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REVIEW

Long-acting Bronchodilators in COPD Management: One or Two?

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ABSTRACT

The management of chronic obstructive pulmonary disease (COPD) has changed significantly in this century, the most important element being the introduction of long-acting bronchodilators (LABD) as the basis of the treatment of patients with symptomatic disease. The benefits of dual bronchodilators versus mono-bronchodilators have been shown in randomized trials and in real-life observational studies and include, besides the expected improvement in lung function, improvement in symptoms, quality of life and exercise capacity, better exacerbation prevention and potential cardiovascular benefits in patients with hyperinflation, with an acceptable safety profile. Dual bronchodilators can be the first-line agents in all symptomatic patients, as well as in exacerbating patients (especially if they have lower blood eosinophils and their exacerbations were treated with antibiotics). The place for mono-LABD (mainly long-acting muscarinic antagonists [LAMA]) remains for the less symptomatic patients without severe hyperinflation. Modern COPD management incorporates the individualized approach of each COPD patient with the appropriate treatment.

Keywords: COPD. LABA/LAMA combinations. Long-acting β-agonists. Long-acting muscarinic antagonists.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a major societal burden that continues to grow in recent years, despite the ongoing research on its causes and management. Despite the widely accepted heterogeneity and the identification of multiple phenotypes and endotypes of COPD, the basis for the diagnosis of COPD is the identification of persistent airflow obstruction, as observed in post-bronchodilator spirometry, which is, often, progressive, especially when the causative factor is not modified[1,2]. Despite the fact that spirometry is a relatively inexpensive diagnostic tool, access to it remains limited in major parts of the world, delaying the early diagnosis of COPD[3] and, therefore, delaying the timely treatment, with a significant increase in the risk of healthcare resource utilization and further burden to the healthcare systems[4].

The management of COPD has changed significantly in this century, with the most important element being the introduction of long-acting bronchodilators (LABD) as the basis of treatment for patients with symptomatic disease, followed by the appropriate recognition of the positioning of inhaled corticosteroids (ICS) and the introduction of the for now only oral anti-inflammatory agent for COPD, roflumilast[3]. The first once-daily LABD was the long-acting muscarinic antagonist (LAMA) tiotropium, that was followed by other LAMAs (aclidinium, glycopyrronium and umeclidinium) but also from once-daily long-acting β2-agonists (LABA, including indacaterol, vilanterol and olodaterol). All these drugs have proven effective long-acting bronchodilation, based on trough forced expiratory volume in one second (FEV_1) measurements and have been also combined in fixed-dose combinations (FDC) of LABA/LAMA (indacaterol/glycopyrronium, vilanterol/umeclidinium, formoterol/aclidinium, olodaterol/tiotropium, formoterol/glycopyrronium, Table 1). These LABA/LAMA FDCs have improved efficacy in general compared to their monocomponents, however, the evidence remains heterogeneous for different combinations[5]. Their safety has also been evaluated extensively in clinical trials, however, real-life data is still needed in more vulnerable, multimorbid populations.

In the present review, we will discuss critically the benefits of dual bronchodilation with LABA/LAMA combinations compared to mono-LABDs (mainly placing emphasis on LAMAs that represent the most popular treatment option), focusing on different elements of response (lung function and measures of hyperinflation, symptoms, health status, exercise capacity, and exacerbations),and we will analyze the potential safety issues of dual bronchodilation.

LUNG FUNCTION BENEFITS

A large body of randomized controlled trials (RCTs) supports the improvements in lung function as evaluated by trough, post-dose and peak FEV_1 by dual bronchodilators compared to LAMA or LABA[5–12]. The benefit in trough FEV_1 is in the order of 70-80 mL in trough FEV_1[6], with higher improvements achieved in post-dose and peak FEV_1 (~ 100-110 mL), evaluated in greater extent in studies of dual bronchodilators with formoterol as the LABA[10,13]. An important characteristic in the design of

Table 1. LABA/LAMA fixed dose combinations (FDCs) approved for the management of COPD in the EU

LABA/LAMA FDCs	Device	Dose per inhalation	Dosing Scheme
Indacaterol/glycopyrronium	Breezhaler®	110/50 μg	One inhalation once daily
Vilanterol/umeclidinium	Ellipta®	22/55 μg	One inhalation once daily
Formoterol/aclidinium	Genuair®	12/400 μg	One inhalation twice daily
Olodaterol/tiotropium	Respimat®	2.5/2.5 μg	Two inhalations once daily
Formoterol/glycopyrrolate	pMDI (Aerosphere®)	7.2/7 μg	Two inhalations twice daily

