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Editorial Comment

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Triple Therapy Is Also Effective in Real-World When Used in Chronic Obstructive Pulmonary Disease Patients Who Are Frequent Exacerbators

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Simultaneous use of 3 drugs, a long-acting β-agonist (LABA), a long-acting muscarinic antagonist (LAMA), and an inhaled corticosteroid (ICS), for treating patients with chronic obstructive pulmonary disease (COPD) is very common in real-world, regardless of disease severity [1, 2]. This prescriptive behavior suggests that management of COPD patients does not generally follow the recommendations of many COPD guidelines or strategies that restrict the use of triple therapy to well-defined clinical conditions but is rather based on physicians' clinical experience. After all, the American Thoracic Society clinical practice guideline for the pharmacologic management of COPD describes as "conditional" the strength of the recommendation to use triple therapy in patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy or in those with a history of one or more acute exacerbations of COPD (AECOPDs) in the past year requiring antibiotics or oral steroids or hospitalization [3]. This means that they leave the decision to use the triple therapy to the experience and preference of the physician and its acceptability by the patient. In contrast, the global initiative for chronic obstructive lung disease (GOLD) is much stricter in its recommendations to add a LAMA to an ICS/LABA combination or an ICS to a LABA/LAMA combination, depending on the treatable trait that best comprises the patient's problem: presence of dyspnea or AECOPDs, as well as the inclusion of the blood eosinophil count as a surrogate marker of potential ICS response [4].

The GOLD recommendations are essentially based on findings of several pivotal randomized controlled trials (RCTs) with triple therapy in fixed dose combination (FDC) that documented the effectiveness of these FDCs, especially their ability to improve dyspnea and reduce the risk of AECOPD [5–11]. The appropriateness of these recommendations are supported by the results of a recent network meta-analysis of these RCTs that ranked the triple ICS/LABA/LAMA FDC as the most effective treatment in reducing the risk of exacerbation and improving lung function [12].

However, an observational study in a real-world setting that used data from a cohort of patients with COPD in the UK Clinical Practice Research Datalink showed that the incidence of AECOPDs over the first year of use in those initiating treatment with a triple therapy was similar to that observed in those under a dual bronchodilator combination therapy [13]. In addition, when compared to LABA/LAMA, triple therapy is associated with a significantly higher risk of pneumonia, which is a class-related risk of ICS [14]. In the end, which patients actually benefit most from triple therapy compared to other treatments remains to be determined [15].

Although RCTs are the gold standard for making evidence-based decision, the question always raises about rec-

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ommendations derived from these trials because they are usually conducted in populations selected by strict inclusion and exclusion criteria, enrolled and followed in a highly controlled setting, while it is well known that people treated in real-life differ from those enrolled in trials [16]. This explains why there are concerns regarding the external validity of RCT data and the ability to broadly extrapolate these data to the real-world patients [17]. Therefore, there is an absolute need for real-world studies that seek to answer the question "does this intervention work under usual conditions?" to confirm the efficacy and safety of drugs that have previously been evaluated in RCTs [18]. Well-designed real-world trials may have the potential to return robust information on real-life benefits, risks, and acceptance of new healthcare interventions [19].

Corrado Pelaia and his colleagues have conducted a single-center real-world trial to evaluate the effects of 24-week treatment with inhaled fluticasone furoate/vilanterol/umeclidinium FDC in COPD patients who were frequent exacerbators and were already being regularly treated with either LAMA/LABA or ICS/LABA combination [20]. Although the enrolled number of patients was rather small, the results confirmed that this triple FDC decreased the frequency of AECOPDs and dyspnea scores, results that are in line with those of the large RCTs. Credit must be given to the authors for having expanded the end points of the study to include important physiological determinants of lung mechanics and gas exchange, which over time the large RCT outcomes have relegated to be secondary or even tertiary outcomes. Detailed analysis of the data shows that triple therapy resulted in a significant improvement not only of FEV_1 but importantly in a decrease in resting end-expiratory lung volume with a mirror image improvement in the inspiratory capacity, the most important determinants of the bothersome perception of dyspnea [21, 22]. Although not measured in this study, improvement in the mechanics of breathing decreases inspiratory muscle load and work of breathing.

Very interestingly, there was a significant improvement in the diffusing capacity of the lung for carbon monoxide (DL_{CO}) in a consistent number of patients. Although specialists in respiratory medicine believe that DL_{CO} should be considered a fundamental functional characterization of the disease [23], all large RCTs with triple therapy did not provide any information on the effect of such therapy on DL_{CO}. In effect, the published literature gives conflicting results on how bronchodilators impact on DL_{CO}[24]. It has been suggested that changes in DL_{CO} over time may be at least in part affected by changes in the airway caliber induced by bronchodilators [25]. In a small study, ICS treatment for 2 months was accompanied by a significant increase in DL_{CO} likely because of an improvement in the small airway diameter, thought due to reduced inflammation of bronchioli and alveoli [26]. These changes can induce an improvement in the lung regional hypoxemic vasoconstriction [27], and DL_{CO} is a global measure of the number of perfused capillaries and ventilated alveoli and therefore is sensitive to microvascular changes [28]. An alternative explanation relates the DLco findings to the change in lung mechanics. Perhaps, the added deflation resulting from the triple therapy may have improved cardiac function, and this, together with increased alveolar ventilation, improved ventilation perfusion matching, as has been shown for shorter term comparisons of either LAMA/LABA or ICS/LABA with placebo [29, 30], but this information is not available. It would be desirable that Pelaia and colleagues expand their studies to confirm and look for explanations for this interesting observation.

Fortunately, the benefits observed in this 24-week study were not offset by the presence of any pneumonia during the observation period, an event that appears to be mainly related to the presence of fluticasone furoate [31]. Whether the patients included in the study by Pelaia and colleagues were selected by a lack of factors known to predispose to pneumonia such as older age, very low lung function, infected sputum, or low blood eosinophils [32] is not reported in the manuscript. We choose to assume that no patients had less than 100 blood eosinophils/μL because they all showed a reduction in the frequency of AECOPDs, and it is known that at this blood eosinophil threshold, ICSs will probably not be able to prevent AECOPDs [32]. In any case, it should not be overlooked that more than half of the enrolled population were already under regular treatment with an ICS; the trial enrolled only 44 patients, and this number may not be enough to show a signal over 24 weeks. Cazzola et al. [31] calculated that about 34 patients receiving fluticasone furoate in the triple combination must be treated for 1 year to encounter one additional pneumonia compared to the LABA/LAMA combination.

Regardless of any other consideration, this study confirms that the use of triple therapy is also effective in the "real-world" when used in COPD patients who are frequent exacerbators. The authors should be commended for expanding their study to include physiological end points that may provide a functional explanation to the subjective outcomes that most studies rely upon.

Conflict of Interest Statement

The authors report no conflicts of interest regarding this editorial.

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