

Triple inhaled therapy in chronic obstructive pulmonary disease. Who is it for?

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) has become the third leading cause of death in the world at the beginning of this decade [1]. COPD management aims at relieving daily symptoms, improving exercise tolerance and quality of life. The prevention of exacerbations is an important goal of COPD treatment as well, because they are linked to disease progression and increased mortality. At the same time, management of the comorbidities of COPD, mainly cardiovascular, is crucial for keeping overall disease burden under control [2].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the use of inhaled therapy with bronchodilators as initial treatment for the maintenance of stable COPD. The most commonly used are long-acting bronchodilators, namely long-acting muscarinic antagonists (LAMAs) and long-acting beta2-agonists (LABAs), alone or in combination. For patients with high blood eosinophil counts (>300 cells per μL), the addition of inhaled corticosteroids (ICS) is considered. Patients that suffer from frequent exacerbations or may have significant dyspnea in follow-up visits should also receive treatment with inhaled corticosteroids (ICS) together with bronchodilators. Currently, there are several inhaler combinations of these three pharmacological classes, including triple therapy in a single inhaler [3].

Clinicians often face the decision of whether to escalate treatment from a LABA/LAMA inhaler to triple

therapy. Existing studies have compared the effectiveness and safety of different single-inhaler triple therapy options with single-inhaler dual bronchodilators, specifically LABA/LAMA, in COPD patients. Interpreting the data from these studies has been challenging.

Evidence from clinical trials

The IMPACT trial compared a single-inhaler triple therapy (umeclidinium, vilanterol, and fluticasone furoate) with two dual inhalers: a LABA/ICS (vilanterol and fluticasone furoate) and a LABA/LAMA (umeclidinium and vilanterol) over one year [2]. The trial included 10,355 COPD patients with moderate-to-severe airflow limitation and a history of exacerbations, including patients with asthma. Triple therapy showed a 25% lower rate of exacerbations and a 42% reduction in all-cause mortality compared to LABA/LAMA [4,5].

The TRIBUTE trial compared a single-inhaler triple therapy (glycopyrronium bromide, formoterol fumarate, and beclomethasone dipropionate) with a dual LABA/LAMA bronchodilator (glycopyrronium and indacaterol) over one year. The study included 1,532 patients with COPD having severe airflow limitation and at least one moderate or severe exacerbation in the previous year. Patients with asthma were included, as well in this study. All patients switched to the LABA/LAMA comparator after discontinuing their maintenance therapy during a 2-week run-in before randomization. Triple therapy arm of the study showed a 15% lower rate of moderate to severe exacerbations compared to the LABA/LAMA arm [6].

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Received: 30 Nov 2023; Accepted: 15 Dec 2023

Key words: COPD; respiratory medicine; GOLD initiative

The ETHOS trial investigated the effectiveness and safety of triple therapy in obstructive lung disease. It compared a single-inhaler triple therapy (consisting of glycopyrrolate, formoterol, and budesonide) with two dual inhalers: LABA/ICS (formoterol and budesonide) and LABA/LAMA (glycopyrrolate and formoterol). The study spanned over one year and involved 8,509 COPD patients with moderate-to-very severe airflow limitation and a history of at least one exacerbation in the past year. Some patients had a previous diagnosis of asthma. During a two-week run-in period, all patients discontinued their regular maintenance therapy and instead used short-acting bronchodilators. However, patients continued using ICS during the run-in and the use of ICS was randomly discontinued at the start of the trial. The results showed that triple therapy led to a 24% lower rate of moderate to severe exacerbations and a 46% lower mortality rate when compared to LABA/LAMA [7,8].

A real-world evidence study compared the effectiveness of single-inhaler triple therapy with dual bronchodilators in COPD patients. The study used data from the UK's Clinical Practice Research Datalink and included patients treated between 2017 and 2020. They looked at patients who had not used ICS but could have used LABA or LAMA. The study followed these patients for one year and adjusted for propensity score weighting to make the treatment groups comparable. The cohort included 4,106 new users of single-inhaler triple therapy and 29,702 users of dual bronchodilators. The results showed that triple therapy had a slightly higher risk of the first moderate or severe exacerbation compared to dual bronchodilators (adjusted hazard ratio of 1.08). However, triple therapy was more effective for patients with two or more previous exacerbations, existing asthma history, and high blood eosinophil count (>300 cells per μL). Triple therapy was associated with increased all-cause mortality and pneumonia [9].

Cardiovascular risk and expected benefit

There is evidence that inhaled maintenance therapy can help relieve symptoms, reduce exacerbations, and improve quality of life. The choice of therapy should be based on a comprehensive assessment of the benefits and risks for each individual patient, considering their specific characteristics [10]. COPD often co-exists with other complex health conditions, such as cardiovascular diseases, anxiety and depression, sarcopenia and peripheral muscle dysfunction, osteopenia and osteoporosis,

lung cancer, anemia, or polycythemia [11].

Cardiovascular diseases are a significant cause of mortality in COPD patients, being second cause of mortality in those with mild-to-moderate airway obstruction, after lung cancer, and second cause after respiratory failure in those with severe airway obstruction. Common risk factors (age, smoking, pollution), systemic inflammation, reduced physical activity, lung hyperinflation, and hypoxemia contribute to the high prevalence of cardiovascular diseases in COPD patients. Exacerbations further increase the risk of cardiovascular events [12,13].

When evaluating the benefits and risks for individual patients, it is important to consider the impact of treatments on cardiovascular risk. The effects of inhaled COPD maintenance treatments on cardiovascular risk remain a topic of debate, with inconclusive evidence from available data.

A recent meta-analysis examined the occurrence of major adverse cardiovascular events in patients receiving combination therapy of LABA/LAMA with or without ICS. The study suggests that both treatment options involving dual bronchodilation increase the risk of cardiovascular events, particularly in patients with severe airflow obstruction. The yearly rate of cardiovascular events is estimated at least 1%. Additionally, the analysis showed that triple therapy (LABA/LAMA/ICS) resulted in fewer cardiovascular deaths than LABA/LAMA dual bronchodilator therapy, indicating a possible protective effect of ICS against cardiovascular events [14].

Withdrawing inhaled steroids

Another important study in the field is the SUNSET study, which examined the efficacy and safety of direct de-escalation from long-term triple therapy to indacaterol/glycopyrronium in non-frequently exacerbating patients with COPD. The results showed that in patients with COPD, but without frequent exacerbations on long-term triple therapy, it is possible to remove the ICS and de-escalate to LABA/LAMA with only a small decrease in lung function and no difference in exacerbations. The higher exacerbation risk was demonstrated in patients with ≥ 300 blood eosinophils per μL ; thus, these patients are likely to benefit from triple therapy [15].

CONCLUSION

Although inhaled therapy can improve COPD prognosis through the reduction of exacerbations and improvement of lung function, inhaled treatments may

also cause adverse effects. Bronchodilator use is linked to increased cardiovascular risk and inhaled corticosteroids are associated with pneumonia and systemic side-effects.

Well-conducted observational studies can provide valuable real-world evidence that complements the major randomized clinical trials. Meanwhile, unbiased data analyses suggest that single-inhaler triple therapy should primarily be reserved for patients with frequent exacerbations, as described in GOLD suggestions. The majority of COPD patients should be given dual bronchodilators, which are proven to be equally effective treatment.

Conflict of interest disclosure: None to declare.

Declaration of funding sources: None to declare.

Author contributions: DL: conception, manuscript preparation; KK: conception, manuscript preparation.

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