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Chapter

COPD Pharmacological Management Update

Stefan-Marian Frent

Abstract

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality worldwide. Although it is considered both preventable and treatable, COPD still represents an important public health challenge. The classes of pharmacological agents widely used for the maintenance treatment are bronchodilators (SABA, SAMA, LABA, LAMA) and inhaled corticosteroids (ICS). While it is largely accepted that inhaled bronchodilators, which are effective and well tolerated in patients with stable disease, are the cornerstone of the pharmacological management of COPD, there is an ongoing debate regarding the role of inhaled corticosteroids. This is also reflected in the last versions of the GOLD recommendations, which suffered dramatic changes in the recent years. The trend for personalized medicine led to the search for biomarkers which could guide the therapeutic decisions. Recent studies demonstrated that blood eosinophils can reasonably predict the ICS relative efficacy in preventing COPD exacerbations and thus could inform the disease management.

Keywords: COPD, lung function, exacerbation, bronchodilators, corticosteroids, biomarkers, eosinophils

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common condition, usually affecting people of >40 years of age significantly exposed to noxious particles or gases [1]. Although considered both preventable and treatable [1], COPD remains a leading cause of morbidity and mortality [2, 3], affecting an estimated 384 million people worldwide [4]. The COPD prevalence is projected to increase in the coming decades [5], as well as its position among the leading causes of mortality [4].

Active or passive cigarette smoking is the most commonly encountered risk factor for COPD across the world [1]; however other factors may play a role in the disease pathogenesis, such as genetic factors [6, 7], exposure to indoor and outdoor air pollutants [8–11], exposure to occupational dusts, chemical agents or fumes [12], infections (HIV, tuberculosis) [13, 14], and socioeconomic status [15].

The normal lung response to the inhalation of noxious factors is an inflammatory reaction of the airways. In patients who develop COPD, the excessive inflammatory response is further enhanced by the oxidative stress and an imbalance of the protease-antiprotease system, leading to the destruction of the lung parenchyma and disruption of normal repair and defense mechanisms. Emphysema and small airway fibrosis are the consequences of these processes, which translate into gas trapping and chronic airflow limitation [1].

By definition, COPD is a chronic condition, and the major symptoms exhibited by the patients suffering from this disease, dyspnea, cough, and sputum production, are usually persistent and/or progressive and have a considerable negative effect on the patient's quality of life. The Global Burden of Disease Study highlighted that COPD is a major contributor to disability and mortality around the world, by ranking COPD as the fifth leading cause of disability-adjusted life years (DALYs) lost in 2013 [16].

The natural course of the disease is grafted by acute episodes of worsening of symptoms triggered by infectious agents, air pollution, and other factors. These events are referred to as "exacerbations" and usually require a change in medication and/or hospitalization. Exacerbations are associated with accelerated lung function decline, reduced quality of life, and increased mortality [17] and, not surprisingly, have been surnamed as "chest attacks" or "strokes of the lung" [18, 19].

2. Pharmacological treatment in stable COPD

The main goals for the management of stable COPD are improvement in quality of life by relieving symptoms and increasing exercise tolerance and reduction of mortality risk by preventing exacerbations and disease progression [1].

Several inhaled, oral, and systemically administered drugs improve lung function, decrease the frequency and severity of COPD exacerbations, and improve patients' quality of life [20].

Non-pharmacological therapies in COPD, including smoking cessation strategies, pulmonary rehabilitation, vaccinations, surgical or bronchoscopic interventions, and noninvasive ventilation have their established role in the management of the disease; however they are not discussed here, as the focus of this chapter is on the pharmacological treatment.

Back in 2001 when the first edition of the GOLD document was released [21], the pharmacological arsenal for the treatment of COPD was rather limited, comprising of short-acting beta2-agonists and anticholinergics, long-acting beta2-agonists, theophyllines, and mucoactive agents. Inhaled corticosteroids, although available as single medication, were never widely recommended for the treatment of COPD in monotherapy and have no current authorization for use outside fixed-dose combinations.

