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PERSPECTIVES

Time To Revise COPD Treatment Algorithm

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Abstract: In 2017, a new two-step algorithm for the treatment of COPD was proposed. This algorithm was based on the severity of symptoms and phenotypes or treatable traits, and patient-specialised assessment targeting eosinophilic inflammation, chronic bronchitis, and frequent infections is recommended after exacerbation occurs despite maximal bronchodilation therapy. However, recent studies have revealed the clinical characteristics of patients who should have second controllers added, such as ICS. We again realized that treatable traits should be assessed and intervened for as early as possible. Moreover, the treatment algorithm is necessary to be adapted to the situation of clinical practice, taking into account the characteristics of the patients. The time to revise COPD treatment algorithm has come and we propose a new 3-step parallel approach for initial COPD treatment. After the diagnosis of COPD, the first assessment is to divide into two categories based on the usual clinical characteristics for patients with COPD and the specific clinical characteristics for each patient with concomitant disease. In the former, the assessment should be based on the level of dyspnea and the frequency of exacerbations. After the assessment, mono- or dual bronchodilator should be selected. In the latter, the assessment should be based on asthma characteristics, chronic bronchitis, and chronic heart failure. After the assessment, patients with asthmatic characteristics may consider treatment with ICS, while patients with chronic bronchitis may consider treatment with roflumilast and/or macrolide, while patients with chronic heart failure may consider treatment with selective β1-blocker. The 3-step parallel approach is completed by adding an additional therapy for patients with concomitant disease to essential therapy for patients with COPD. In addition, it is important to review the response around 4 weeks after the initial therapy. This COPD management proposal might be considered as an approach based on patients' clinical characteristics and on personalized therapy.

Keywords: parallel approach, treatable traits, ICS, personalized therapy

Introduction

In 2017, a new two-step algorithm for the treatment of chronic obstructive pulmonary disease (COPD) was proposed.[1] This treatment algorithm was based on the severity of symptoms and history of exacerbations. It can be argued that these are treatable traits. The algorithm underlies the importance to identify what are the COPD exacerbation's precipitating factors, in order to provide patients' with appropriate prevention therapy. In this algorithm, patient-specialised assessment targeting eosinophilic inflammation, chronic bronchitis, and frequent infections is recommended after exacerbation occurs despite maximal bronchodilation therapy. However, even just one severe exacerbation appears to accelerate the decline in lung function, inducing physical inactivity, poorer quality of life, and an increased risk of death.[2] Recent studies have revealed the clinical characteristics of patients

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who should be added second controllers such as inhaled corticosteroids (ICS).[3–6] Based on these evidence, we again realized that treatable traits should be assessed and intervened as early as possible. Moreover, the treatment algorithm must be adapted to the situation of clinical practice, taking into account the characteristics of the patients. The time to revise COPD treatment algorithm has come and we propose a new 3-step parallel approach for initial COPD treatment.

State Of The Art

According to the latest 2019 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report, pharmacological treatment was divided into two algorithms, "initial treatment" and "follow-up treatment".[7] Initial pharmacological treatment has been recommended by the ABCD grouping based on symptom burden and risk of exacerbation after the initial diagnosis of COPD. In initial pharmacological management, use of ICS is recommended only for Group D patients with blood eosinophil counts ≥ 300/μL or a history of asthma. If there is no response to the initial treatment, GOLD 2019 report proposes considering the predominant treatable trait to target (dyspnea or exacerbations). The dyspnea algorithm pathway recommends escalation using additional long-acting bronchodilator (LABD) treatment for breathlessness. For patients with breathlessness who are already treated with a dual bronchodilator or dual bronchodilator and ICS combination, it is recommended to switch molecules or inhaler device and to investigate other possible causes of dyspnea such as heart failure and pulmonary hypertension. The exacerbation algorithm pathway recommends escalation using additional LABD or ICS. If the above-mentioned steps do not work, addition of roflumilast or macrolide was recommended.

