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REVIEW

Indacaterol/Glycopyrronium Combination for COPD

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ABSTRACT

In all current guidelines and recommendations of the management of COPD, inhaled bronchodilators are the pillar of therapy at each stage of the disease. Dual bronchodilation with long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) is always more effective than the LAMA or LABA alone in terms of the improvement in trough FEV_1, and transitional dyspnea index and St. George's Respiratory Questionnaire scores. Indacaterol/glycopyrronium has been the first LABA/LAMA to be developed and approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. It has received approval from numerous regulatory authorities around the world because of the results of the pivotal Phase III programs IGNITE, which explored indacaterol/glycopyrronium 110/50 μg once-daily across 52 countries, and EXPEDITION, which explored indacaterol/glycopyrronium 27.5/15.6 μg twice-daily in US. Although guidelines and recommendations suggest a "slow" gradual therapeutic strategy, we advocate the need to start immediately, until the time of diagnosis, the treatment of COPD patients with indacaterol/glycopyrronium in order to optimize bronchodilation, because we strongly believe the rapid improvement in symptoms that it is able to elicit could help patients' adherence to treatment, which may be otherwise discouraged by a "slow" gradual therapeutic approach.

Keywords: COPD; Dual bronchodilation; Fixed dose combination; Glycopyrronium; Indacaterol; LABA; LAMA

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BACKGROUND AROUND COPD AND THE ASSOCIATED MORBIDITY AND MORTALITY

Chronic obstructive pulmonary disease (COPD) is a major non-communicable disease, associated with substantial morbidity and mortality [1]. There is a general agreement that an estimated number of 328 million people have COPD worldwide, of which 168 million are men and 160 million are women [2]. It is likely that in 2020, of 68 million deaths worldwide, 4.3 million will be caused by COPD [3], although there was a downward trend in COPD mortality at least in Europe between 1994 and 2010 [4]. However, the World Health Organization estimates that by 2030, COPD will become globally the third-leading cause of death also because almost 90% of COPD deaths will occur in low- and middle-income countries [5].

COPD has a major effect on healthcare costs, particularly direct medical costs. Thus, appropriate long-term interventions are recommended to lower the economic burden of COPD [6]. Although the economic burden of COPD is considerable across countries, and requires targeted resources to optimise COPD management encompassing the control of symptoms, prevention of exacerbations and effective treatment of comorbidities [7], the three most important factors in individual patients that determine the economic and societal costs of COPD are always disease severity, presence of frequent exacerbations of disease and the presence of comorbidities, which are common (30–57%) in COPD patients [8].

Consequently, drug treatment of COPD is mainly aimed at reducing symptoms, frequency and severity of exacerbations, and in improving quality of life, lung function and exercise tolerance [9, 10]. In general, the presence of comorbidities should not alter COPD treatment and comorbidities should be treated as if the patient did not have COPD [9].

In all current guidelines and recommendations of the management of COPD, inhaled bronchodilators are the pillar of therapy at each stage of the disease [9–11]. A recent systematic review with meta-analysis has suggested that dual bronchodilation with long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) is always more effective than the LAMA or LABA alone in terms of the improvement in trough FEV_1 [12]. Furthermore, LAMA/LABA fixed dose combinations (FDCs) also improve both transitional dyspnea index (TDI) and St. George's Respiratory Questionnaire (SGRQ) scores, and do not increase the cardiovascular risk when compared with monocomponents.

Several LABA/LAMA FDCs have been developed or are in clinical development [13]. Indacaterol/glycopyrronium (QVA149) has been the first LABA/LAMA FDC to be developed and approved as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD [12, 14]. In this article we review the evidence that supports use of this FDC in the treatment of COPD. The review is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

MECHANISM OF ACTION, DOSE AND ADMINISTRATION OF THE INDACATEROL/GLYCOPYRRONIUM COMBINATION

The nature of interaction between the two systems is not yet fully understood, but there is enough evidence to suggest that the pharmacological mechanism of action that justifies the combinations of bronchodilators lies also in the intricate reciprocal influences of cholinergic and adrenergic systems at pre-synaptic and post-synaptic levels [15]. Furthermore, there is evidence that the functional antagonism between β_2-adrenergic receptors and muscarinic receptors (i.e., relaxation and contraction in airway smooth muscle) is due to K_{Ca} channel activity regulated by G proteins (G_s and G_i) connected to each individual receptor. Moreover, voltage-dependent Ca^{2+} (VDC) channel activity regulated by the G_s/K_{Ca} channel stimulatory linkage and the G_i/K_{Ca} channel inhibitory linkage contributes not only to airflow limitation, but also to β_2-adrenergic desensitization, synergism between these two receptors, and airway remodeling [16].