COPD: chronic obstructive pulmonary disease; pMDI: pressurized metered dose inhaler.

the majority of the aforementioned trials is that patients who were receiving ICS at baseline continued to receive an equivalent dose of ICS throughout the trial, rendering the comparison to that of triple therapy versus ICS+LAMA (or LABA) in a large proportion of the patients included[14]. An exception to that rule was the large Early MAXimisation of bronchodilation for improving COPD stability (EMAX) trial that included symptomatic patients (Global Initiative for Chronic Obstructive Lung Disease [GOLD] group B) who were not receiving ICS; the study showed a benefit of 66 mL in trough FEV_1 for the combination of umeclidinium/vilanterol versus umeclidinium and 141 mL versus salmeterol[15]. This study also showed significant improvements in inspiratory capacity (IC), further supporting findings from other trials[16] and enhancing the role of long-acting bronchodilators as "deflators"[17]. Moreover, it demonstrated differences in the bronchodilative effects of different LABA/LAMA combinations versus different LABAs, in this case vilanterol versus salmeterol, that had been highlighted also in previous analyses[18]. These benefits of dual bronchodilation versus single LABDs on lung function have also been supported in pragmatic real-life open-label studies[19].

IMPROVEMENTS IN SYMPTOMS IN HEALTH STATUS AND QUALITY OF LIFE

In addition to their additive bronchodilative effect, dual bronchodilators compared to mono-LABD provide additional improvements in symptoms, especially dyspnea as expressed by standardized markers such as the transition dyspnea index (TDI) and with other questionnaires used in clinical trials[5]. The results of the existing studies are not uniform in all studies and for all combinations, as in some cases dual bronchodilators have not shown superiority versus LAMA[20,21] or LABA[9] in a few studies; yet in the majority of studies, all available dual bronchodilators provide better improvement in TDI compared to their mono-components or other LABDs[7,9,21,22], and this can be considered a universal class effect of these combinations. Interestingly, similar effects were observed not only in patients who were receiving previous treatments with LABD, but also in LABD-naive patients, i.e., those not receiving LABD prior to their enrolment in clinical trials. In a post-hoc pooled analysis of data of the Indacaterol and GlycopyrroNium bromide clInical sTudiEs (IGNITE) program of indacaterol/glycopyrronium, Muro and colleagues[23] showed

statistically and clinically relevant improvements in TDI and symptom scores with the dual bronchodilator versus glycopyrronium or open-label tiotropium. Similar results were shown by Singh and colleagues[24] in a post-hoc pooled analysis of maintenance-naive patients from the Evaluation of the Efficacy and Safety of Two Doses of Aclidinium and Formoterol in Fixed-Dose Combination in Patients With COPD (ACLIFORM) and Efficacy and safety of a fixed-dose combination of aclidinium bromide and formoterol fumarate in COPD patients (AUGMENT) trials, where besides the improvements in TDI the authors showed significant improvements in the EXACT-Respiratory Symptoms (E-RS) score and in early morning and night-time symptom scores. In both these analyses, the improvements in dyspnea were accompanied by relevant improvements in lung function, supporting the better efficacy of dual bronchodilators in treatment-naive patients.

In a similar manner, dual bronchodilators improved health status and health-related quality of life (HRQoL), as measured with various patient-reported outcomes, the most commonly used being the Saint George's Respiratory Questionnaire (SGRQ), with a modest overall effect[5,6]. The mean difference at weeks 12-52 varied between 1.8 to 1.2 points in a meta-analysis[6], with the minimal clinically important difference being 4 points[25]. The measured improvement in quality of life was not universal, as the combinations of formoterol/glycopyrrolate, formoterol/aclidinium, and vilanterol/umeclidinium did not provide universal improvement in SGRQ versus their monocomponents in some of their studies[10,20,26]. In the majority of these studies, however, the effect was in favor of dual bronchodilators and did not reach statistical significance for various reasons, plausibly related to study designs and placebo effects.

A systematic review and meta-analysis of RCTs in support of the American Thoracic Society (ATS) clinical practice guidelines, showed small statistically significant differences in dyspnea scores and HRQoL, that did not meet clinically relevant thresholds[27]. The clinical significance of these small overall differences, however, is accompanied by clinically relevant improvements in lung function. In the large pragmatic observational Effect of glyCopyrronium or indacaterol maleate and glYcopyrronium bromide fixed-dose combination on SympToms and heALth status in patients with moderate COPD (CRYSTAL) trial, indacaterol glycopyrronium improved TDI by 1.26 units versus LABA or LAMA, with accompanying improvements in ehealth status, as assessed by the COPD Assessment Test (CAT) and the Clinical COPD Questionnaire[19]. As in the double-blind RCTs, the improvements in health status and quality of life in the CRYSTAL trial are in agreement with objective improvements in lung function. Similar results have been seen in observational studies of dual bronchodilators in real-life settings[28]. The combination of RCT and real-life data that support the clinical effectiveness of dual bronchodilation add to the overall clinical benefits of these combinations versus mono-bronchodilators.

