Chronic obstructive pulmonary disease – a treatable disease

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Summary

Chronic obstructive pulmonary disease (COPD) is a global health challenge and a leading cause of death worldwide. Several risk factors have been identified, with cigarette smoking being the most important. Diagnostic assessment is based on symptoms, risk of exacerbations and results of lung function testing. A fixed post-bronchodilator ratio for forced expiratory volume in one second to forced expiratory volume (FEV1/FVC) of <0.7 is required to make the diagnosis, and the severity of airflow obstruction defines the grade according to GOLD (Global Strategy for the Diagnosis, Management, and Prevention of COPD). The GOLD strategy makes therapeutic recommendations taking into account the grade, symptomatic assessment and future risk of exacerbations. This review focuses on the therapeutic options for COPD, in accordance with the GOLD strategy. Smoking cessation is the most effective treatment option in all COPD stages. Bronchodilators, namely long-acting antimuscarinic drugs and long-acting beta-agonists, form the mainstay of treatment in COPD. Patients with frequent exacerbations also benefited from the addition of inhaled corticosteroids. Roflumilast is an add-on option for patients with severe COPD. Several controversies are the subject of discussion: (1) whether pharmacotherapy can modify the natural history of COPD; (2) whether pharmacotherapy should be started in the early stages of COPD; (3) the impact of therapy on comorbidities; (4) whether patients benefit from a combination therapy with a long-acting beta-agonist, a long-acting antimuscarinic drug and an inhaled corticosteroid; (5) step-down therapy. This overview also reviews the evidence for recommended vaccines in COPD, as well as nonpharmacological therapies. Rehabilitation is an essential part of COPD treatment. Oxygen therapy, noninvasive nocturnal ventilation and surgical treatment options only apply to a highly selected group of patients. Disease management programmes and guideline adherence are briefly discussed.

In conclusion, although there is debate as to the extent with which pharmacological therapies influence mortality, adherence to the GOLD strategy is recommended.

Key words: COPD: smoking cessation; pharmacological therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a “preventable and treatable disease, which is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases” [1]. COPD is and will be a global health challenge in the next decades. It is currently the fourth leading cause of death worldwide and is expected to rise to the third leading cause [2]. The most important risk factor for COPD is cigarette smoking, but other risk factors have been identified, and may be particularly important in women, especially in low-income countries [3–6]. Air pollution and occupational exposure have also been linked to the development of COPD [5]. The diagnosis of COPD is based on exposure to risk factors, symptoms (possibly underreported because patients have adapted to these) and a fixed post-bronchodilator ratio of forced expiratory volume in one second (FEV1) to forced expiratory volume (FVC) of <0.7 [1]. Therapeutic options include smoking cessation, which has the greatest impact on the natural history of COPD, pharmacological therapy, mainly inhaled bronchodilators, and nonpharmacological treatment options such as rehabilitation [1]. This review will focus on the therapeutic scope in COPD and give an overview of the different possibilities and their impact on disease progress and symptom control.

Diagnosis and assessment

Common symptoms of COPD include dyspnoea, chronic cough and sputum production. Spirometry is needed to confirm a suspected diagnosis of COPD. The presence of
airflow limitation with a fixed post-bronchodilator ratio of FEV₁/FVC <0.7 is required to make the diagnosis. With the fixed ratio criterion there is some risk of misdiagnosis in the elderly population and in persons below 45 years of age [7]. There seems to be an overestimation of COPD diagnosis in the elderly [8–11], whereas in younger subjects with existing airflow limitation some cases might be missed when the fixed cut-off criterion are used [11, 12]. However, a definition based on a cut-off using the lower limit of normal values for FEV₁/FVC has not been validated by longitudinal studies and depends on reference equations that have not been validated either [13]. Further, age and risk of COPD due to previous exposures may interact to increase significantly the probability of having an obstructive ratio that points to the presence of airflow limitation [14].

Generally, many people with COPD remain undiagnosed, especially those with mild and moderate disease [15, 16]. This can also be assumed to be the case in Switzerland [17]. Although screening asymptomatic patients with spirometry is not warranted [18], case finding may be a cost-effective strategy that identifies patients who will respond to interventions for COPD [19–21].

The GOLD strategy

The “Global Strategy for the Diagnosis, Management, and Prevention of COPD” (GOLD strategy), revised in 2011, summarises current evidence on management and prevention strategies.