The pharmacological characterisation of the interaction between glycopyrronium bromide and indacaterol fumarate in human isolated bronchi, small airways and bronchial epithelial cells has shown that the co-administration of these two bronchodilators leads to a synergistic improvement of bronchodilation, which was evaluated using the Bliss Independence Criterion for assessing the contributions of each agent, by increasing 3′-5′-cyclic adenosine monophosphate (cAMP) concentrations in both airway smooth muscle and bronchial epithelium, especially when these drugs are administered at low concentrations, and by decreasing non-neuronal acetylcholine release from the epithelium, but not from bronchi [17]. It must be mentioned that, when indacaterol and glycopyrronium were administered at low concentrations in this experimental setting, their ratio was consistent with that of the currently approved FDCs, namely 27.5/15.6 μg in the United States and 110/50 μg in the European Union. A translational study searching for synergy between glycopyrronium 50 μg and indacaterol 150 μg in patients with COPD suggested that the combination ensures a broncholytic effect that is greater than that induced by the single monocomponents and evidenced an additive effect for FEV_1 between 5 min and 180 min post-inhalation, with synergistic interaction at 15 min post-administration, compared to the bronchodilation induced by these drugs administered alone [18].

THE CLINICAL DATA THAT LED TO ITS NUMEROUS APPROVALS

Indacaterol/glycopyrronium FDC has received approval from numerous regulatory authorities around the world because of the results of the pivotal Phase III programs IGNITE, which explored indacaterol/glycopyrronium 110/50 μg once-daily across 52 countries, and EXPEDITION, which explored indacaterol/glycopyrronium 27.5/15.6 μg twice-daily in US, showing that it is able to produce a significant improvement in lung function and patient-reported outcomes, including breathlessness, health related quality of life (HRQoL) and rescue medication use, and reduced rates of COPD exacerbations when compared with current standard of care [14].

In particular, the Phase III IGNITE program, which enrolled >10,000 patients (ILLUMINATE, SHINE, BRIGHT, ENLIGHTEN, SPARK, BLAZE, ARISE, BEACON, RADIATE, LANTERN, FLAME),

plus the QUANTIFY trial documented that once-daily indacaterol/glycopyrronium 110/50 μg once-daily provided a rapid onset of action [19] and sustained bronchodilation from Day 1, which was significant and remained relatively constant through time compared with indacaterol, glycopyrronium, tiotropium, salmeterol-fluticasone and the free-dose combination of tiotropium plus formoterol [20–25]. Furthermore, it provided superior improvements in patient-reported dyspnea compared with tiotropium, salmeterol/fluticasone FDC, and the free-dose combination of tiotropium plus formoterol [24–26] and was associated with a lower incidence of nighttime and daytime COPD symptoms compared with glycopyrronium, tiotropium and salmeterol/fluticasone combination [21, 27]. Indacaterol/glycopyrronium improved HRQoL more than glycopyrronium, and tiotropium and significantly increased the rate of patients achieving a minimal clinically important difference (MCID) in the SGRQ total score compared with those receiving tiotropium or glycopyrronium [28].

Also the EXPEDITION program has confirmed that indacaterol/glycopyrronium FDC, although at a lower dose and administered twice per day, is more effective than monocomponents. The pivotal FLIGHT 1 and 2 studies documented statistically significant and clinically meaningful improvements in lung function (FEV_1 $AUC_{0–12h}$), TDI and SGRQ scores at Week 12, compared to indacaterol and glycopyrronium and/or placebo [29]. The results on both lung function and patient reported outcomes (PROs) in the FLIGHT studies compare well with the effects of once-daily higher doses of this FDC [30]. Unexpectedly, the gradient of effectiveness calculated using available results of clinical trials suggests that indacaterol/glycopyrronium 27.5/15.6 μg twice-daily is slightly better than indacaterol/glycopyrronium 110/50 μg once-daily with the change in trough FEV_1 being the primary outcome [12].

