of myocardial infarction and stroke [14], decline in lung function [15], decline in quality of life, and an overall 14-18% 1-year mortality [16].

Recent advances

Pharmacologic agents

Long-acting antimuscarinic agents

Anticholinergic agents in COPD may be beneficial because of the increased vagal tone in the airways of patients with COPD [17]. Tiotropium is a once-daily, inhaled anticholinergic therapy that was recently examined in the 4-year UPLIFT (Understanding Potential Long-Term Impacts on Function with Tiotropium) trial [18]. In this study, patients were at least 40 years of age (mean age 64.5), 90% had GOLD stage 2 or 3 COPD, and more than 60% were already on long-acting beta-agonists (LABAs) or inhaled corticosteroids (ICSs) (or both). Tiotropium was not shown to significantly reduce the rate of decline in FEV_1 but was associated with improvements in quality of life, reduced time to first exacerbation (16.7 versus 12.5 months), delayed time to first hospitalization for an exacerbation, and a reduced mean number of exacerbations by 14% (P <0.001) during the 4-year period [18].

Long-acting bronchodilator and inhaled corticosteroids

The addition of a long-acting bronchodilator is recommended for patients with moderate (FEV_1/forced vital capacity ratio of <70%, FEV_1 of <80%) or worse COPD based on GOLD staging, and ICSs are recommended for patients with an FEV_1 of less than 50% or with frequent exacerbations. Studies examining the effects of ICSs alone have not shown any effect on lung function decline over time and have had conflicting results in regard to exacerbation rate reduction [19-21].

Current LABA-ICS combinations are marketed under the trade names Advair (salmeterol/fluticasone propionate; GlaxoSmithKline, Uxbridge, Middlesex, UK) and Symbicort (formoterol/budesonide; AstraZeneca, London, UK). The TORCH (Towards a Revolution in COPD Health) trial examined the effects of salmeterol and fluticasone propionate on survival in COPD over the course of 3 years [10]. A non-statistically significant trend in improved survival was observed in patients receiving the LABA-ICS combination compared with placebo (P = 0.052) or either of the individual components. The LABA-ICS combination group did have a reduced annual rate of exacerbations (1.13 to 0.85) and improved health status according to the St George's Respiratory Questionnaire [10]. A *post hoc* analysis found that treatment with salmeterol-fluticasone propionate reduced the rate of decline in FEV_1 in patients with moderate to severe COPD – a finding that has not been demonstrated with other pharmacologic therapies [22].

'Triple' combination therapy

In one study, 660 patients with moderate, severe, or very severe COPD (mean FEV_1 1.1 L) were randomly assigned to receive tiotropium plus placebo and tiotropium plus budesonide/formoterol over the course of 12 weeks. Patients on triple-combination therapy showed statistically significant improvement in their pre-dose and post-dose FEV_1, capacity of daily living questionnaire, and COPD symptoms. Furthermore, the number of severe exacerbations was reduced by 62% (rate ratio 0.38, 95% confidence interval [CI] 0.25-0.57, P <0.001) [23].

In the OPTIMAL (Optimal Therapy of Chronic Obstructive Pulmonary Disease To Prevent Exacerbations and Improve Quality of Life) study looking at tiotropium in combination with salmeterol-fluticasone, lung function and quality of life were also shown to improve compared with tiotropium plus placebo or salmeterol alone over the course of 1 year. However, in this study, mortality and the proportion of patients who experienced an exacerbation did not differ between the groups, although the number of hospitalizations required because of an exacerbation was reduced in patients on tiotropium plus salmeterol-fluticasone (rate ratio 0.53, 95% CI 0.33-0.86) [24].

Other pharmacologic treatments

Other pharmacologic treatments for COPD have targeted the inflammatory process and cardiovascular comorbidity. Chronic low-dose macrolide therapy has been shown to reduce exacerbation frequency and shorten duration of exacerbations, although the antibacterial and anti-inflammatory mechanisms remain unclear [25]. Roflumilast is an oral phosphodiesterase-4 inhibitor that showed improvements in lung function (39-mL increase in post-bronchodilator FEV_1 compared with placebo, $P = 0.001$) and exacerbation frequency (0.86 versus 0.92 exacerbations/patient per year for roflumilast versus placebo) after 1 year of use in patients with severe COPD [26]. Roflumilast is currently under study in Europe, but the US Food and Drug Administration recently rejected the application for drug approval in the US because of concerns over possible adverse events such as the possibility that neuropsychiatric reactions would offset the 'modest' increase in lung function.