Nowadays, there is a broader range of molecules recommended for the treatment of stable COPD that can be classified in the following classes of pharmacological agents:

- Beta2-agonists: short-acting (SABA) and long-acting (LABA)
- Anticholinergics: short-acting (SAMA) and long-acting (LAMA)
- Fixed-dose combinations: SABA/SAMA, LABA/ICS, LABA/LAMA, LABA/LAMA/ICS
- Methylxanthines
- Phosphodiesterase-4 (PDE4) inhibitors
- Mucolytics
- Antibiotics

Additionally, a new acquisition in the bronchodilator portfolio could be the potential use of dual agents or bifunctional muscarinic antagonists and beta2-agonists (MABAs), which combine both antimuscarinic and adrenergic properties in a single molecule [22]. Some of these molecules are already in clinical trials, but a major caveat is the difficulty to balance the antimuscarinic and adrenergic activities, without expressing a tendency toward one of them [23].

Efforts have been made for the discovery of new pharmacological agents, either belonging to the mentioned classes or addressing new therapeutic targets: new corticosteroids, novel classes of bronchodilators, kinase inhibitors, mediator antagonists (including biological therapies, such as cytokine inhibitors), antioxidants, etc. Unfortunately, many of these molecules never made it to the market or were not granted approval for COPD due to safety, efficacy, or delivery issues; several others are still in the development process [23].

Currently available pharmacological agents and other therapies are mainly used as pathogenic or symptomatic treatment.

2.1 Improvement of lung function and symptoms

Chronic airflow limitation is a central characteristic of COPD and is the result of the combination in varying degrees of several pathological processes such as narrowing of the airways, mucus hypersecretion, and loss of small conducting airways [24]. The consequences of these anatomic changes are expiratory airflow limitation, air trapping, and ventilation-perfusion mismatch [22, 25]. Additionally, the loss of elastic recoil and hyperinflation adversely affect thoracic and diaphragmatic mechanics, increasing the work of breathing and ultimately leading to dynamic hyperinflation [26]. Hyperinflation is an independent predictor of mortality in COPD [27].

The clinical expression of airflow limitation is chronic, progressive dyspnea, which typically worsens with physical exercise. Chronic cough with or without sputum production is usually a reflection of the ongoing inflammatory process in the airways of COPD patients. However, there is no linear correlation between the severity of the airflow limitation and the level of symptoms. Some patients may have little subjective complaints, although the lung function testing reveals various degrees of airflow limitation, while other patients may have significant complaints, with little or no evidence of airflow obstruction [28]. In some cases, the symptoms may precede the development of airflow limitation by many years [1].

Treatment with inhaled bronchodilators can reduce hyperinflation, improve dyspnea, and increase exercise tolerance [29], and therefore, bronchodilators are considered as a cornerstone in the management of stable COPD [30].

While short-acting bronchodilators are an option for patients with occasional dyspnea at low risk of exacerbations, the majority of patients have breathlessness leading to exercise limitation at the time of diagnosis and may require more intensive treatment than short-acting bronchodilators alone [30]. For these patients, whether or not they are also at higher risk of exacerbations, long-acting bronchodilators (as monotherapy or in combination) are recommended as a preferred treatment choice in the GOLD strategy report [1].

Airway tone is controlled by both the sympathetic and parasympathetic nervous systems. These mechanisms interact and may potentiate each other and are employed alone or in combination therapeutically. Relaxation of airway smooth muscle is caused by blockade of acetylcholine activity at the receptor (muscarinic antagonist) or stimulation of the G protein-coupled receptor (beta-agonist) [31].

Anticholinergic drugs in the form of smoked alkaloids were among the first effective treatments for asthma [32]. In the mid-twentieth century, parenteral

muscarinic antagonists and beta-agonists were used for acute attacks of asthma [33]. The major disadvantages of the systemic delivery were the side effects and a short duration of benefit. As such, subsequent work has both optimized the receptor specificity and the duration of action [22].

Beta-agonists were in use in Chinese medicine for millennia in the form of ephedra. Developments in the mid-twentieth century yielded compounds that specifically target the beta2-adrenergic receptor, reducing the side effects from beta1-agonists [31].

Since the approval by the US Food and Drug Administration (FDA) in 2004 of the first LAMA, tiotropium, long-acting bronchodilators have begun to play a central role in the management of stable COPD. Currently available molecules for inhalation delivery are summarized in **Table 1**.