THE ROLE OF LAMA/LABA AND DUAL BRONCHODILATION IN TREATMENT STRATEGIES

Since there is no solid guidance on when to combine two bronchodilators with different mechanisms of action, an answer to the question "whether and when a second bronchodilator can or must be added in patients with stable COPD" is imperative [13]. The 2017 updated version of Global Initiative for Chronic Obstructive Lung Disease (GOLD) report stated that combinations of a LABA and a LAMA significantly increase lung function and in studies where patient reported outcomes (PROs) are the primary endpoint or in pooled analyses, combination bronchodilators have a greater impact on PROs compared to monotherapies [9]. As already mentioned, a systematic review with meta-analysis that incorporated the data from trials lasting at least 3 months to evaluate the effectiveness of LAMA/LABA FDCs for COPD treatment documented that dual bronchodilation is always more effective than the LAMA or LABA alone in terms of the improvement in trough FEV_1, TDI, and SGRQ scores compared with monocomponents [12]. Although the mean difference between LAMA/LABA FDCs and monocomponents for TDI score is usually 0.5 and that for SGRQ score is 2, both statistically significant but lower than the MCID thresholds, the associated reductions in reliever medication use suggest clinical relevance [31].

Accordingly, we advocate the need to start immediately, until the time of diagnosis, the

treatment of COPD patients with LABA/LAMA FDC in order to optimize bronchodilation using the full doses currently approved for the treatment of COPD, although we strongly believe that the synergistic interaction between LABAs and LAMAs supports the possibility of an intervention with low doses of LABA/LAMA combination to optimise bronchodilation and reduce the risk of adverse events that characterise both LABAs and LAMAs, especially when administered at the full doses currently approved for the treatment of COPD [32].

LAMA/LABA IN THE PREVENTION OF EXACERBATIONS

There is a general agreement that, given the high prevalence of COPD, the impact of exacerbations on quality of life and the costs incurred, effective ways for the prevention of exacerbations and for reductions in the severity and duration of COPD symptoms are needed [33].

A post hoc analysis of the ILLUMINATE trial, a multicentre double-blind, double-dummy, parallel-group study that enrolled COPD patients without exacerbations in the previous year, although 19.8% of them had severe COPD, and aimed to demonstrate the superiority of indacaterol/glycopyrronium compared with salmeterol/fluticasone for the standardised area under the curve from 0 to 12 h post dose for FEV_1 after 26 weeks of treatment [24], showed that indacaterol/glycopyrronium delayed the time to first exacerbation when compared with salmeterol/fluticasone [34].

The LANTERN study, a double-blind, double-dummy, parallel-group study focused on noninferiority of indacaterol/glycopyrronium versus salmeterol/fluticasone for trough FEV_1 at week 26, enrolled 744 patients with moderate-to-severe COPD with a history of ≤1 exacerbations in the previous year who were randomized (1:1) to indacaterol/glycopyrronium 110/50 μg once daily or salmeterol/fluticasone 50/500 μg twice daily for 26 weeks [35]. In the overall patient population, indacaterol/glycopyrronium decreased the annualized rate of moderate or severe COPD exacerbations by 31%, significantly prolonged the time to first moderate or severe exacerbation, and reduced the hazard of having such exacerbations by 35% when compared with salmeterol/fluticasone treatment. However, in patients with a history of moderate or severe exacerbations at baseline, the annualized rate of moderate or severe COPD exacerbations was 40% lower in the indacaterol/glycopyrronium treatment arm compared with the salmeterol/fluticasone treatment arm.

The results of the study FLAME, a randomised, double-blind, double dummy, non-inferiority trial lasting 52 weeks that enrolled 3362 patients suffering from COPD with a postbronchodilator FEV_1 of at least 25% to <60% of the predicted value and a history of at least one exacerbation treated with systemic corticosteroids, antibiotics or both during the previous year, showed that indacaterol/glycopyrronium was more effective than salmeterol/fluticasone in preventing COPD exacerbations in these patients [36]. The annual rate of all COPD exacerbations (−11%, 3.59 vs 4.03) and that of moderate or severe exacerbations (−17%, 0.98 vs 1.19) were lower in the group I than in the group II. Furthermore, the time to the first exacerbation (71 vs 51 days, 16% lower risk) and that to the first moderate or severe exacerbation (127 vs 87 days, 22% lower risk) were longer with indacaterol/glycopyrronium than salmeterol/fluticasone.

