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Triple therapy in chronic obstructive pulmonary disease: consideration under new evidence

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Chronic obstructive pulmonary disease (COPD) is the most common chronic airway disease worldwide. Recent epidemiologic survey shown that as many as 100 million people have COPD in China, leading to heavy disease burden comparable to hypertension and diabetes.[1] Therefore, COPD has been listed as one of the public health priorities in "Action Plan of Heathy China 2030". It has been recognized worldwide that the goals of long-term treatment of COPD are optimization of symptom relief, prevention and treatment of exacerbations, prevention of disease progression and reduction of mortality.[2]

The choice of pharmacological therapy for stable COPD has been substantially evolved in the past 50 years from a short-acting bronchodilator, oral theophylline and mucolytics being central to the management of COPD in 1960s, to an inhaled corticosteroid (ICS) plus long-acting β2 agonist (LABA) (ICS/LABA) in 1990s, to multiple long-acting muscarinic antagonists (LAMAs) and more potent LABAs in 2000s, to "fixed triple" (ICS/LABA/LAMA) in a single inhaler after 2010. The drivers of these therapeutic advance are from the facts that many COPD patients continue to have symptoms, exacerbations, and disease progression whilst receiving optimal medical therapy.[3]

The emergence of a fixed-dose combination of LABA, LAMA and ICS in a single inhalation device has changed the approach to inhaled therapy. Most double-blind, international multicenter, randomized controlled trials of triple therapy have shown to lead to a lower risk of COPD exacerbation, a greater reduction in symptoms, a slower disease progression, better lung function and a promising signal of reduced all-cause mortality than dual therapies as shown in Supplementary Table 1, http://links.lww.com/SCS/C239.[4-9] A current hot topic for discussion in COPD is that how clinicians can incorporate these updated evidence to clinical practice and establish personal therapy based on individualized characteristics. To do this, the following issues should be considered.

First, COPD is a heterogeneous and complex disease with different types of phenotypes (*ie,* chronic bronchitis, emphysema, frequent exacerbator, COPD-asthma overlap, *etc.*), disease severity (group A, B, C and D), frequency, causes and severity of exacerbation and patterns of disease progression.[2] The complexity and heterogeneity justify the need for personalization of the assessment and clinical management of COPD to improve quality of life, optimize outcomes, minimize pharmacological treatment burden and adverse effects.

Second, the features of triple therapy clinical trials in COPD should be reviewed [Supplementary Table 1, http://links.lww.com/SCS/C239]. To summarize, (1) all clinical trials performed, to date, with triple therapy have included patients with high symptom burden (COPD assessment test [CAT] ≥10) and moderate-to-very severe airflow limitation.[4-10] (2) Most of the clinical trials with triple therapy to date included patients with increased risk of exacerbation (at least one moderate-to-severe exacerbation per year) while receiving LAMA, LABA/LAMA or LABA/ICS therapy.[4-8,10] (3) All triple therapy trials included COPD patients with a history of asthma.[4-10] Actually, a further analysis of TRIBUTE and IMPACT trials[4,6] found that the differences in the rate of exacerbation between ICS/LABA/LAMA and LABA/LAMA over follow-up were in the first-month's surge of exacerbation, with no differences in the remaining 11 months. The inclusion of patients with a history of asthma and the withdrawal of ICS in patients who had received ICS treatment before entering the clinical trial could be an explanation of the early surge in exacerbation in patients

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receiving LABA/LAMA therapy. Therefore, further research is needed to elucidate whether triple therapy is superior to dual therapy in patients without a history of asthma or history of ICS use. Based on these clinical trial characteristics, patients with high symptom burden, moderate-to-very severe airflow limitation, increased risk of exacerbations and concomitant with a history of asthma or history of ICS use might be the indications of initiating triple therapy. Patients who have received dual bronchodilators or LABA/ICS therapy and still have severe symptoms and frequent exacerbations deserve to switch to triple treatment.