The benefits of long-acting bronchodilator monotherapy have been well proven across a range of clinical studies [30] and include improvement of the airflow limitation [34–39], dyspnea [34, 35, 39], physical activity/exercise capacity [29, 40–42], health status [34, 35, 37–39], and prevention of exacerbations [35, 39, 43, 44]; however, many patients remain symptomatic despite treatment [45].

Dual bronchodilation improves lung function compared with a single bronchodilator [30]. Long-acting beta2-agonists and long-acting muscarinic antagonists act via different mechanisms; when used together in patients with COPD, they exert additional bronchodilating effects [46]. Multiple studies have assessed [30] and demonstrated that the use of LABA/LAMA dual bronchodilation results in additional improvements in lung function, exacerbation rates, health status, and other outcome measures when compared with monobronchodilation, while the safety profile of the dual bronchodilators was similar to that observed with placebo and individual monocomponents. Currently available LABA/LAMA combinations are listed in **Table 2**.

According to current guidelines and strategy reports, long-acting bronchodilators in monotherapy are adequate options for the majority of COPD patients, regardless of the disease severity. However, in the GOLD report 2019 [1], the authors provide a clarification of the concept of "escalation" and "de-escalation" of the COPD therapy, which was introduced in a previous version. While "de-escalation" is mainly employed for the withdrawal of ICS due to lack of response or

	Delivery type	Duration of action (h)
Long-acting beta2-agonists (LABA)		
Arformoterol	Nebulized	12
Formoterol	DPI	12
Indacaterol	DPI	24
Olodaterol	SMI	24
Salmeterol	MDI, DPI	12
Long-acting anticholinergics (LAMA)		
Aclidinium bromide	DPI, MDI	12
Glycopyrronium bromide	DPI	12–24
Tiotropium	DPI, SMI	24
Umeclidinium	DPI	24

DPI = dry powder inhaler; MDI = metered dose inhaler; SMI = soft mist inhaler.

Table 1.
Currently available LABAs and LAMAs as monotherapy.

	Delivery type	Duration of action (h)
Fixed-dose combinations of LABA and LAMA (LABA/LAMA)		
Formoterol/Aclidinium	DPI	12
Formoterol/Glycopyrronium	MDI	12
Indacaterol/Glycopyrronium	DPI	12–24
Olodaterol/Tiotropium	SMI	24
Vilanterol/Umeclidinium	DPI	24

DPI = dry powder inhaler; MDI = metered dose inhaler; SMI = soft mist inhaler.

Table 2.
Currently available fixed-dose combinations of LABA/LAMA.

side effects, such as pneumonia, the "escalation" of treatment should be prompted by either inappropriate symptomatic response to the initial therapy or by the presence of exacerbations despite regular treatment and consists of adding a second class of bronchodilator and/or an ICS and/or other pharmacological agents (azithromycin, roflumilast) in order to ensure maximal symptom relief and to curb the risk of exacerbations.

The choice of the bronchodilator treatment should take into account several factors, such as physiological impairment, symptom burden, and exacerbation risk, and should be individualized according to the drug safety profile, cost, and patients' preference for device and medication [1, 20].

One of the current controversies in COPD [20] is the following: what is best, a progressive escalation of bronchodilator therapy or "maximizing" bronchodilator therapy with dual bronchodilator therapy ab initio? The members of the GOLD Scientific Committee suggest that ensuring a maximal bronchodilation from the beginning could be a reasonable approach for both patients with high symptom burden and patients less severely affected. The latter may underreport their symptoms, masking an underlying resting and exercise lung hyperinflation, which is further linked to increased mortality and risk of severe exacerbations [20]. However, if a single agent is preferred, currently available evidence supports the use of a LAMA (tiotropium) since it improves lung function and health status even in patients with milder disease [47].

2.2 Prevention of exacerbations

COPD exacerbations represent acute worsening of symptoms requiring changes in medication and/or hospitalization [1]. Anthonisen and colleagues' criteria [48] have been used for decades now in an attempt to standardize the evaluation of these events; however COPD exacerbations still have no universally established definition [49] and are subject to diagnostic uncertainty [50].