In our opinion, the capacity of indacaterol/glycopyrronium FDC in preventing COPD exacerbations is due to its capacity to decrease

hyperinflation and reset lung function dynamics because of a synergistic inhibition of the entire (bronchi and small airways) airway smooth muscle tone via modulating the cAMP dependent pathway [37]. The greater effectiveness of the indacaterol/glycopyrronium combination on small airways, compared with the partial effect of glycopyrronium or indacaterol alone [17], might be of particular clinical relevance for improving air-trapping related to the obstruction of bronchioles. In fact, as airway patency over time increases with longer duration of a more potent bronchodilator action, emptying of peripheral airways with trapped air is facilitated, thus reducing hyperinflation and improving breathing mechanics (pharmacological lung volume reduction) [38], and consequently reducing the risk of acute exacerbations of COPD.

We believe that also the reduced release of non-neuronal acetylcholine from the epithelium but not from bronchi caused by the co-administration of indacaterol and glycopyrronium is extremely important to explain the potential ability of dual bronchodilation in preventing acute exacerbations of COPD [37]. Actually, it is well known that non-neuronal acetylcholine plays an important inflammatory role [39]. In any case, the reduction in the release of non-neuronal acetylcholine from the epithelium is also important in generating the relevant synergistic interaction between glycopyrronium and indacaterol in small airways where the density of vagal innervation is insignificant or even absent [40], thus suggesting a role of the non-neuronal cholinergic system in regulating bronchial tone.

Regrettably, all these studies do not allow determining the real value of preventing COPD exacerbations when patients are treated according to the reported severity of exacerbations. Furthermore, they do not establish whether dual bronchodilation is effective in preventing COPD exacerbations regardless of their nature.

LABA/LAMA FDC AND REAL-LIFE TREATMENT PATTERNS OF COPD

In the absence of a solid recommendation in the guidelines regarding the use of dual bronchodilation, a consensus initiative for optimising therapeutic appropriateness among Italian specialists concluded that in patients not fully controlled with one long-acting bronchodilator, maximizing bronchodilation (i.e., adding another bronchodilator with a different mechanism of action) might be useful to achieve clinical improvement [41].

However, this view contrasts with worldwide real-life treatment patterns of COPD. In fact, considerable proportions of patients receive LABA/ICS, either alone or in combination with a LAMA irrespective of severity of airflow limitation, asthma diagnosis, and exacerbation history [42], although many patients on treatment continue to have symptoms [43].

A retrospective analysis of a cross-sectional, multicenter survey conducted in the US during 2012 assessed the degree of concordance between patients with COPD and their physicians when independently reporting patient-specific information on a variety of disease-specific attributes, including symptom type, frequency, severity, and impact on quality of life [44]. Dual therapy (free- and fixed-dose ICS and LABA, ICS and LAMA, or LABA and LAMA) rather than monotherapy was more frequently prescribed for patients who experienced bronchospasm and cough in the last 4 weeks. Dual regimens were more likely to be reported than triple therapy for patients with no symptoms in the preceding 4 weeks and

those who experienced wheezing. Triple therapy rates were higher compared with monotherapy for all but two of the reported symptoms of COPD.

All these studies were conducted before approval of the LABA/LAMA FDCs that are now available for the treatment of COPD but the use of LABA + LAMA free combinations was minimal. This is not really surprising considering that, according to the British National Institute for Health and Care Excellence guidelines [45], not yet updated, treatment with LAMAs plus LABAs is recommended in people with COPD who remain symptomatic on treatment with a LABA alone, whereas the LABA/LAMA combination is not recommended in those already taking a LAMA as sole maintenance therapy. Actually, there is documentation from a retrospective study, which used real-life data, that tiotropium is associated with significantly better disease outcomes in all measures investigated when compared to salbutamol/ipratropium [46]. Unfortunately, there is no data yet available on the benefit of LABA/LAMA FDC over LAMA, and also LABA, in real life although the results of pivotal randomized clinical trials indicate that this is the case.

Pending these data, it is important to decide whether it makes sense to switch all patients from a LABA/ICS regimen to a LABA/LAMA regimen on the basis of the improvement in lung function and the lower exacerbation rates. A recent meta-analysis of randomized clinical trials of at least 12 weeks of duration comparing LABA/LAMA and LABA/ICS combinations has shown that LABA/LAMA was associated with greater improvement in FEV_1 than LABA/ICS, but both treatments appeared clinically equivalent in improving SGRQ, TDI, and CAT scores [47]. Due to the recognized limitation of FEV_1, interest in PROs is increasing and the impact of LABA/ICS FDCs on SGRQ, TDI, and CAT scores could explain why they are still widely used in many patients at low risk of exacerbation.

