Expert Opinion

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A new pharmacotherapy strategy for chronic obstructive pulmonary disease (COPD): Expert perspectives

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Abstract:

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report is widely accepted as a global guide for chronic obstructive pulmonary disease (COPD) management. However, in our country, where time constraints often hinder comprehensive patient evaluation, pulmonologists face difficulties in applying the complex treatment recommendations of the GOLD guidelines. To date, no COPD treatment strategy report tailored to the specific realities of our country has been developed. Therefore, we aimed to create a COPD pharmacological treatment strategy report that facilitates rapid patient assessment and treatment planning. Our algorithm does not rely on COPD Assessment Test (CAT) scores or forced expiratory volume in one second (FEV1) values for patient evaluation. We recommend transitioning to long-acting beta-agonist (LABA) or long-acting muscarinic antagonist (LAMA) monotherapy as needed in selected cases. For patients on LAMA therapy, we advise the use of short-acting beta-agonists (SABA) as rescue medication only. For patients with a Modified Medical Research Council (mMRC) dyspnea score of ≥2 and a high risk of exacerbation, we recommend initiating triple therapy from the outset. Due to insufficient data, we excluded the use of eosinophils as a biomarker in treatment planning. Phosphodiesterase-4 inhibitors were omitted from our algorithm due to their unavailability in our country. For patients who have experienced at least two infectious exacerbations in the past year despite effective COPD treatment, we recommend daily azithromycin therapy during the winter months or three times a week as needed.

Keywords:

Chronic airway diseases, chronic obstructive lung disease, inhalation therapies

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Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by irreversible airflow obstruction and exacerbations, with clinical features that vary significantly among individuals.[1] Exacerbations are critical events that negatively impact the course of COPD by worsening lung function and increasing the risk of mortality.[2] Due to the heterogeneous nature and complex

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pathogenesis of the disease, an international management guide has not been established. While the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report is widely accepted as a guide, some countries have developed their own strategy reports for the pharmacologic treatment of stable COPD. However, no COPD treatment strategy tailored to the realities of our country has been developed to date. In our country, the patient load in chest diseases outpatient clinics is very high, resulting from an imbalance between the number of patients and available chest physicians. Because comprehensive patient evaluations cannot always be performed due to time constraints, physicians face difficulties in applying the complex GOLD treatment recommendations.[1] To address these challenges, we aimed to develop a pharmacological treatment strategy report for stable COPD that facilitates rapid patient assessment and treatment planning [Fig. 1]. The treatment plan in our report was adapted from the Canadian Thoracic Society Guideline, which we found most suitable for our purposes among the GOLD guidelines and national COPD treatment recommendations.[3]

Exacerbations were classified in line with the GOLD recommendations as follows:[1]

- Mild: Treated with short-acting bronchodilators (SABDs) only.
- Moderate: Treated with SABDs and oral corticosteroids, with or without antibiotics.
- Severe: Requiring admission to the emergency department, hospitalization, or intensive care unit.

Exacerbation risk was further categorized into "low" and "high" risk:

- Low risk: Defined as ≤1 moderate exacerbation in the past year.
- High risk: Defined as ≥2 moderate exacerbations or ≥1 severe exacerbation in the past year.

We recommend using the Modified Medical Research Council (mMRC) scale instead of the COPD Assessment Test (CAT) for symptom evaluation. This preference arises because the CAT is time-consuming, subjective, and requires specific training. To assess mMRC 2 for treatment decisions, the question, "Do you walk slower than people of your same age on the level because of breathlessness, or do you need to stop for breath when walking at your own pace on the level?" should be asked. Alternatively, mMRC 2 may be assessed with a simpler question: "Do you get short of breath when walking on a flat road?"

Short-acting bronchodilators—short-acting β2 agonists (SABA) or a combination of short-acting β2 agonists and short-acting anticholinergics (SABA/SAMA)—are

