

# Classical and Emerging Therapies against Chronic Obstructive Pulmonary Disease

Han-Rong Feng, Chao Zhang, Song-Min Ying

Department of Pharmacology & Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang 310058, China

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a worldwide respiratory disease which always co-exists with multiple extrapulmonary comorbidities such as cardiovascular diseases and osteoporosis. The World Health Organization pointed out that till 2030, COPD would be the third leading reason of mortality.<sup>[1]</sup> In spite of the advanced medical research and health-care efforts, COPD still shows continuously increasing quantity of death. Tobacco smoking, indoor and outdoor air pollution (for example, biomass fuel), virus, and pulmonary dysplasia are the main risk factors for COPD. All these factors eventually destroy lung parenchymal tissue and disturb repair and defense system, which eventually lead to emphysema and small airway fibrosis [Figure 1].

The main pathological features of COPD are airway inflammation, oxidative stress, imbalance of protease/antiprotease, and mucus hypersecretion. Inhaled corticosteroids (ICS) and bronchodilators are the most common representatives for COPD therapies. In this editorial, we compare the efficacy and safety of several medications and introduce the emerging biologic therapies for COPD.

## INHALED CORTICOSTEROIDS

ICS are a commonly used treatment for 70% of COPD patients, and some of these patients are at low risk of exacerbations. Current guidelines for the management of COPD recommend limiting dose of ICS to patients with more severe disease and increased exacerbation risks.<sup>[2]</sup> However, the adverse effects of using ICS cannot be ignored. For example, cataract, osteoporosis, and pneumonia have a

greater incidence among elderly ICS-administrated patients, which indicates that ICS may have significant side effects related to age.<sup>[3]</sup> For this reason, the use of ICS in elderly COPD patients should be treated more cautiously.

## BETA<sub>2</sub>-ADRENOCEPTOR AGONISTS

Beta<sub>2</sub> (β<sub>2</sub>)-adrenoceptor agonists are the most widely used bronchodilators. This kind of agonists has a significant effect on relaxing airway smooth muscle (ASM) as the targeting sites of β<sub>2</sub>-adrenoceptors (β<sub>2</sub>-ARs) are located on ASM.<sup>[4]</sup>

β<sub>2</sub>-adrenoceptor agonists are classified into two groups according to the acting time: the short-acting β<sub>2</sub>-adrenoceptor agonists (SABAs) for short-acting time (4–6 h) and the long-acting β<sub>2</sub>-adrenoceptor agonists (LABAs) for long-acting time (12 h). Respiratory physicians now use LABAs as prophylactic management for bronchoconstriction and SABAs to relieve acute exacerbations.<sup>[5]</sup>

SABAs are only used as the initial treatment for relieving breathlessness for COPD patients. The most commonly used SABAs are fenoterol, levalbuterol, salbutamol, and terbutaline. They all strongly and specifically react with β<sub>2</sub>-ARs but not to α-ARs. The advantage of SABAs is that the reacting time is usually within 3–30 min. For example, atomized inhaled salbutamol improves breathing in 5 min

**Address for correspondence:** Dr. Song-Min Ying, Department of Pharmacology & Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang 310058, China  
E-Mail: yings@zju.edu.cn

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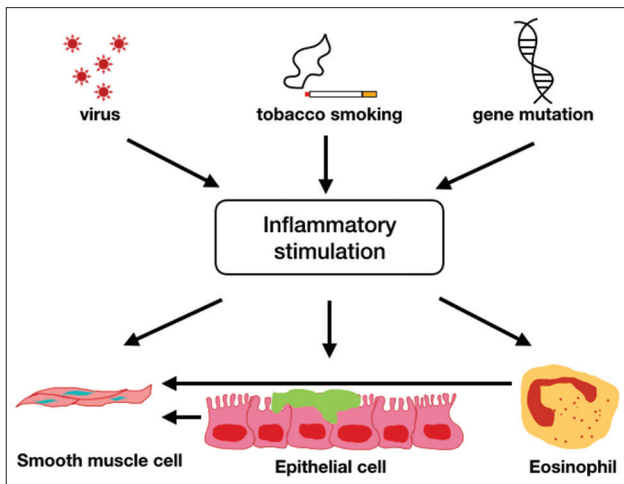
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**Figure 1:** Diagram for the etiology and pathogenesis of COPD. COPD: Chronic obstructive pulmonary disease.