Algorithm

GOLD 2019 report and many other algorithms recommend that the use of drugs other than LABDs should be after exacerbation occurs. However, considering the burden of exacerbations,[8,9] it is very important to preemptive treatment tailored to the treatable trait at the initial treatment. There are various risk factors and triggers for exacerbations,[10] while risk factors and triggers can be roughly divided into two categories. It is the usual clinical characteristics for patients with COPD and the specific clinical characteristics for patients with concomitant disease. The usual clinical characteristics for patients with COPD are dyspnea, exacerbation, smoking, airflow limitation and physical inactivity, while specific clinical characteristics for patients with concomitant disease are chronic bronchitis, cardiovascular disease, anxiety, depression and other concomitant medical conditions.[11] It is our firm belief that the approach of considering the specific concomitant disease in parallel with the usual clinical characteristics is extremely important. We newly advocate a parallel approach for the management of COPD (Figure 1).

In accordance with a concept of parallel approach for the management of COPD, we propose a new 3-step parallel approach for initial COPD treatment based on the evidence of recent studies (Figure 2).

Once the diagnosis of COPD has been confirmed by spirometry, the first assessment is to divide into two categories based on the usual clinical characteristics for patients with COPD and the specific clinical characteristics for each patient with concomitant disease.

In usual clinical characteristics for patients with COPD, the assessment (Step 1: assessment) should be based on the level of dyspnea (as measured by the modified Medical Research Council dyspnea scale, mMRC) and the frequency of exacerbations. After the assessment, patients with a mMRC score of 0 or 1 or no more than one exacerbation during the previous year may start treatment with a mono-bronchodilator [a long-acting muscarinic antagonist (LAMA) or a long-acting β-agonist (LABA)] whereas patients with either a mMRC score higher than 1 or with more than one exacerbation in the previous year should start with a dual bronchodilator (LABA/LAMA) (Step 2: drug selection). For patients with persistent breathlessness on a monotherapy of LABDs, there might be room to consider a combination therapy of LABDs. Our proposal based on the level of dyspnea and the frequency of exacerbations is similar to the algorithm published by Miravitlles and Anzueto in 2017.[1] Additionally, for patients with COPD, it goes without saying that smoking cessation, pulmonary rehabilitation (or regular exercise) and vaccination are important as a treatment other than bronchodilator, and they should be included under general recommendations to all patients.[7]

In specific clinical characteristics for patients with concomitant disease, the assessment (Step 1: assessment) should be based on the asthma characteristics, chronic bronchitis,[12] and chronic heart failure.[13] Most importantly, our approach differs from many other algorithms in that the use of ICS has priority for the patients with asthma characteristics. There is now more evidence that patients