Mucolytics with anti-inflammatory and antioxidant activity such as carbocisteine have also been shown to reduce exacerbations in patients with moderate or worse COPD [27]. The 3-hydroxy 3-methylglutaryl coenzyme A reductase inhibitors (statins) may reduce the number of COPD exacerbations and mortality from COPD, presumably via anti-inflammatory mechanisms, although most previous studies do have inherent methodological limitations [28,29]. Likewise, treatment with beta-blockers may reduce the risk of exacerbations and improve survival in patients with COPD, possibly as a result of cardiopulmonary protective properties [30]. Exacerbation number and severity may also be reduced with treatment with non-typeable *Haemophilus influenzae* oral immunotherapeutic HI-164OV [31]. Vitamin D replacement is currently the subject of a placebo-controlled double-blinded randomized controlled trial [32].

Side effects of treatment

The use of ICSs causes some concern over the risk for osteoporosis and pneumonia. In the TORCH trial, osteoporosis was highly prevalent in patients with COPD (18% of men and 30% of women at baseline), but the use of ICSs had no significant effect on bone mineral density compared with placebo [33]. In contrast, a meta-analysis of 18 randomized controlled trials looking at the risk of pneumonia with long-term use (at least 24 weeks) of ICSs in COPD did find a significant increased risk of pneumonia (relative risk 1.60, 95% CI 1.33-1.92, $P<0.001$) but without a significantly increased risk of pneumonia-related mortality or overall mortality [34]. Analysis of the TORCH study also found a greater risk of pneumonia in patients on ICSs alone or in combination compared with placebo (84 and 88 versus 52 per 1000 treatment-years, respectively) [35]. The definition of pneumonia (i.e., whether radiologic confirmation is required) may alter these findings. A meta-analysis looking at fatal and non-fatal cardiovascular events in patients treated with tiotropium found that tiotropium did not significantly increase the risk of adverse major cardiovascular events among patients with COPD [36].

Other management modalities

Because it ameliorates decline in lung function, smoking cessation remains the most important management issue in COPD patients who continue to smoke. Other considerations in the management of COPD include assessing the need for chronic oxygen therapy given that oxygen has been shown to improve mortality in patients with chronic respiratory failure [37]; referral for pulmonary rehabilitation, which improves quality of life [38] and exacerbation severity [39]; and the use of non-invasive ventilation, which improves quality of life with variable effects on survival [40,41]. Importantly, increased physical activity at home also translates into a substantially reduced risk of readmission due to a COPD exacerbation. Patients who walk at least 60 minutes a day had a statistically significant reduction in risk of hospital readmission by almost 50%, and this association did not change when adjusted for COPD severity, nutritional status factors, or respiratory rehabilitation [42]. A recent study has suggested that abnormal coordination of swallowing may lead to prandial aspiration and trigger COPD exacerbations [43,44].

Referrals for lung volume reduction surgery and lung transplant must also be considered for patients with COPD. Lung volume reduction surgery should be considered, especially for patients with both predominately upper-lobe emphysema and low-baseline exercise capacity, as this surgery offers a survival benefit, improved quality of life, and reduction in exacerbations. In contrast, patients with non-upper lobe emphysema and high-baseline exercise capacity are poor candidates and have a higher mortality than patients treated with medical therapy alone [45].

Outcomes

Recent data from the US suggest that COPD hospitalization rates are no longer increasing and that COPD mortality rates are starting to decrease [46,47]. These findings are encouraging and may be a result of improved diagnosis and better treatment.

Implications for clinical practice

COPD is now recognized as a systemic illness. Evidence supports the use of inhaled pharmacotherapy to improve

lung function, quality of life, and exacerbation frequency and severity in patients with severe and very severe disease and in many patients with moderate disease. Until recently, only smoking cessation was found to reduce the decline in FEV_1, but there are now some data that show that pharmacotherapy may also be effective [48]. Furthermore, early intervention may have effects that are more dramatic and decrease the time to first exacerbation [49]. Maintenance therapy for moderate to severe COPD with long-acting antimuscarinics and LABA-ICS combinations appears to provide benefits in health status, exacerbation rates, and probably mortality. We continue to recognize the important role that exacerbations play in the course of COPD, and therapy directed toward reducing exacerbation rate and severity will hopefully lead to further improvements in quality of life, lung function, and mortality.

Abbreviations

CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; TORCH, Towards a Revolution in Chronic Obstructive Pulmonary Disease Health.

Competing interests

AKM declares that she has no competing interests. DMM has received research funding from GlaxoSmithKline (Uxbridge, Middlesex, UK), Pfizer (New York, NY, USA), Novartis (Basel, Switzerland), and AstraZeneca (London, UK) and has served as a consultant for GlaxoSmithKline, Pfizer, Novartis, Forest (New York, NY, USA), Boehringer Ingelheim (Ingelheim, Germany), and AstraZeneca.

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