Depending on the severity of airflow obstruction, four grades are classified by GOLD: mild disease (FEV₁ ≥80% predicted), moderate disease (50% ≤ FEV₁ <80% predicted), severe disease (30% ≤ FEV₁ <50%), and very severe disease (FEV₁ <30% predicted), and the results of this classification lead to treatment choice [1]. However, FEV₁ has only limited value in predicting disease impact [22] and this is taken into account by including symptoms and the risk of exacerbations in the assessment for treatment choice [1]. GOLD strategy recommends use of the modified British Medical Research Council (mMRC) questionnaire or the COPD Assessment Test (CAT) to assess symptoms. Together with the frequency of exacerbations within the last year (defined as an acute event with worsening of symptoms that leads to a change in medication) patients are placed in categories A–D and treatment recommendations are based on the spirometric evaluation as well as the symptomatic assessment (table 1) [1].

Therapeutic options

The first and most important step in COPD therapy, at all stages, is smoking cessation, which reduces the yearly decline in FEV₁ and lowers mortality [23–25]. Advice from doctors or nurses, counselling and pharmacotherapy supports and increases successful quit rates compared with brief smoking cessation advice alone [26]. There is little evidence as to whether biomedical risk assessment such as interpretation of spirometric results, measurement of exhaled carbon monoxide or visualising plaque formation in the carotid artery will help patients to quit smoking [27]. However, ongoing studies in the primary care setting aim to clarify if structured information about spirometric results will lead to higher smoking cessation rates [28, 29]. Higher quit rates can be achieved by offering nicotine replacement therapy in any available form [30]. Bupropion [31] and varenicline [32] have also been shown to promote abstinence. Combined pharmacotherapy and behavioural support increase successful smoking cessation compared with pharmacotherapy or behavioural support alone, and offering more intense behavioural interventions, as well as face-to-face contact, might have a greater effect than telephone contact offered by quitlines [33]. Implementing tobacco control policies would also reduce smoking prevalence [34].

Pharmacological therapies

Pharmacological therapy aims to reduce symptoms and exacerbations, and to improve quality of life and exercise tolerance. The GOLD strategy recommends a stepwise treatment plan taking into account the COPD grade based on spirometry, symptoms and the future risk of exacerbations [1].

Bronchodilators form the mainstay of therapy for COPD. Short-acting beta-agonists are used on an-as-needed basis or regularly for symptomatic relief in the early stages or

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<th>Table 1: First-choice treatment recommendations according to the GOLD strategy.</th>
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<td><strong>Patient category</strong></td>
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GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV₁ = forced expiratory volume in one second; mMRC = modified British Medical Research Council questionnaire; CAT = COPD Assessment Test.

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in COPD patients with a low symptom burden, and have been shown to reduce dyspnoea intensity [35]. Long-acting beta-agonists and the long-acting antimuscarinic drug tiotropium improve health status and reduce the number and severity of exacerbations [36–38]. The ultra–long-acting beta-agonist indacaterol has also been shown to have a good profile of tolerability regardless of COPD severity or concurrent inhaled corticosteroid use [39]. For patients whose symptoms are not controlled by the use of a long-acting beta-agonist or long-acting antimuscarinic drug, combination of these is recommended [1]. Compared with single-agent therapy the aforementioned combination therapy resulted in symptomatic improvements as well as less airflow obstruction [39–43]. However, long-term data are missing [44].

To date, the major anti-inflammatory treatment for COPD has been inhaled corticosteroids, which improve quality of life and reduce exacerbation rate especially in patients with severe diseases. No benefit with regard to disease progression or mortality has been shown in several studies when inhaled corticosteroids used as monotherapy are compared with placebo [37, 45–48]. Lower respiratory tract infections and pneumonia are reported with greater frequency in COPD patients treated with inhaled corticosteroids [45]. However, patients benefited from the fixed combination of inhaled long-acting beta-agonists and corticosteroids in large interventional trials, and the combination was superior to the individual components [37, 49, 50]. Withdrawal of inhaled corticosteroids causes an increased exacerbation rate and this has fed the controversy on inhaled corticosteroid intervention studies [51, 52].

In severe and very severe COPD, roflumilast, a new oral phosphodiesterase-4 inhibitor, decreased the frequency of exacerbations [53] and improved lung function when given in combination with inhaled salmeterol or tiotropium [54]. The most common side effect of roflumilast is diarrhoea; other common side effects include insomnia and weight loss [55]. Data on the effect of roflumilast when added to an existing treatment of inhaled bronchodilator and inhaled corticosteroids are expected for 2014 [55].

Owing to the side effects of prolonged treatment with oral corticosteroids, there is limited data on their effect in stable COPD [56, 57]. Their value, however, has been shown in the treatment of acute exacerbations [58] although the optimal duration of therapy has yet to be defined [59].