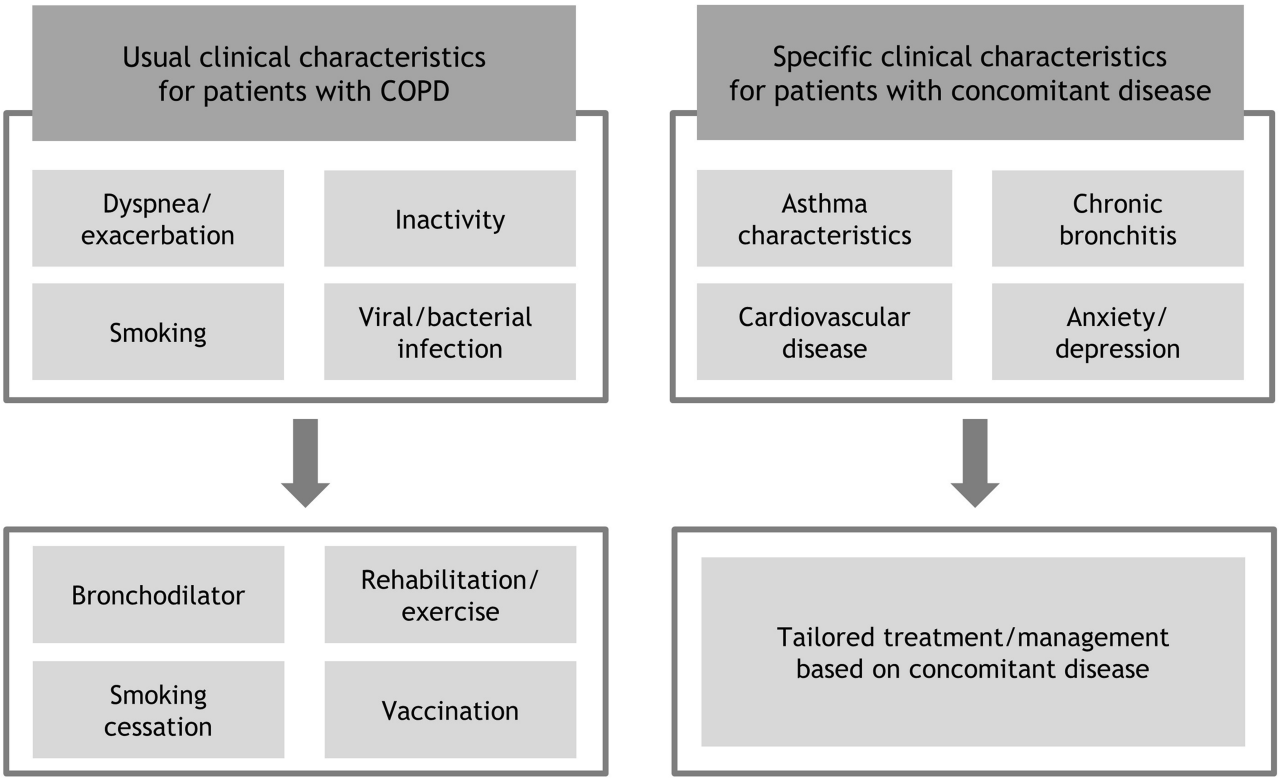

Figure 1 A concept of parallel approach for the management of chronic obstructive pulmonary disease (COPD).

with COPD and characteristics of asthma [asthma-COPD overlap (ACO)] are recognized in several national and international guidelines.[14–16] Because the definitive definition and diagnostic criteria have not been established, the prevalence of ACO among patients previously diagnosed as COPD has varied widely in studies: from 15% to 55%.[14] To manage COPD patients with asthma characteristics effectively, it is important to make the diagnosis.[17] It is inaccurate to distinguish based on clinical characteristics because no significant difference was observed in baseline characteristics between patients with ACO and non-ACO.[18] Therefore, ACO patients without history of asthma are easily overlooked. There is a COPD subgroup characterized by asthma-like gene expression signatures of type 2 inflammation associated with airway eosinophilia and ICS responsiveness.[19] In clinical practice, the designation of the type 2 signature is commonly used in the presence of atopy and/or eosinophilic inflammation, identified on the basis of blood eosinophilia (≥ 300/μL) and high level of fraction of exhaled nitric oxide (FeNO) (≥ 35 ppb). Although FeNO has variability in patients with COPD,[20] these persistently elevated type 2 biomarkers may reflect eosinophilic airway inflammation and predict ICS responsiveness in patients with COPD.[3–6] After the assessment, patients with asthmatic characteristics may consider treatment with ICS (Step 2: drug selection). From the viewpoint of the effectiveness and the risk of side effects such as pneumonia, osteoporosis and mycobacterial infection, there is a need to identify which patients will benefit from ICS.