However, there is evidence that indacaterol/glycopyrronium is faster in its onset of action than salmeterol/fluticasone from Day 1 up to Week 26 [19]. It might be expected that fast-onset bronchodilation would translate into fast relief of dyspnea (as in the case of salbutamol used as rescue medication). It has been highlighted that on repeated dosing, fast onset may not be particularly useful in patients who take their treatment regularly and have relatively stable symptoms [48]. Conversely, it might be of help in patients with suboptimal adherence to treatment, since perceived rapid efficacy could reinforce compliance. It could also be useful in patients with more variable symptoms [49]. We strongly believe the rapid improvement in symptoms could help patients' adherence to treatment, which may be otherwise discouraged by a "slow" gradual therapeutic strategy as suggested by guidelines and recommendations [50]. However, also the relative simplicity and convenience of once-daily dosing (compared with multiple daily dosing) may encourage patients' adherence and persistence with their long-term medications [48]. It is clear that at this stage we need a long-term study in real life to confirm that the fast onset and sustained duration of effect are critical to ensure adherence to treatment by patients who are under regular treatment with indacaterol/glycopyrronium FDC. We must also determine whether this LABA/LAMA FDC impacts better than a once-daily LABA/ICS FDC on PROs.

Since the treatment of COPD must be maintained over time, it is important to highlight that the overall superiority of LABA/LAMA FDCs is greater after 3 months of

treatment, while it slightly diminished after 6 and 12 months of treatment [51]. This trend suggests that continued improvements in FEV_1 elicited by LABA/LAMA combinations can be expected over the first 3 months of treatment; after that, the greater benefits of dual bronchodilation remains stable. Thus, it seems that for long-acting bronchodilator agents the time taken to reach the clinical bronchorelaxant steady state is considerably longer than the time taken to achieve the pharmacodynamic steady state, meaning that the LABA/LAMA interaction is fundamental, not only after acute administration, but also over time in the course of chronic treatment [51].

Choosing the optimum therapy for our patients with COPD is becoming increasingly difficult. From the perspective of a third-party payer, the optimum combination may be one that carries the lowest immediate cost, or that has the most favourable cost/risk ratio [52]. Lowering co-pays for maintenance drugs could result in improved adherence and, ultimately, decreased overall health-care spending [53].

Data generated using a patient-level simulation model in which Monte Carlo simulation methods were used to follow individual patients over various time horizons in a Swedish healthcare setting have shown that indacaterol/glycopyrronium FDC is cost-saving when compared with the free combination of indacaterol + glycopyrronium and cost-effective when compared with salmeterol/fluticasone FDC, in patients with moderate or severe COPD and low exacerbation risk [54].

Another study that assessed the cost effectiveness of the dual bronchodilator indacaterol/glycopyrronium compared with salmeterol/fluticasone combination in patients with moderate-to-severe COPD who had a history of one or no exacerbations in the previous year, used a patient-level simulation that was developed to compare the costs and outcomes of the two combinations based on data from the LANTERN trial [55]. Indacaterol/glycopyrronium was found to be the dominant (more effective and less costly) treatment option compared with SFC in Canada, France, Italy, and Portugal. The use of indacaterol/glycopyrronium was associated with mean total cost savings per patient over a lifetime of €6202, €1974, €1611, and €220 in Canada, France, Italy, and Portugal, respectively. Sensitivity analysis showed that exacerbation rates had the largest impact on incremental costs and quality-adjusted life-years (QALYs). The probability of indacaterol/glycopyrronium being cost effective was estimated to be >95% for thresholds above €5000/QALY.

INDACATEROL/GLYCOPYRRONIUM: CHOOSING THE RIGHT DEVICE

While the choice of drug used for treatment is reasonably easy for the majority of COPD patients, the choice of delivery device is less clear, particularly in view of the ever growing, and at times confusing, number and types of devices that contain the same chemical entity [56]. The ideal device to be used by a COPD patient has a universal design, is independent of patient inspiratory force and can deliver a consistent and reproducible dose into the lungs with patient compliance [57].

Indacaterol/glycopyrronium is delivered via the Breezhaler dry powder inhaler (DPI). DPIs do not need coordination of inhalation with activation and do not require hand strength. However, in the elderly the ability to generate adequate inspiratory flows through DPIs is compromised. The majority of patients with COPD are advanced at the time of diagnosis.

They are middle-aged or older and some of the more severely affected patients are elderly.