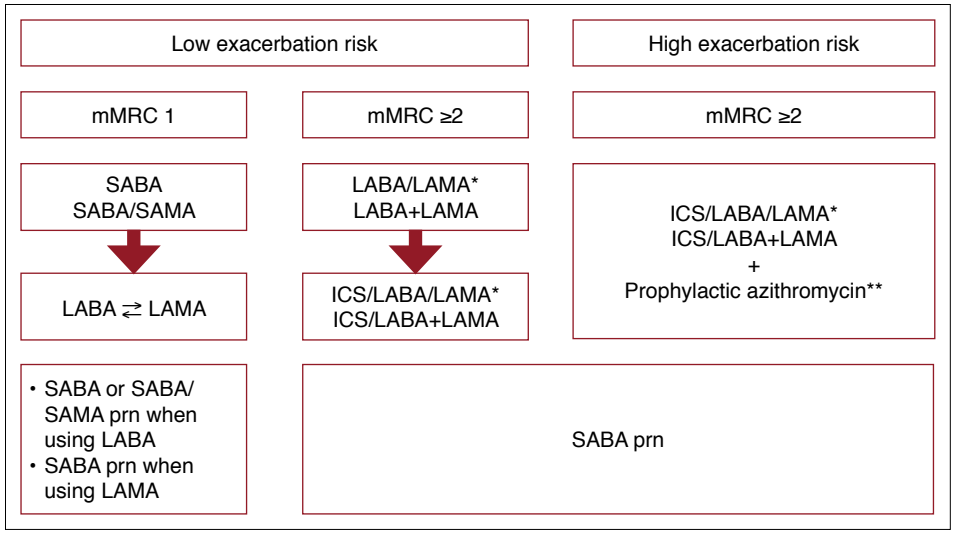

Figure 1: Pharmacotherapy for stable chronic obstructive pulmonary disease (COPD)

*: Fixed LABA/LAMA and triple ICS/LAMA/LABA combination therapy should preferanly be administered in a single inhaler, **: ≥2 moderately infected exacerbations per year despite effective COPD treatment mMRC, modified Medical Research Council. SABA: short-acting β2 agonists as needed, SAMA: Short-acting anticholinergics as needed, LABA: Long-acting β2 agonists, LAMA: Long-acting muscarinic antagonists, ICS: Inhaled corticosteroid, prn: As needed

recommended as rescue therapy for COPD patients experiencing intermittent dyspnea. If dyspnea persists at mMRC level 1, long-acting β2 agonists (LABA) or long-acting muscarinic antagonists (LAMA) should be prescribed as maintenance treatment. However, there is insufficient evidence to determine which of the long-acting bronchodilators is more effective in early-stage COPD patients. Turan et al.[4] reported that LAMA therapy significantly improved symptom scores compared to LABA therapy by the end of the first year in GOLD A group COPD patients. If adequate symptom control is not achieved and/or side effects occur, switching to the other bronchodilator class is an option.

For patients with a dyspnea score of mMRC≥2 and a low risk of exacerbation, combined LABA and LAMA therapy should be initiated. If dual bronchodilator therapy fails to achieve adequate symptom control in these patients, inhaled corticosteroids (ICS) in combination with LABA and LAMA (ICS/LABA/LAMA triple therapy) can be initiated.[5] Studies have reported that starting single-inhaler fluticasone furoate/umeclidinium/vilanterol therapy after the first moderate-to-severe exacerbation significantly reduces exacerbations and healthcare costs.[6] In patients with a dyspnea score of mMRC≥2 and a high risk of exacerbation, triple therapy should be initiated without delay.[7–9] Evidence indicates that triple therapy prevents exacerbations, provides greater symptom relief, improves lung function, enhances health-related quality of life, and reduces mortality compared to dual therapies.[7–12]

It is not recommended to switch from dual therapy to monotherapy or from triple therapy to dual bronchodilator therapy due to the lack of sufficient data on de-escalation strategies. It is known that the use of ICS in COPD patients increases the risk of pneumonia.[13] Therefore, the GOLD guidelines recommend discontinuing ICS from triple therapy in patients who develop pneumonia.[1] However, the relationship between pneumonia and ICS is not yet fully understood. Various clinical studies have reported an increased incidence of pneumonia associated with ICS treatment.[14,15] However, these findings may be influenced by overdiagnosis of pneumonia in the studies due to insufficient rigorous definitions of pneumonia, such as the lack of confirmation by chest radiography. Conversely, other reports have indicated that ICS does not increase the risk of pneumonia and pneumonia-related mortality.[16–18] A systematic review and meta-analysis evaluating the results of 13 randomized controlled trials (RCTs) concluded that high-dose ICS treatment did not result in a statistically significant difference in the risk of acute exacerbations of COPD (AECOPD), mortality, or pneumonia compared to medium-dose ICS therapy.[19] Moreover, evidence indicates that current ICS users with COPD had significantly lower 30-day mortality compared to non-users, particularly among patients with frequent exacerbations.[20] The critical factor affecting mortality in COPD patients is not the pneumonia caused by ICS use but the exacerbations that occur due to the absence of ICS therapy. Moreover, the data regarding the role of ICS in COPD treatment are inconclusive, and there is a possibility that withdrawing ICS may worsen the progression of COPD and increase the risk of exacerbations.[21] Therefore, discontinuing ICS treatment in patients at risk of exacerbation may not be a rational approach.