Patients with chronic bronchitis may consider treatment with roflumilast and/or macrolide (Step 2: drug selection). Although gastrointestinal adverse effects and weight loss were common, pooled analysis of recently completed two phase IV clinical studies confirmed the benefit of the phosphodiesterase (PDE) 4 inhibitor roflumilast in preventing exacerbations in patients with prior hospitalization for exacerbation and higher exacerbation frequency.[21] The mechanisms for the helpful therapeutic effects of macrolide can go beyond their direct anti-infective effect because latest data presented that they exert multiple effects on the structure and composition of the lower airway microbiota with increased production of bacterial metabolites with anti-inflammatory properties.[22,23] Mucolytic therapy such as *N*-acetylcysteine, ambroxol or carbocisteine can also be considered for patients with chronic bronchitis. The ERS/ATS task force on the management of COPD exacerbations has reported the beneficial effect of the high-dose mucolytic

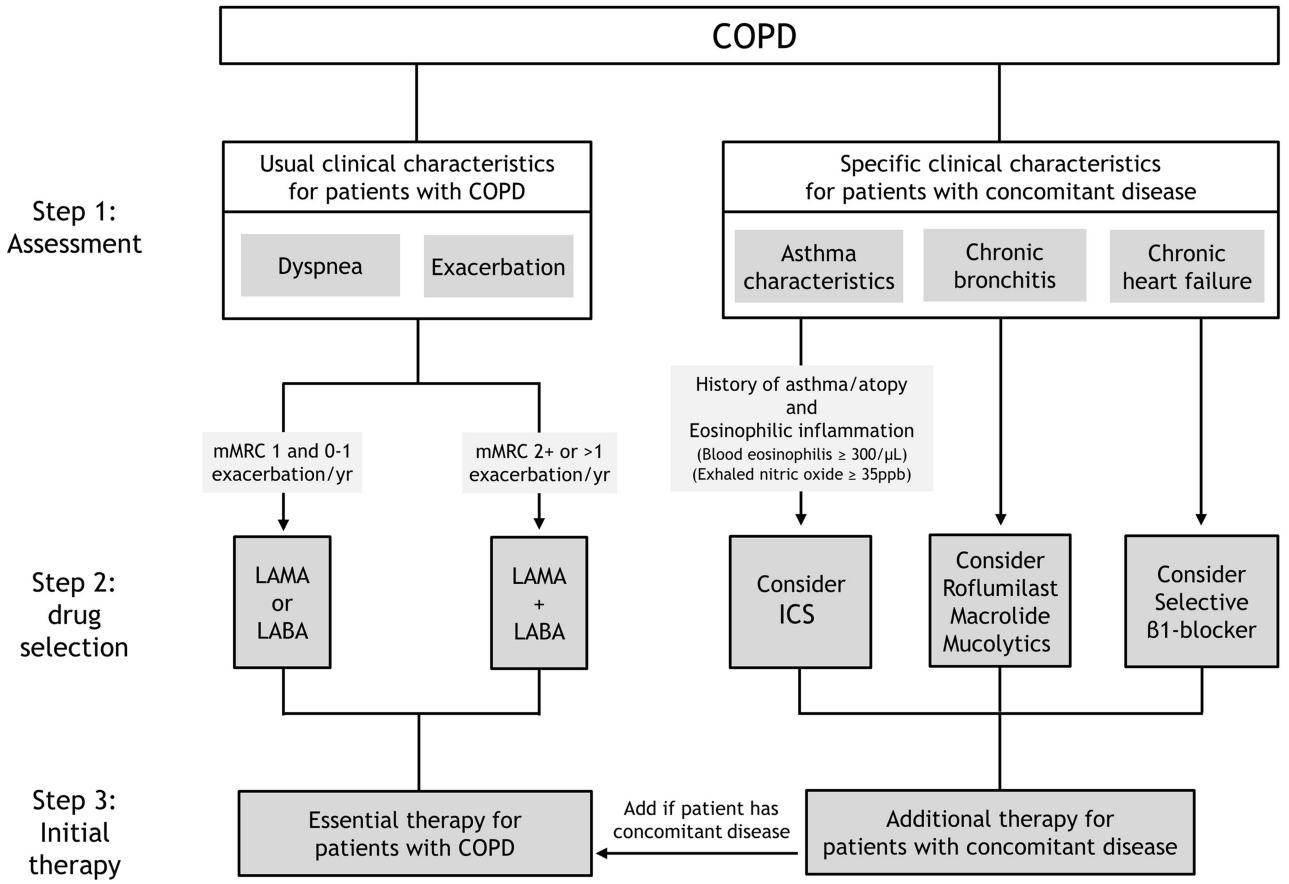

Figure 2 A new 3-step parallel approach for initial chronic obstructive pulmonary disease (COPD) treatment.
Abbreviations: mMRC, modified Medical Research Council dyspnoea scale; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroids; FeNO, fraction of exhaled nitric oxide.

