

Combination Therapy for COPD: Efficacy and Prospects of Multiple Therapy

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Abstract. Chronic obstructive pulmonary disease (COPD) is one of the most popular respiratory diseases among the world. Due to the unclear pathogenesis of COPD, the current treatment direction is mostly to prevent and relieve the existing symptoms. The current direction of treatment for COPD is to control the disease and delay its progression through medication, physical therapy, and surgery in severe cases. Inhaled glucocorticoids, long-acting β agonists (LABA) and long-acting muscarine anticholinergic (LAMA) are widely used in the treatment of COPD. This article discusses the specific symptoms of COPD, and discusses the feasibility and development level of combined therapy combined with the current situation of relevant drug therapy.

Keywords: COPD, LABA/LAMA/ICS, Combined Treatment.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a one kind of respiratory disease that common in people, with the significant morbidity as well as the mortality. However, COPD is underdiagnosed with many that are not diagnosed until late in the clinical stage of the disease, especially in the current COVID-19 epidemic [1]. The patients with this disease always show signs of persistent airflow restriction. Patients with COPD usually have cough, dyspnea, and expectoration, and can have sudden exacerbations (exacerbations), which is usually the result of respiratory infection [2]. Evidence-based big data so far suggests that COPD is the preventable and the treatable diseases. Once diagnosed, patients need lifelong treatment. There are many pathogenesis factors are not clear enough, smoking and ageing are established as principal risk factors [3]. There is no drug to cure COPD, most of the treatment is to alleviate the symptoms of patients, such as lowering blood pressure, airway relaxation, etc.

β_2 receptor agonists are a kind of agonists that can excite the distribution in airway smooth muscle β_2 receptor is an asthma therapeutic drug that produces bronchodilation, which belong to bronchodilators and can quickly improve the symptoms of dyspnea, cough and so on. Long-acting β agonists (LABA), along with long-acting muscarine anticholinergic (LAMA), and LABA/ inhaled corticosteroids (ICS) are common long-acting bronchodilators. Combination therapy of these drugs is usually used in patients with COPD (with moderate to severe severity of the disease) or other severe airway diseases to control symptoms such as dyspnea, cough and prevent exacerbation [4]. When there is a need for two drugs, LAMA combines with LABA (LAMA+LABA) and LABA combines with ICS (LABA+ICS) are fairly appropriate decision, although there are needs for two kinds of drugs, they can be administered through a single drug device. However, what is still not clear is that which group of inhalers is better effective methods or whether any particular formulation is better than other inhalers in the same group or category. This paper aims to discuss the treatment progress of the combination therapy in COPD from the perspective of mechanism and treatment progress.

2. Pathological mechanism in COPD

The pathogenesis of COPD is on account of inhalation of toxic particles and gases, which will cause innate and adaptive inflammatory immune response [5]. Smoking, as all know, is the main reason

that result in the injury of this inhalation, while many other environmental exposures and genetic (genetic) risks may also play a role in the pathogenesis of COPD [6]. The immune response associated with COPD produces inflammation, and subsequent tissue repair and remodeling processes increase mucus production, leading to emphysema. Some COPD patients may have specific symptoms like a prolonged cough, which may be dry or mucous; fatigue; shortness of breath or frequent respiratory infections. The cause is disruption of the lung surface where gas is exchanged. By observing the organ characteristics of smokers and patients with emphysema, common emphysema begins in the respiratory bronchioles that was near the thickened and the narrowed bronchioles and for which are the main obstruction site of COPD. However, the mechanism by which the small airway wall thickens so close to emphysema damaged lung tissue remains an unsolved mystery.

3. Treatment for COPD

LAMA a long-acting anticholinergic drug, can make parasympathetic nerve regulates airway smooth muscle tension and airway inflammation in patients with chronic airway diseases through peripheral cholinergic receptor signaling pathway. dilates the airway by selectively blocking acetylcholine M3 receptor and inhibiting bronchoconstriction. Whatever the severity of the disease, the LAMA inhalers' curative effect in improving symptoms, increasing exercise capacity and reducing the frequency of deterioration has been fully demonstrated in patients with COPD, supporting the use of Lama as a first-line treatment for patients with symptomatic COPD [5,7,8].