We propose a different approach compared to other reports by additionally recommending the use of rescue short-acting bronchodilators for patients on long-acting bronchodilator therapy. For as-needed symptom control, a SABA or SABA/SAMA combination may be preferable for patients using LABA, while only SABA may be suitable for those using LAMA. The clinical benefit and significance of combining LAMA and SAMA compared to monotherapy has not been demonstrated, and serious cumulative anticholinergic side effects may occur, particularly in elderly patients.[22] The UPLIFT study (Understanding Potential Long-term Impacts on Function with Tiotropium) reported positive effects on lung function, quality of life, and exacerbations over a four-year period with tiotropium monotherapy, without the addition of ipratropium.[23] It has also been theoretically proposed that an antagonistic interaction may occur due to competitive binding at muscarinic receptor sites when LAMA and SAMA are used in combination.[24]

We did not include blood eosinophil levels as a biomarker in our treatment recommendations. There is ongoing debate about whether peripheral blood eosinophil levels can serve as a reliable biomarker to predict exacerbation risk or identify patients who may benefit clinically from inhaled corticosteroids.[25–27] Both the GOLD and GesEPOC (Spanish COPD Guidelines) treatment guidelines include blood eosinophil count as an important biomarker in COPD management.[1,28] It has been noted that the risk of exacerbations may be higher in the eosinophilic COPD

phenotype, although opinions on this remain divided.[29–32] Furthermore, numerous studies have shown that adding ICS to treatment in eosinophilic COPD patients can effectively reduce exacerbations.[33,34] However, the underlying mechanisms linking high eosinophil levels to ICS activity have not been fully elucidated.[29] Additionally, eosinophilic airway inflammation does not always respond consistently to ICS therapy.[35,36] Discussions also address the variability of blood eosinophil counts, appropriate cutoff values, the correlation between blood eosinophilia and eosinophilic airway inflammation, and other factors influencing eosinophil levels.

Blood eosinophil levels vary significantly among healthy individuals and throughout the course of COPD.[37,38] In a study assessing the stability of high blood eosinophil levels (≥300 cells/μL), 43.8% of eosinophil counts fluctuated above and below the cutoff point across three separate visits.[39] Persistent blood eosinophil levels were observed in 15.8% of patients in the CHAIN cohort (COPD History Assessment in Spain) and 12.3% in the BODE (Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity) group in the same study. Similarly, a post-hoc analysis of three randomized controlled trials indicated consistent variability in blood eosinophil counts.[34] In the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints), blood eosinophil counts fluctuated in 49% of patients over a three-year follow-up period when using a cutoff value of 2%.[40] Additionally, factors such as diurnal variation, medications, infections, exacerbations, tobacco use, and comorbidities may influence blood eosinophil counts.[37,41–44] In conclusion, due to its significant variability, blood eosinophil count cannot be considered a stable biomarker for long-term planning of COPD treatment.

Blood eosinophil levels are proposed as a practical, rapid, and cost-effective marker to predict sputum eosinophil levels and eosinophilic airway inflammation in COPD patients.[45] However, findings from studies are controversial, and it is not definitively established that peripheral eosinophilia reliably indicates eosinophilic airway inflammation.[40,46] A moderate correlation between blood and sputum eosinophil levels was observed in the ECLIPSE study.[39] Nonetheless, blood eosinophils alone were not reliable for predicting sputum eosinophils in the SPIROMICS cohort (Subpopulations and Intermediate Outcomes in COPD Study).[47] Another cohort study found no significant relationship between blood eosinophils and lung parenchyma or airways in COPD patients.[48] An important issue is determining the appropriate cutoff value for defining blood eosinophilia. Currently, a scientifically and clinically meaningful eosinophil cutoff level that would guide decisions on ICS treatment has not been established. GOLD guidelines recommend a cutoff value of 300 cells/μL for blood eosinophilia,[1] but various COPD studies have employed different cutoff values.[23,42,47,49,50]

We lack sufficient data to support the use of eosinophils as a definitive biomarker for planning stable COPD treatment. Therefore, until uncertainties regarding the use of eosinophil counts as biomarkers are resolved and a well-designed protocol is established, COPD treatment recommendations should be based on the severity of the patient's respiratory symptoms and exacerbation history.

For patients experiencing at least two infectious exacerbations in the past year despite effective COPD treatment, daily azithromycin may be recommended to enhance the immune response against potential pathogens causing airway infections.[51] Alternatively, sufficient bactericidal effects can be achieved by using azithromycin three days a week (Monday, Wednesday, and Friday).[52] Before initiating azithromycin prophylaxis, an assessment of the QT interval, concurrent use of other QT-prolonging medications, tuberculosis infection status, risk of hearing loss, and high-risk cardiovascular disease should be conducted. Phosphodiesterase-4 inhibitors have been excluded from our treatment algorithm due to their unavailability in our country.

In summary, our algorithm does not incorporate CAT or FEV1 values for patient evaluation. We recommend switching to LABA and LAMA monotherapy in selected cases as needed. For patients using LAMA, we advise the use of only SABA as a rescue medication. In patients with a dyspnea score of mMRC≥2 and a high risk of exacerbations, we recommend initiating triple therapy. Due to insufficient data, the use of eosinophils as a biomarker for treatment planning has been excluded. Phosphodiesterase-4 inhibitors have also been omitted from our algorithm due to their unavailability in our country. For patients experiencing at least two infectious exacerbations in the past year despite effective COPD treatment, daily azithromycin may be recommended during the winter months and three days a week as needed.

Conflicts of Interest Statement

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