agent in patients with frequent exacerbation despite optimal inhaled therapy.[24]

Patients with chronic heart failure may consider treatment with selective β1-blocker (Step 2: drug selection). The prevalence of heart failure patients combined with COPD is one-third.[25] β-Blockers were thought to be potentially unsafe to COPD patients. However, a reduction in COPD-related mortality of 31% with usage of new selective β1-blocker was pointed out in a systematic review and meta-analysis of retrospective cohort studies.[26] Despite increasing evidence that selective β1-blocker is safe and beneficial in patients with COPD, they are often underused in this group worldwide.

The 3-step parallel approach is completed by adding the additional therapy for patients with concomitant disease to essential therapy for patients with COPD (Step 3: initial therapy). In addition, it is important to review the response around 4 weeks after the initial therapy. The evaluation factors are inhaler technique, adherence, symptoms, exacerbations, side effects, patient satisfaction, lung function and eosinophilic inflammation.

We now recognize that COPD patients also have other concomitant conditions which include anxiety/depression, skeletal muscle dysfunction, osteoporosis, gastroesophageal reflux (GERD), bronchiectasis, metabolic syndrome, and lung cancer. COPD patients had a higher prevalence of anxiety/depression, and anxiety/depression are associated with poorer quality of life and survival.[27] In contrast, there remain unanswered questions about adequate treatment strategies of comorbid anxiety/depression in patients with COPD. Skeletal muscle dysfunction affects both ventilatory and nonventilatory muscle groups, leading to poor quality of life and increasing mortality.[28] Muscle recovery actions combined with pulmonary rehabilitation and optimized nutrition contribute to a better prognosis. Osteoporosis in COPD are often underdiagnosed and undertreated.[29] Although there is no evidence that osteoporosis treatment improves the prognosis of COPD patients, it seems reasonable to treat osteoporosis according to usual guidelines. GERD is known to be a risk factor for frequent exacerbation.[11] Although there is not enough

evidence in pharmacological treatment, proton pump inhibitors may be effective for COPD patients with GERD.[30] Bronchiectasis coexisting with COPD is often identified with an increasing use of computed tomography (CT) in the assessment of COPD patients.[31] It is associated with longer exacerbations and increased mortality.[32,33] COPD patients with bronchiectasis might be a potential population to benefit from macrolide and/or mucolytic therapy. Moreover, since there is significant evidence that the use of ICS increases the risk of mycobacterium infection in patients with COPD,[34] we should consider bronchiectasis in the initial assessment. Lung cancer is common in COPD patients and one of the main cause of death. Smoking cessation is very important not only for the treatment of COPD but also for the prevention of lung cancer.

It is fully known that the proposed algorithm will need to be validated, particularly in the real world. Moreover, there are some limitations to use this algorithm. Medical resources vary greatly from country to country. At the present time, roflumilast is not approved in many Asian countries. In some areas, there is difficult access to some diagnosis tools, such as CT, echocardiography, and FeNO. Low utilization of these diagnostic techniques is a significant barrier to adequate disease management.

Conclusion

This perspective article proposes to identify treatable clinical features early and to treat usual and specific clinical characteristics in parallel. The management of COPD patients should be a teamwork among primary care providers, pulmonary specialists, and other physicians. This new 3-step parallel approach might be a restructuring of the existing approach of treatment of COPD and considered as an approach based on patients' clinical characteristics and on personalized therapy.

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