LABA relaxes airway smooth muscle by connecting to β 2-adrenergic receptors. Studies have shown that LABAs may also provide anti-inflammatory and protective effects on bronchoconstrictors. It is not recommended that patients with asthma or COPD regularly use short acting drugs with rapid onset and lasting for 4 to 6 hours β Receptor agonists. Laba lasting about 12 to 24 hours is considered a maintenance drug.

If the risk of recurrent seizures is high, inhaled corticosteroids (ICS) can be considered. ICS have taken center stage in the treatment of COPD, and are used in combination with various substances to alleviate symptoms of COPD and respiratory tract inflammation in a variety of ways [9].

For particularly symptomatic patients, use LAMA and LABA dual bronchodilator therapy has been shown to provide more symptom relief than bronchodilator alone. Previous GOLD guidelines recommended that ICS be combined with LAMA for COPD patients with severe airflow restriction or high risk of acute exacerbation. Both are the dual therapy of COPD, It will also be used clinically the triple therapy (a combination of ICS, LABA and LAMA).

3.1. The dual therapy of COPD

3.1.1 LAMA/LABA

With regard to the mechanism of the combined treatment of LAMA and LABA, one possibility is to observe the corticosteroid saving activity of adding LAMA and placebo during the gradual reduction of blood pressure by mannitol stimulation, nitric oxide and other non-invasive inflammatory surgery. Another pharmacological mechanism may cause the protective effect of tiotropium bromide. These mechanisms may infer the potential synergy between LAMA and LABA [9].

The reasonable principle of the combination of LABA and LAMA in the treatment of COPD is that they provide the synergistic effect of airway smooth muscle relaxation in small and medium-sized human airway. Since muscarinic M3 receptor mainly appears in the bronchus, and the density gradually decreases from segmental to sub segmental bronchus, it is missing in the parenchyma of the lung. In contrast, the effect of the β 2-adrenergic receptors is to increase along the airway, the density in subsegmental bronchus, also lung parenchyma was about twice that of mAChR. The differential distribution of these receptors may finally lead to improve the efficacy of COPD patients, thus is the basic. When using LABA and LAMA for 12 weeks, the lung function (FEV1) was significantly improved, compared with the use of the LABA alone (also 12 weeks). These effects were sustained

over time. Prominent change in TDI and SGRQ scores were observed for LABA/LAMA FDCs with each comparator that was evaluated. For the reduction of the rate of acute exacerbation, only LABA/LAMA FDC indaterol/gulammonium was superior to LAMA in reducing the rate of acute exacerbation, while odaterol/tiotropium bromide and indaterol/gulammonium bromide showed the effect of improving ET and IC [10].

3.1.2 ICS/LABA

The classic pathway of the basic mechanism of ICS anti-inflammatory effect is that GS is easy to enter the cell through the cell membrane, combine with the glucocorticoid receptor in the cytoplasm to form an activated GS-GR complex, enter the nucleus to start gene transcription, cause the increase or decrease of transcription, change the level of mediator related proteins, and exert anti-inflammatory effect by affecting the cells and molecules necessary for inflammatory response.

Compared with LABA alone, ICS/LABA can significantly lower the annual incidence of the exacerbations, and at the same time, improve the patient's lung function, especially in patients with a history of frequent exacerbations [11].

Nannini et al. found that when COPD patients were treated with LABA alone, it can have a 5% higher risk of worsening within one year than those treated with LABA/ICS, which shows that the LABA/ICS can reduce the frequency of acute attacks compared with the use of LABA alone (long-term β_2 The average attack of 2 receptor agonist is once a year, while the average attack of combined inhaler is 0.76 times a year) [11]. Compared with the two drugs alone, ICS/LABA can improve function of the lung and reduce the deterioration of the COPD [12]. According to Cochrane's systematic review of 14 studies involving 11794 participants with severe COPD, the increased risk of fixed dose ICS / LABA combined inhaler was reduced by 24% compared with LABA alone [11].