Long-term antibiotic treatment in stable COPD is a subject of debate. There are data suggesting a reduction in the risk of exacerbations with continuous treatment with azithromycin [60, 61]. There might also be a benefit with pulsed therapy with moxifloxacin with regard to reducing the exacerbation rate [62]. There is increasing evidence that prompt antibiotic therapy reduces the frequency and duration of COPD exacerbations [63, 64].

Since oxidative stress and mucus formation play an important role in the pathogenesis of COPD, antioxidant and mucolytic agents such as N-acetyl-L-cysteine have been used in the treatment of patients with COPD, with mixed results [65]. A review of smaller studies showed an effect in reducing exacerbations [66]; however, one large randomised controlled trial did not show any benefit in terms of reducing the rate of exacerbations with 600 mg of N-acetyl-L-cysteine daily [67]. Whether higher doses of N-acetyl-L-cysteine are effective and safe to use in patients with COPD is currently being investigated [68].

Oral bacterial lysates (e.g. Broncho-vaxom) have been used in patients with COPD to reduce exacerbations. Although, some studies have shown a clinical benefit in terms of reducing exacerbations [69, 70], there is no clear and consistent evidence to recommend this treatment for a well-defined patient group with COPD [71, 72].

Despite effective treatment for COPD, several controversial issues remain

The first question is whether pharmacotherapy can modify the natural history of COPD. To date, there is no direct evidence showing conclusively that recommended therapy slows the rate of decline in FEV1 [23, 46–48, 73]. Smoking cessation is the only effective step for slowing the decline of FEV1 [23, 24] and lowering mortality [25]; the latter also applies for oxygen therapy for a selected group of patients.

A fixed combination of an inhaled long-acting beta-agonist and a corticosteroid showed a trend toward lower mortality in one of the landmark studies [37], but this needs to be confirmed in other large prospective trials. Also, a post-hoc analysis of the TORCH trial showed a small effect on decline of FEV1 with a fixed combination treatment of salmeterol and fluticasone propionate [74].

The second question is whether pharmacotherapy should be started in the early stages of COPD (GOLD stages 1 and 2). Evidence is scarce as the large interventional studies did not specifically target this group of patients [75]. However, subgroup analysis of the two landmark studies showed a beneficial effect regarding FEV1 decline in patients with GOLD stage 2 COPD for salmeterol [76] and tiotropium [77]. Airway hyper-responsiveness testing with inhaled mannitol might identify patients who will benefit from add-on therapy with inhaled corticosteroids in the early stages of COPD [78].

More frequent exacerbations are associated with faster FEV1 decline [79] and more than 20% of patients with GOLD stage 2 have frequent exacerbations [80]. So, early and effective treatment and possibly prevention of exacerbations should result in a reduced rate of decline.

Tiotropium was more effective than salmeterol in reducing exacerbations in patients with COPD GOLD stages 2–4 [36]. Patients with a predicted FEV1 of >70% were excluded in the aforementioned big studies and therefore the question as to whether therapy with long-acting bronchodilators or combinations with inhaled corticosteroids is warranted in these patients remains unanswered.

Antibiotics and oral corticosteroids are usually used to treat acute exacerbations. Lung function improves with systemic corticosteroids in exacerbations, and recovery time is shorter [81–85]. The use of antibiotics in exacerbations has been a subject of debate because exacerbations might be precipitated by a viral or bacterial infection. Patients with rather severe COPD and more purulent sputum probably benefit from antibiotic therapy [64]. Also, antibiotics may prolong the time to a subsequent exacerbation when added to oral corticosteroids in an acute exacerbation [63]. The measurement of procalcitonin, as a marker for bacterial infection, can be used as guidance for the use of antibiotics in...
acute exacerbations of COPD [86]. However, it is not always readily available. Thirdly, comorbidities must be taken into account. Will the treatment with bronchodilators or inhaled corticosteroids have an effect on comorbidities [87]? There are no data to give an answer to this question. Statins, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been shown to reduce morbidity and mortality in patients with COPD [88]. Treatment with cardioselective beta-blockers may also be beneficial for patients in COPD as they seem to lower the exacerbation rate [89] and reduce mortality [89, 90]. In addition, there is debate as to which patients benefit from combination therapy with a long-acting beta-agonist, a long-acting antimuscarinic and inhaled corticosteroid therapy (triple therapy), and as to which patients benefit from a combination of just two components. Studies have shown improvements in quality of life, symptom burden and use of relief medication [39, 91–93], and one study showed a reduction in severe exacerbations [91]. However, no long-term studies exist and therefore it is too early to draw reliable conclusions on the efficacy and safety of triple therapy [42, 94]. Lastly, the GOLD strategy gives guidelines for the initial therapy of patients with COPD, but there are no specific recommendations for a step-down of therapy and what such a decision should be based on. Further studies are needed to address this important question.