and lasts for the next 4–6 h. LABAs are a frontline treatment for COPD patients. Comparing with SABAs, LABAs show longer duration time which is always more than 12 h. Currently, the commonly used LABAs are formoterol and salmeterol.<sup>[5]</sup> Recently, the ultra-LABAs, which are often efficient for 24 h, have attracted much attention. LABAs and ultra-LABAs both significantly relieve dynamic pulmonary hyperinflation and improve dyspnea and health-related quality of life (HRQoL). Besides, LABAs are more convenient and suitable for COPD patients, while SABAs are mainly used as adjuvant treatment or for temporary need.<sup>[5]</sup>

### INHALED CORTICOSTEROIDS IN COMBINATION WITH LONG-ACTING BETA<sub>2</sub>-ADRENOCEPTOR AGONISTS

ICS are also constantly recommended for treating COPD patients in combination with LABAs. ICS mainly improve airway inflammation, and LABAs dilate bronchial smooth muscle. The combination of these two medications helps COPD patients with a better clinical control. There are several ICS/LABA combinations, for example, budesonide/formoterol and fluticasone/salmeterol are the two frequently used ICS/LABA combinations. Even though when considering an ICS/LABA combination as the therapy for COPD patients, the risk-benefit ratio should still be evaluated strictly.<sup>[6]</sup>

### LONG-ACTING MUSCARINIC ANTAGONISTS

Long-acting muscarinic antagonists (LAMAs) is a selective M3-receptor antagonist with obvious efficiency and fewer adverse reactions. Some LAMA/device systems are approved therapies for treating COPD. These medications improve pulmonary function and reduce acute bronchial exacerbations with good safety.<sup>[7]</sup> Glycopyrronium bromide and aclidinium bromide are two represent LAMAs. Once-daily inhaled glycopyrronium bromide has significant effects on the level of forced expiratory volume in 1 second (FEV1) in patients with moderate-to-severe COPD.

Furthermore, a nearly report indicated that once-daily inhaled glycopyrronium bromide provides rapid onset for bronchodilatation and sustains for 24 h.<sup>[8]</sup>

### LONG-ACTING MUSCARINIC ANTAGONIST IN COMBINATION WITH LONG-ACTING BETA<sub>2</sub>-ADRENOCEPTOR AGONIST

In clinical trials, dual bronchodilation of LAMA/LABA combination was applied over the past few years.<sup>[9]</sup> Recent preclinical studies found that the combination of these two medications induced better bronchodilation than LAMA alone. Meanwhile, the combination improved many patient-reported outcomes significantly.<sup>[10,11]</sup> Furthermore, some studies drew a comparison between LAMA/LABA inhalers and ICS/LABA combination inhalers in moderate-to-severe COPD patients. A study showed that indacaterol–glycopyrronium (a LAMA/LABA combination) was more effectual than salmeterol–fluticasone (a ICS/LABA combination) in preventing COPD exacerbations in patients who had a long history of exacerbations.<sup>[12]</sup> Another study compared all the currently available LABAs/LAMAs and found that compared to LAMA or LABA/ICS, LAMA/LABA showed greater efficacy and comparable safety profiles, supporting LAMA/LABA combinations as the first-line treatment options for COPD.<sup>[13]</sup> Moreover, LAMA/LABA provided larger improvement in trough FEV1 versus ICS/LABA.<sup>[14]</sup> The 2017 guidelines for the Global Initiative for Chronic Obstructive Lung Disease (GOLD) placed LAMA/LABA earlier than ICS in the stepwise escalation of COPD therapy.<sup>[15]</sup>

These studies demonstrated that LAMA/LABA combinations work synergistically on ASM relaxation. The results also indicated using LAMA/LABA combinations as therapies for COPD.<sup>[16]</sup> However, it is still a strong medical demand to determine the most suitable LAMA/LABA doses.