IMPROVEMENTS IN EXERCISE CAPACITY

A cardinal feature of COPD is chronic airflow limitation that leads to air-trapping and dynamic hyperinflation that results in a vicious

circle of dyspnoea on exertion and inactivity[29], limiting overall the exercise capacity and physical activity of patients with COPD[30], with profound effects on their physical condition and HRQoL, as well as on survival[31]. One of the most important efficacy outcomes provided by long-acting bronchodilators is the improvement in exercise tolerance or capacity that is related to the improvement in quality of life and daily living. Tiotropium was the first agent to be evaluated in large randomized placebo-controlled trials[16], followed by glycopyrronium[32] and other agents. Importantly, the benefits of LAMA in exercise tolerance were more pronounced when they were combined with exercise training, ideally in the form of pulmonary rehabilitation programs[33]. A number of studies of dual bronchodilators followed, comparing these with placebo or mono-LABD; dual bronchodilation provided improvements in exercise capacity versus placebo, however, the results versus mono-LABD were contradictory. A recent systematic review showed that LABA/LAMA combinations were overall superior to monotherapy in improving exercise capacity; in detail, however, the analysis showed only trends of improvement versus monotherapy in endurance shuttle walk test and constant work rate cycle ergometry, but significantly improved the six-minute walking test and number of steps per day[34]. Interestingly, in some of these studies, with the well-designed MORACTO studies being an example, dual bronchodilation improved lung hyperinflation (both static and importantly dynamic), but not exercise endurance[16]. A recent elegant study of formoterol/aclidinium has shown improvements in night-time inspiratory capacity, suggesting potential effects in dynamic night-time respiratory mechanics and inspiratory neural drive, without changes in ventilation or breathing pattern[35]. A potential explanation may lie in the fact that some of these studies did not implement an exercise training or disease modification intervention, combined with the long-acting bronchodilators, and this study design may at least in part account for the absence of statistically significant differences in exercise capacity versus monotherapies. In the PHYSACTO trial, Troosters and colleagues[36] implemented a self-management behavior-modification program combined with exercise training in patients receiving olodaterol/tiotropium or tiotropium; this study showed elegantly that the combination of dual bronchodilation and exercise training improved exercise tolerance in COPD patients, however, behavior modification is needed to have sustained improvements in physical activity[36]. Additional studies further support improvements in respiratory mechanics that may favor exercise tolerance by these combinations. Real-world data further support the improvement in physical functioning and activity, as in the case of a large international open-label single-arm study of olodaterol/tiotropium that showed significant improvements in the self-reported Physical Functioning questionnaire (PF-10) score[37]. The overall evaluation of LABA/LAMA combinations, both in RCT and real-life settings, suggests an added beneficial effect on exercise intolerance and capacity versus monotherapy.

EXACERBATION PREVENTION WITH LABA/LAMA VERSUS LAMA

LAMAs have been shown to reduce exacerbations effectively versus placebo[38], and are overall superior to LABAs in that direction[39]. There is a strong rationale for the exacerbation

prevention role of dual bronchodilators in COPD, with potential mechanisms being a reduction in hyperinflation and stabilization of the airway, decreased mucus production and increased mucociliary clearance, improvement of the symptom threshold and severity and potential anti-inflammatory properties (mainly based on in vitro data from LAMA)[40]. Two large RCTs have evaluated the potential superiority of LABA/LAMA combinations versus LAMA in exacerbation prevention. In the SPARK study, the combination of indacaterol/glycopyrronium provided a 12% lower rate of moderate to severe COPD exacerbations compared to glycopyrronium, and had a similar trend of 10% reduction versus open-label tiotropium that did not reach statistical significance[11]. In the large Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO) trial, the combination of olodaterol/tiotropium provided a 7% reduction in exacerbations versus tiotropium, which did not reach the prespecified level of statistical significance that was chosen to be 0.01 in this study[41]. The other three LABA/LAMA combinations do not have dedicated studies, but have shown similar trends for exacerbation prevention versus mono-LABDs in secondary, post-hoc and pooled analyses of their randomized trials[10,20,42]. Overall, besides the effects on lung function and symptoms, dual bronchodilators seem overall to have a greater exacerbation prevention effect than monotherapies, which was shown to be in the order of 20% in the recent ATS meta-analysis, which included also studies with free LABA+LAMA combinations[27]. In the same meta-analysis, dual bronchodilators reduced COPD hospitalizations by 11% versus LAMA[27], further supporting the role of these combinations in exacerbating patients for exacerbation and hospitalization prevention.