3.2. Triple therapy of COPD

Triple inhalation therapy for COPD consists of a combination of ICS, LABA and LAMA. In 2017, the first COPD triple compound new drug (Trelegy Ellipta) was approved by FDA. Compared with monotherapy using bronchodilators alone, the combined use of bronchodilators with different mechanisms of action, such as LABA and LAMA, may increase the degree of bronchiectasis and reduce symptoms. Available evidence shows that although ICS/LABA or LAMA / LABA dual treatment is feasible, the triple combination of ICS, LAMA and LABA, whether fixed dose or open combination therapy can effectively reduce the COPD risk and improve the function of the lung, and may reduce the continuous deterioration, persistent dyspnea and mortality of COPD. However, when triple therapy is recommended, the guidelines and strategies for the disease are not very comprehensive. Some scholars also believe that triple therapy was not applicable for the most COPD patients, because most patients have mild symptoms and the risk leading to deterioration is very low [13]. Therefore, the individualized research of triple therapy may still need to be further explored.

Take budesonide/glycopyrronium/formoterol as an example, the exacerbations and pulmonary function benefits associated with budesonide/glycopyrrone/formoterol were seen regardless of gender, age, race, history of exacerbation of COPD, cat score, previous use of ICS, reversibility of bronchodilators, and FEV1 after bronchodilators. The current idea is that the pathogenesis of COPD is closely related to autoimmune imbalance. Eosinophils may participate in the pathophysiological process of COPD by participating in autoimmune imbalance. In addition, the beneficial effects of budesonide/glycopyrrolidone/formoterol can be observed in a wide range of baseline eosinophil counts, and the treatment benefits of patients are more significant with the increase of eosinophil count [14].

Although the therapeutic effects of ICS containing therapies such as ICS/LAMA/LABA and ICS/LABA increase with the increase of blood eosinophil count, the exact mechanism of this benefit in patients with COPD is still unclear [15]. A RCT was conducted to explore the efficacy of single inhalation, triple inhalation and double inhalation therapy for 52 weeks. The primary end point was all-cause mortality. They found that the risk of death was apparently lower in the triple inhalation FDC group than in the double inhalation therapy group ($p=0.006$), but in mortality, there was no

apparent difference between the triple inhalation FDC and double inhalation therapy treatment groups($p=0.66$). Besides, patients treated with triple inhalation FDC had less moderate or severe exacerbation than those in the dual treatment group. However, the risk of pneumonia of the triple inhalation FDC group is higher than the double inhalation therapy group[16].

4. Better selection of treatment options based on COPD phenotype

COPD has different clinical phenotypes. For instance, chronic cough, cough expectoration, shortness of breath or dyspnea, wheezing and chest tightness, weight loss and anxiety. The definition of these phenotypes may enable us to better understand which patients may get more benefits from the ICS and which patients may use LABA.

For example, LABA and/or LAMA and rehabilitation therapy are the primary treatment of choice due to the poor response of the emphysema phenotype to the treatment of now available anti-inflammatory drugs. ICS was unable to inhibit inflammation due to the significant reduction of histone deacetylase-2 (ribozyme required for corticosteroids to turn off activated inflammatory genes). More and more evidence clearly shows that we should treat each patient with COPD according to their respective phenotypes. Therefore, the concept of treating COPD based on disease phenotype deserves great attention.

5. Discussion

COPD is Chronic obstructive pulmonary disease (COPD) is a one kind of respiratory disease that common in people, with the significant morbidity as well as the mortality. There is no curable drug to treat, mainly to alleviate symptoms. New treatment options (dual therapy (LABA/LAMA, LABA/ICS), triple therapy (ICS/LABA/LAMA)) open the door to provide more personalized management methods for patients with COPD in clinical practice. Dual therapy can improve the lung function of patients, increase the degree of bronchiectasis and reduce symptoms, but patients still have a high risk of malignant transformation. Triple therapy is the most effective drug treatment for COPD patients with moderate to very severe airflow restriction, especially those with a history of exacerbation. While compared with LABA/LAMA, they may increase the risk of pneumonia. More personalized approach for pharmacotherapy should be focused on and based on the different phenotypes, selecting the most suitable scheme for patients.

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