Nevertheless, the Breezhaler device is a low-resistance (specific airflow resistance of 2.2×10^{-2} kPa^{½}l^{-1} min) capsule-based DPI. The Breezhaler requires less inspiratory effort than other DPIs to achieve a given inspiratory flow or, as reflected in the inspiratory flow profiles, permits a higher inspiratory flow for a given effort [58]. Consequently, it is suitable for use by patients with a wide range of COPD severities, delivering a consistent dose irrespective of disease severity and age [59].

In a cross-sectional study that use the validated Patient Satisfaction and Preference Questionnaire (PASAPQ) to assess the handling and satisfaction for Respimat Soft Mist Inhaler (SMI) compared with the Breezhaler DPI among patients with COPD in Spain, there was not a statistically significant difference in the mean PASAPQ total score between the Respimat and Breezhaler groups (80.7 and 79.9, respectively) [60]. Intriguingly, the PASAPQ total score for Breezhaler DPI was relatively higher compared with those for other DPIs (Turbuhaler and Diskus) obtained in other studies comparing these DPIs with the Respimat SMI [61, 62].

The delivery characteristics, patients' correct use, and preference of two single-dose dry powder inhalers (Breezhaler and HandiHaler) were evaluated in two complementary studies [58]. Patient inhalation profiles showed average peak inspiratory flows of 72 l/min through Breezhaler and 36 l/min through HandiHaler. For Breezhaler and HandiHaler, fine particle fractions were 27% and 10%, respectively. Correct use of Breezhaler and HandiHaler was achieved by >77% of patients for any step after 7 days of daily use; 61% of patients showed an overall preference for Breezhaler and 31% for HandiHaler. Most patients used both inhalers correctly after 7 days, but more patients showed an overall preference for the Breezhaler compared with the HandiHaler. Furthermore, another study also showed that Breezhaler delivers a higher fine particle fraction and generates a greater and more consistent intrathoracic deposition irrespective of age and disease severity compared to HandiHaler [63].

THE FUTURE OF COPD TREATMENT AND HOW INDACATEROL/GLYCOPYRRONIUM FITS INTO IT

COPD is a heterogeneous disease, likely a disorder. Therefore, it is important to group COPD patients at least in clinical phenotypes because subjects included in the same subgroup/phenotype are expected to have similar disease, progression of disease and response to treatments [64].

Among all phenotypes described, Miravitlles et al. [65] have identified three fundamental phenotypes, the exacerbator, the overlap COPD-asthma, and the emphysema-hyperinflation, which are associated with prognosis and especially with a different response to currently available therapies. In the emphysema-hyperinflation phenotype, which is less prone to experiencing exacerbations unless it is present simultaneously with bronchial wall thickening, a feature of chronic bronchitis [64], long-acting bronchodilators are the first choice because they facilitate emptying of peripheral airways with trapped air, thus reducing hyperinflation and improving breathing mechanics [32]. The use of LABA/LAMA combination therapy offers a further functional benefit.

The approach to treatment according to clinical phenotypes is representing a substantial change in the therapeutic approach to COPD, from a FEV_1-guided treatment to a

more personalised approach directed by clinical features such as symptoms and exacerbations [66]. However, often COPD phenotypes overlap. Also to overcome this critical issue, Agusti et al. [67] have recently proposed a precision medicine strategy for the management of patients with airway disease that is "label-free" and based on the identification of "treatable traits" in each patient. LABA/LAMA combinations must be considered the first choice for treating the airway smooth muscle contraction. This indication is entirely acceptable also considering that the FLAME trial has shown that indacaterol/glycopyrronium is an effective alternative strategy to prevent exacerbation without ICS [36]. However, the evidence that LABA/LAMA combinations can prevent or at least delay the onset of exacerbations raises the fundamental question whether it makes sense to switch all patients from a LABA/ICS regimen to a LABA/LAMA regimen on the basis of the improvement in lung function and the lower exacerbation rates or there is a subgroup of patients with COPD who may benefit the most from this therapy [37].

A possible answer to this question will come in a future that we hope will not be too far when treatable traits will be used simultaneously with the assessment of endotype and/or disease activity biomarkers [31]. The identification of a distinct biologic COPD exacerbation phenotype (e.g., bacteria predominant vs eosinophilic predominant phenotype) could help to prescribe more effective targeting of preventive treatments (i.e., LABA/LAMA combination ± macrolides vs ICS-containing regimen), although this may prove difficult, because exacerbation mechanisms can change from one exacerbation to the next [31].

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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