BROADER BENEFITS FROM EFFECTIVE BRONCHODILATION

Dual bronchodilators are the most potent bronchodilating and deflating agents that we have had so far in our clinical practice and their efficacy is likely greatest in patients with marked air-trapping and hyperinflation, as the provision of "pharmacological stenting" can have broader beneficial effects in such patients. In the double-blind crossover Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD (CLAIM) trial in patients with marked hyperinflation, as expressed by a residual volume (RV) > 135% of predicted and without unstable cardiovascular disease, dual bronchodilation with indacaterol/glycopyrronium improved cardiac function, as evaluated by the left-ventricular end-diastolic volume, while achieving also marked reduction in hyperinflation and other improvements in cardiac volumes and function[43]. In a subsequent analysis of the same study, this LABA/LAMA combination improved total and regional pulmonary microvascular blood flow and increased regional ventilation[44]. Similar results of improved ventilation and perfusion were shown in another more recent study of a broader population of moderate-to-severe COPD that used functional magnetic resonance imaging (MRI)[45], suggesting that effective dual bronchodilation addresses the fundamental pathophysiological mechanism of ventilation/perfusion mismatch in COPD.

DUAL BRONCHODILATORS IN THE DE-ESCALATION OF PATIENTS RECEIVING ICS

A recent European Respiratory Society guideline has addressed the clinically relevant question of ICS withdrawal in patients with COPD, suggesting that in patients with < 2 moderate exacerbations in the previous year (without hospitalization) and a blood eosinophil count < 300 cells/μL, ICS can be withdrawn in appropriate patients[46]. This conditional recommendation was based mainly on the data of a post-hoc analysis of the WISDOM trial[47] and a prespecified analysis of the Study to Understand the Safety and Efficacy of ICS Withdrawal from Triple Therapy in COPD (SUNSET) trial[48]. In both these studies, the de-escalation from triple therapy was done to a dual LABA+LAMA combination, and this has also been reflected in the GOLD recommendations[1,2]. It is, therefore, important to acknowledge that the de-escalation of ICS in appropriate COPD patients should always be towards a dual bronchodilation combination, and this is another position for these combinations instead of monotherapies (Fig. 1).

POTENTIAL SAFETY CONCERNS

Both drug categories, LABA and LAMA, have individual well-known class-related adverse events. Concerns have been raised in terms of their potential cardiovascular risk, mainly in population-based studies. A population-based study in Ontario, Canada, showed that in older individuals with COPD, the new use of LABA or LAMA was associated with an increased risk of cardiovascular events[49]. However, there was no evidence of increased safety issues as evaluated by overall and of treatment-emergent adverse effects with LABA/LAMA combinations versus LAMA in randomized controlled trials[5,6,27]. A recent population-based study in the UK showed an increased risk of acute coronary syndrome in patients who used concurrently LABA and LAMA versus the current use of LAMA by approximately 30%, which was also evident in an analysis of the fatal cases[50]. Interestingly, in an elegant analysis in a large database, the increased cardiovascular risk from first-time LABA or LAMA users was observed in the first 30 days of their use, whereas there was no risk or even a lower risk in the longer term with the regular use of these agents[51]. Plausibly, the increased risk of cardiovascular events with long-acting bronchodilators at the beginning of their use may be related to pre-existing cardiovascular disease that may be presenting with similar symptoms. Overall, the safety profile of dual bronchodilators outweighs their potential risks in the majority of patients, yet in specific patients with overt cardiovascular disease or at high risk for potential side-effects and individualized approach is needed.