### TRIPLE INHALED THERAPY: LONG-ACTING MUSCARINIC ANTAGONIST + LONG-ACTING BETA<sub>2</sub>-ADRENOCEPTOR AGONIST + INHALED CORTICOSTEROIDS

Triple inhaled therapy for COPD is constituted with an ICS, a LAMA, and a LABA, which is recommended in the GOLD management tactics for COPD patients who have clinically significant symptoms and of high risk of getting frequent or severe exacerbations in spite of treatment with the combination of ICS/LABA or LAMA/LABA.<sup>[17]</sup> A study showed that consuming the once-daily single-inhaler triple therapy with fluticasone furoate, umeclidinium, and vilanterol improved a better lung function and HRQoL and a significantly lower rate of moderate or severe COPD exacerbations compared to dual therapy with fluticasone ICS/LABA or LAMA/LABA. In addition, the triple therapy also decreased the rate of hospitalization than

LAMA/LABA.<sup>[18]</sup> Another study proved that the advantages of single-inhaler triple therapy were remarkable compared with ICS/LABA therapy in advanced COPD patients.<sup>[19]</sup>

## NOVEL ANTI-EOSINOPHILIC TREATMENTS

COPD is conspicuously associated with neutrophilic inflammation, comparing with T-helper 2-mediated eosinophilic airway inflammation which mainly observed in asthma. However, eosinophils might also act as a key role in 10–40% of COPD patients.<sup>[19]</sup> Interleukin (IL)-5 is a decisive factor in the differentiation and maturation of eosinophils, which is binding to surface receptors of progenitors of eosinophils.<sup>[20]</sup> Monoclonal IL-5 and IL-5 receptor- $\alpha$  (IL-5R $\alpha$ ) antibodies neutralizing IL-5 or blocking IL-5R $\alpha$  are recently developed medications for asthma patients, such as mepolizumab and benralizumab, while they were also reported as effective therapies for COPD.<sup>[21]</sup>

Mepolizumab blocks IL-5 to reduce eosinophil counts in blood and pulmonary tissues. A recent study showed that mepolizumab was related to a lower rate of moderate or severe exacerbations than placebo among COPD patients.<sup>[22]</sup> Benralizumab is also a humanized monoclonal antibody targeting IL-5R $\alpha$ . The first research of the biologic therapies in COPD reported that benralizumab improved FEV<sub>1</sub>, without decreasing the rates of exacerbation.<sup>[23]</sup> These results proved that anti-IL-5 had good effects on lung function in eosinophilic COPD, suggesting that eosinophilic airway inflammation contributed to COPD exacerbations, but the role of eosinophils in COPD exacerbations remains to be clarified.

## PHOSPHODIESTERASE-4 INHIBITOR

Phosphodiesterase-4 (PDE-4) is a major cAMP-metabolizing enzyme existing both in lung structural and inflammatory cells. The inhibition of PDE-4 increases intracellular cAMP and reduces the activation of inflammatory cells, and PDE-4 inhibitors are a novel medication approved for COPD.<sup>[24]</sup> Currently, several selective PDE-4 inhibitors are being developed for the treatment of COPD, such as roflumilast, cilomilast, arofylline, AWD-12-281, and SCH-351591. Roflumilast was associated with a prominent ( $P < 0.01$ ) decrease in neutrophil and eosinophil levels and serum levels of pro-inflammatory cytokines. It reduced pulmonary inflammation by decreasing prolyl endopeptidase activity and acetyl-proline-glycine-proline.<sup>[25]</sup> In a therapeutic protocol, the influence of using PDE-4 inhibitors to reduce lung fibrosis was almost same to nintedanib and pirfenidone. These results indicated that PDE-4 inhibition could be used for treating fibrotic lung disease.<sup>[26]</sup> Nevertheless, the fact that PDE-4 inhibitors had side effects on symptoms cannot be ignored. It is common for the patients to get weight loss and gastrointestinal adverse effects.<sup>[27]</sup> According to the GOLD 2017 guidelines, PDE-4 inhibitors may be better used as add-on therapy in the patients who have persistent symptoms or already accepted optimal COPD management but still in exacerbations.<sup>[15]</sup>

In conclusion, COPD is a type of obstructive pulmonary disease characterized by long-term breathing problems and poor airflow. This editorial attempts to list some emerging biologic therapies for COPD patients. The main purpose of COPD treatment is to reduce the rate of exacerbations and mortality. In recent decades, much more new therapies have been developed successfully and proved to be effective. However, all the current treatments are reliever medications, which cannot completely prevent the progress of the disease. Thus, the development of new medications to COPD is still the research focus in this field.

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