Historically, the level of healthcare resource use (HCRU) required for the management of COPD exacerbations was used both to define and quantify the severity of the exacerbations, with moderate exacerbations requiring administration of oral steroids and/or antibiotics and severe exacerbations requiring hospitalization [49, 51–53]. However, healthcare use in COPD varies widely depending on access, leading to disparities across different healthcare systems [54]. Furthermore, in order to be treated, an acute event should be reported to healthcare professionals; hence unreported events may not be captured by HCRU definitions. In some reports, such events comprise up to two-thirds of exacerbations and can impair health-related quality of life [55, 56] and increase the risk of hospitalization [57].

Another approach to define exacerbations is based on the systematic and standardized assessment of daily symptoms recorded using specific questionnaires (diaries) administered to the patients on paper or electronically. These questionnaires were developed with the ability to detect worsening of symptoms beyond a pre-specified threshold, based on patients' reporting of their daily symptoms [58, 59]. Advantages of a standardized, validated assessment of COPD symptoms in exacerbation studies include uniform metrics, reduced recall bias, and the ability to fully characterize exacerbations of COPD, including the estimated 50–70% of events that are unreported [55, 56, 59]. Although attractive, this kind of approach is more difficult to implement outside the clinical trial setting, and the concordance with the HCRU-defined events is modest [54, 60].

COPD exacerbations have a marked negative effect on both the patient and underlying disease processes [61] and can result in hospitalization and readmission, an increased risk of death [62], and a significant reduction in health status [55]. Exacerbations are also associated with long-term decline in lung function and a high socioeconomic cost [63, 64]. A history of frequent exacerbations is a good predictor for future exacerbation risk and defines the "frequent exacerbator" phenotype [65]. Thus, optimizing the prevention and management of COPD exacerbations are important clinical issues [61].

The GOLD strategy report stratifies COPD patients based on the severity of their airflow limitation, symptom burden, and the risk of exacerbations; however the recommendations for the pharmacological treatment rely exclusively on the level of symptoms and exacerbation risk [1].

While the initial assessment of exacerbation risk may be biased by the patients' ability to recall historical episodes of symptom worsening prior to being diagnosed with COPD, the reassessment of risk after initial pharmacological treatment should be able to identify patients requiring an escalation of treatment for a better prevention of future exacerbation episodes.

The preferred treatment options for patients at high risk of exacerbation are a LAMA in monotherapy, a LABA/LAMA, or a LABA/ICS combination [1].

There is evidence that both LABAs and LAMAs significantly improve the exacerbation rate versus placebo [66–68]; however, clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment [69, 70].

There is a strong evidence that treatment with fixed-dose combinations of LABA/LAMA improves lung function, symptoms, and health-related quality of life compared to placebo or its individual bronchodilator components [71–73]. The superiority of dual bronchodilation in the prevention of exacerbations compared to monocomponents was demonstrated for a LABA/LAMA combination [74], while another large study found that combining a LABA with a LAMA did not reduce exacerbation rate as much as expected compared to LAMA alone [75].

Similarly, an ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with a history of exacerbations and moderate to very severe COPD [76, 77]. Currently available ICS/LABA combinations are listed in **Table 3**.

Furthermore, another study demonstrated the superiority of a LABA/LAMA combination versus an ICS/LABA combination in the prevention of exacerbations in patients with moderate to very severe COPD and a history of exacerbations, regardless of baseline blood eosinophils [78].

In a recently published review, a group of experts critically evaluated mechanisms potentially responsible for the increased benefit of LABA/LAMA combinations over single long-acting bronchodilators or LABA/inhaled corticosteroids in decreasing exacerbation. These included effects on lung hyperinflation and

	Delivery type	Duration of action (h)
Fixed-dose combinations of LABA and ICS (LABA/ICS)		
Formoterol/Beclometasone	MDI	12
Formoterol/Budesonide	MDI, DPI	12
Formoterol/Mometasone	MDI	12
Salmeterol/Fluticasone	MDI, DPI	12
Vilanterol/Fluticasone furoate	DPI	24

DPI = dry powder inhaler; MDI = metered dose inhaler.

Table 3.
Currently available fixed-dose combinations of LABA/ICS.

	Delivery type	Duration of action (h)
Fixed-dose combinations of LABA, LAMA and ICS (LABA/LAMA/ICS)		
Formoterol/Glycopyrronium/Beclometasone	MDI	12
Vilanterol/Umeclidinium/Fluticasone furoate	DPI	24
Formoterol/Glycopyrronium/Budesonide	MDI	12

DPI = dry powder inhaler; MDI = metered dose inhaler.