CONCLUSIONS

The benefits of effective dual bronchodilation with LABA/LAMA fixed dose combinations versus mono-LABD have been shown in randomized trials and in real-life observational studies and include, besides the expected improvement in lung function, improvement in symptoms, quality of life and exercise capacity, better exacerbation prevention and potential cardiovascular benefits in patients with

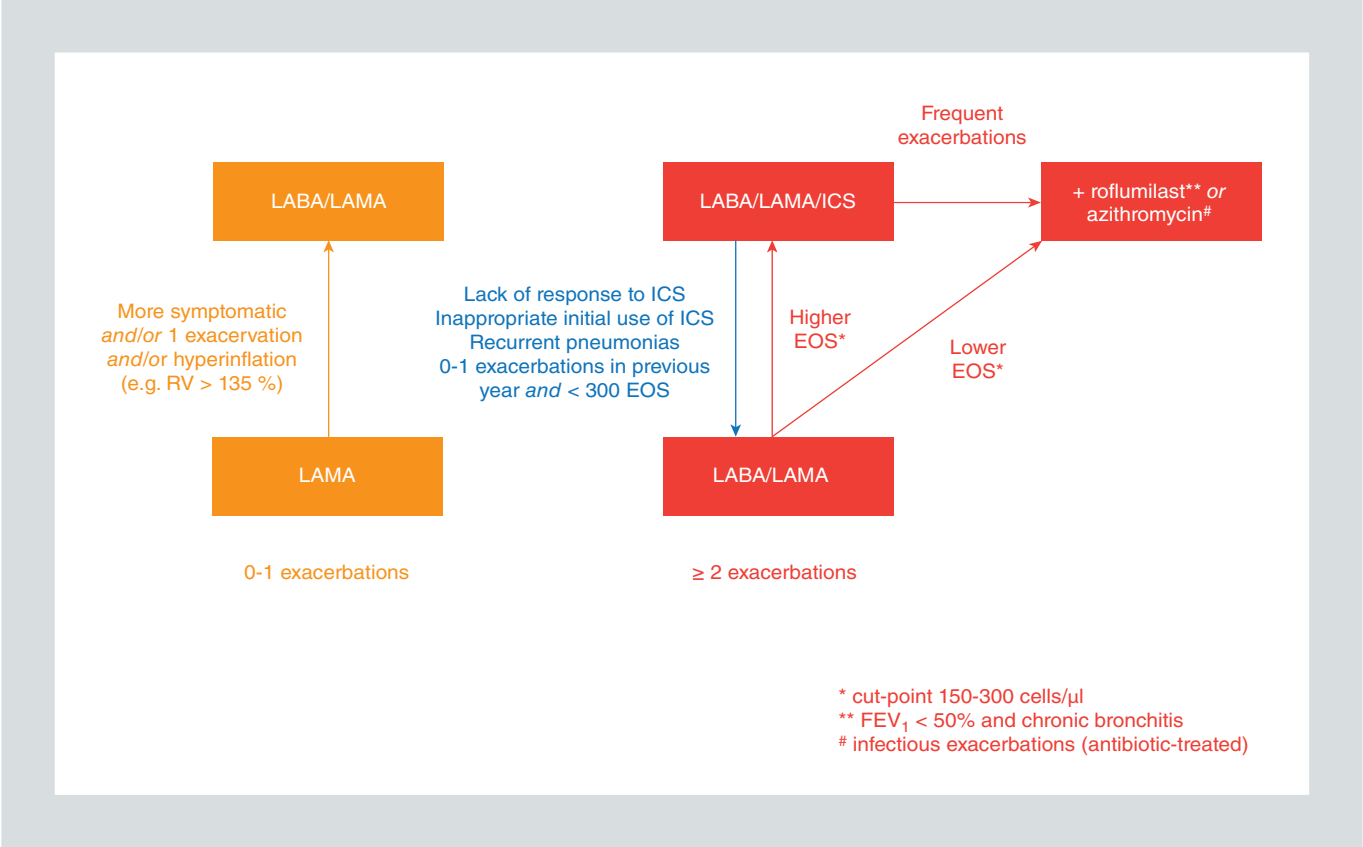

Figure 1. Positioning of dual (LABA/LAMA) versus mono-LABD in the individualized management of COPD patients: a comprehensive overview. COPD: chronic obstructive pulmonary disease; EOS: blood eosinophils; FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroids; LABA: long-acting β-agonists; LABD: long-acting bronchodilators; LAMA: long-acting muscarinic antagonists; RV: residual volume.

hyperinflation, with an acceptable safety profile. Dual bronchodilators can be the first-line agents in all symptomatic patients, as well as in exacerbating patients (especially if they have lower blood eosinophils and their exacerbations were treated with antibiotics)[52]. The place for mono-LABD (mainly LAMA) remains for the less symptomatic patients without severe hyperinflation. Dual bronchodilators represent also the only option for the de-escalation of ICS in appropriate patients who may not need this treatment. The positioning of mono- and dual-bronchodilators in the modern management of COPD is depicted in figure 1, which incorporates the current evidence in an algorithmic approach for the respiratory specialist. The individualized approach of each COPD patient with the appropriate treatment represents the modern way of COPD management.

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