Third, we should carefully review the strength of evidence of current clinical markers in order to better direct future research. A number of recent studies[8,11-13] have shown that blood eosinophil counts and frequent exacerbations can be used to identify patients with the greatest likelihood of treatment benefit with ICS containing triple therapy. However, COPD exacerbations are highly heterogenous events with different endotypes (*ie,* bacterial, eosinophilic, viral and pauci-granulocytic exacerbations).[14] The evidence of blood eosinophil counts to predict ICS-containing regimen effects is from *post-hoc* analysis of triple therapy clinical trials,[11,12] which requires confirmation in specifically designed randomized controlled trials. The blood eosinophil counts can be affected by multiple factors, therefore the repeatability and optimal threshold of blood eosinophil counts are still under debate.[15,16] Meanwhile, it has been suggested that exacerbations associated with increased sputum or blood eosinophil may be more responsive to ICS-containing triple therapy. In contrast, bacterial associated exacerbations may be less responsive to ICS-containing triple therapy but associated with an increased risk of pneumonia. And there is emerging evidence to suggest that patients with low blood eosinophils (<100 cells/μL) are at higher risk of pneumonia when taking ICS-containing therapy.[17,18] All in all, further studies are urgently warranted to investigate more precise biomarkers for predicting the beneficial response to ICS containing triple therapy.

Fourth, pharmacological management of COPD should be reviewed, assessed and adjusted as necessary after initial treatment according to the recommendations of guideline,[2] which can be regarded as an "individual cross-over trial". The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020[2] recommends triple therapy only as a step-up from LAMA/LABA or LABA/ICS in patients who develop further exacerbations and have predominant symptoms of breathlessness while on maintenance therapy. The detailed recommendations are as follows: (1) In patients who develop further exacerbations on LABA/LAMA therapy, ICS can be added to escalate to triple therapy if blood eosinophil counts ≥ 100 cells/μL, with a greater magnitude of response more likely with higher eosinophil counts; (2) In patients with persistent breathlessness or further exacerbations on LABA/ICS therapy, LAMA can be added to escalate to triple therapy; (3) In patients on triple therapy, treatment can be switched to LABA/LAMA if ICS side effects warrant discontinuation, or if there has been a lack of response to ICS treatment. A patient with an eosinophil count > 300 cells/μL who is likely to experience more exacerbations after ICS withdrawal should be followed closely for relapse of exacerbations. In addition, a patient without a history of exacerbations can consider ICS withdrawal if blood eosinophil count is <300 cells/μL and without a history of asthma.

In addition, we suppose that triple therapy could be considered as the first choice but not as an escalation therapy in patients with COPD at the following scenarios despite without any evidence[19]: (1) In patients discharged from the hospital after a severe exacerbation of COPD, and with history of frequent exacerbation and blood eosinophils ≥300 cells/μL. These patients are often prescribed the treatment with nebulized bronchodilators (commonly short-acting β2-agonists in combination with short-acting muscarinic antagonists), antibiotics and systemic corticosteroid during their hospitalization. Evidence has accumulated that these patients are at high risk of re-hospitalization after discharge; (2) In patients who are diagnosed with severe airway obstruction (forced expiratory volume in one second <50%) for the first time, are symptomatic, are at high risk of exacerbations (had ≥2 moderate exacerbations or ≥1 hospitalization in the previous year), and have high eosinophil counts (≥300 cells/μL) or history of asthma. We believe that it is rational to prescribe triple therapy as the first choice in patients with these characteristics, and then dynamically assess treatment response and timely adjust the regimens if necessary.

In conclusion, triple therapy not only has been shown to better improve symptoms and lung function, and reduce risk of exacerbation and disease progression, but also shows a promising effect on survival benefit compared to LABA/ICS or LAMA/LABA. However, further investigations should be conducted to better identify patients with a greater likelihood of a beneficial response to triple therapy and patients less responsive to ICS due to the heterogeneity of COPD. Based on current evidence, triple therapy should be considered in patients who have frequent or severe exacerbations, have received "open triple" combinations or LABA/ICS or LAMA/LABA or single bronchodilator treatment, or have a history of asthma or blood eosinophil counts ≥300 cells/μL. And we should assess clinical response and potential side effects after adjusting pharmacological treatment, and timely stop ICS if there are adverse effects (such as pneumonia) in order to achieve optimal management and minimize side effects of pharmacological treatment.

Conflicts of interest

None.

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