Table 4.
Currently available fixed-dose combinations of LABA/LAMA/ICS.

mechanical stress, inflammation, excessive mucus production with impaired mucociliary clearance, and symptom severity [79].

Although triple therapy in separate inhalers is already in use for COPD patients for a couple of years now, fixed triple therapy combining an ICS, a LABA, and a LAMA in a single inhaler recently emerged on the market. Currently, there are only two products approved by the European Medicines Agency (EMA) for use in COPD, and a third one was recently approved in Japan (see **Table 4**) [80].

Several recent studies have demonstrated that single-inhaler triple therapy is more effective in reducing the exacerbation than LAMA alone, a LABA/ICS, or a LABA/LAMA combination [81–84].

The GOLD algorithm for the escalation of treatment in patients with persistent risk of exacerbations despite regular treatment provides that patients taking a single bronchodilator should be switched to dual bronchodilation and then to triple therapy and/or additional therapies. Alternatively, some patients with high blood eosinophils may benefit from a LABA/ICS combination prior to receiving triple therapy [1].

The use of ICS in COPD has become very controversial in the last years, owing on the one hand to the limited effect on lung function and on the other hand to potential side effects associated with long-term use at the higher doses recommended for the treatment of COPD. These include:

- Risk of infections such as pneumonia [85], tuberculosis and non-tuberculous mycobacterial disease [86], and oropharyngeal candidiasis [87]

- Skin lesions [88]

- Diabetes onset and progression [89]

- Increased risk of bone fractures [90]
- Cataracts [91]

The use of ICS alone is discouraged in COPD [20]; however several studies have demonstrated a consistent effect on exacerbation reduction of LABA/ICS fixed-dose combinations versus individual monocomponents [76, 77, 87, 92, 93].

The need for biomarkers accurately assessing disease activity and response to therapy in order to develop better COPD treatment is well acknowledged [94]. Peripheral blood eosinophil level has emerged in the recent years as a promising biomarker, showing capabilities to predict both the risk of exacerbation and the magnitude of response to ICS therapy [95–97]. Thus, several post hoc or pre-specified analyses of clinical trials have shown that blood eosinophil levels may indicate which patients can benefit from a reduction of exacerbations by the treatment with ICS-containing regimens [84, 96, 98]. Various cutoff points were proposed for the level of blood eosinophils in order to identify the patients who would benefit most from the ICS therapy. A recent pooled analysis (n = 4528) evidenced that a level of blood eosinophils >300/mmc^3 suggests a beneficial role of ICS, while a low level of blood eosinophils (<100/mmc^3) may be a negative predictor of the ICS effects. This was previously observed in other two post hoc analyses [99, 100] and was confirmed in a pre-specified analysis of another randomized clinical trial [101].

Other classes of pharmacological agents, such as PDE4-inhibitors (roflumilast) or antibiotics (azithromycin) administered orally on top of inhaled therapy, may bring an additional benefit in reducing exacerbations [102, 103]. The side effects, however, limit their use to selected patients only.

2.3 Mortality risk

Two large clinical trials have failed to demonstrate a positive effect of the active treatments (LABA/ICS, ICS alone, and LABA alone) versus placebo on the mortality risk [36, 104].

Smoking cessation, vaccinations, supplemental oxygen for hypoxemic patients, and lung volume reduction surgery in selected patients are the only therapies that have been proven to improve survival; smoking cessation also attenuates disease progression [20].

3. Conclusions

Inhaled long-acting bronchodilator treatment plays a central role in the management of stable COPD. Anti-inflammatory treatment with inhaled corticosteroids in combination with a long-acting beta2 agonist or with dual bronchodilation (LABA and LAMA) as part of the triple therapy improves outcomes especially in patients with high blood eosinophil level.

Despite all the progress made in the recent years in the field of COPD, we are still lacking drugs that can effectively modify the course of the disease [23].

The unmet needs in COPD warrant further research for the discovery of new biomarkers and effective therapeutic agents able to radically improve short-term and long-term outcomes in patients suffering of this disease.

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Author details

Stefan-Marian Frent
Department of Pulmonology, University of Medicine and Pharmacy Timisoara, Timisoara, Romania

*Address all correspondence to: frentz.stefan@umft.ro

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