Vaccines
The Swiss Respiratory Society recommends yearly vaccination against influenza and pneumococcal vaccination in persons with COPD, particularly those over 65 years of age [95]. There might be a risk reduction for acute exacerbations with influenza vaccines, but data are very limited regarding the effectiveness of influenza vaccination in persons with COPD [96, 97]. Pneumococcal vaccination might reduce morbidity in subjects with COPD, but evidence that allows reliable conclusions is lacking [98, 99]. It is possible that the newer conjugated pneumococcal vaccines will have greater efficacy in reducing pneumonia incidence and mortality in COPD, but this is yet to be tested [100, 101].

Nonpharmacological therapies
Rehabilitation
Rehabilitation with exercise training as a core component is an essential part of the treatment of COPD. It is safe, and improves symptoms and quality of life [102]. There might even be a mortality benefit, but studies have been underpowered to show conclusively a lower mortality with rehabilitation [103]. Patients of all disease stages and ages profit from rehabilitation programmes [104], and even starting rehabilitation during an exacerbation seems to be safe and feasible [105]. Rehabilitation should include education about COPD and treatment options, exercise training, nutritional intervention and psychosocial support. Effectiveness has been well documented for in-patient, outpatient and home-based programmes [103].

Oxygen therapy and noninvasive ventilation
The administration of oxygen >15 hours per day improves survival in COPD patients with chronic respiratory failure and severe resting hypoxaemia [106]. In patients without resting hypoxaemia a clear benefit has not been shown for oxygen supplementation and it is currently not recommended [107]. A survival benefit was noted for nocturnal noninvasive ventilation in patients with very severe, oxygen-dependent COPD and daytime hypercapnia. However, this intervention reduced their quality of life [108].

Surgical treatments
Surgical treatments such as lung volume reduction surgery, bronchoscopic lung volume reduction, bullectomy and lung transplantation are treatment options for very selected groups of patients. Patients with severe, predominantly upper lobe emphysema and low exercise capacity after rehabilitation show improved survival with lung volume reduction surgery, and patients with high exercise capacity after rehabilitation show improved quality of life and exercise capacity after lung volume reduction surgery [109]. Bronchoscopic lung volume reduction entails the positioning of endobronchial valves. Patients with advanced heterogeneous emphysema profited from endobronchial valves, with increased lung function and exercise capacity. However, this might be at the cost of a higher rate of subsequent exacerbations [110], pneumonia and haemoptysis [110]. As mentioned before, this treatment option only applies to a highly selected group of patients with COPD. Bullectomy in patients with a single giant bulla results in improved quality of life, and improves symptoms and lung function [111]. Lung transplantation in COPD is limited by the availability of donor organs. Carefully selected patients with very severe COPD benefit in terms of better functional capacity and quality of life [112].

Disease management strategies
Self-management education in patients with COPD might be associated with a reduction in hospital admissions, but there is still insufficient evidence to make clear recommendations on the form and content of these programmes [113]. A recent study of a comprehensive care management programme including individual educational sessions, an action plan and proactive telephone calls was stopped early because of excess mortality in the intervention group [114]. Another recent study of self-management interventions in the primary care setting showed no benefit in terms of quality of life, self efficacy or frequency of exacerbations with ongoing telephone support and tailored sessions or routine monitoring compared with usual care [115].

Guideline adherence
Although the GOLD strategy summarises the evidence for the different treatment options and makes therapeutic recommendations, many patients with COPD are not treated in accordance with these guidelines [116–119]. One study found no benefit for Swiss patients treated in accordance with guidelines, as compared with those that were not, in terms of rate of exacerbation and lung function decline
within one year of follow-up [117]. Lower costs have, however, been associated with adherence to the GOLD strategy [120]. The most recent GOLD strategy recommends assessment of symptoms and exacerbation history in addition to the GOLD stage, in order to estimate risk and decide on appropriate therapy [1]. This new paradigm has yet to be tested formally in relation to its impact on COPD outcomes.

**Conclusion**

Effective treatment for COPD exists. Smoking cessation is paramount. Although there is still debate as to the extent with which pharmacological therapies influence mortality, adherence to the GOLD strategy is recommended.

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