Treatment of Chronic Obstructive Pulmonary Disease by Dual Bronchodilation with Coformulation of Indacaterol/Glycopyrronium

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Key Words

Long-acting β_2 -adrenergic agonist · Long-acting muscarinic receptor antagonist · Indacaterol · Glycopyrronium · Synergism · Dual bronchodilation · Coformulation · QVA149

Abstract

Bronchodilators are the cornerstone of the treatment of chronic obstructive pulmonary disease (COPD). In particular, the most commonly used drugs are inhaled long-acting agents, including long-acting β_2 -adrenergic agonists (LABAs) and long-acting muscarinic receptor antagonists (LAMAs). The combination of a LABA with a LAMA, i.e. of molecules characterized by different mechanisms of action, results in a synergistic enhancement of their clinical and functional effects. Therefore, this combined treatment can be implemented in a number of cases in which disease control is not adequately achieved by a single active agent such as a LABA or a LAMA. Several LABA/LAMA fixed-dose combinations, mainly made up of newly developed compounds, are currently in advanced phases of experimental evaluation. Within such a context, the aim of this review is to outline the pharmacological basis of dual bronchodilation as well as to discuss the results of the main trials carried out using the drug combination consisting of indacaterol and glycopyrronium, a LABA and a LAMA recently introduced in the treatment of COPD.

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Introduction

Bronchodilators are the cornerstone of current chronic obstructive pulmonary disease (COPD) treatment [1]. These drugs include β_2 -adrenergic agonists and antagonists of muscarinic acetylcholine (ACh) receptors [2]. The rationale of using these two drug classes is based on the high density of β_2 -adrenergic receptors (β_2 -ARs) present throughout the respiratory tree, and on the key pathogenic role played by neurogenic cholinergic mechanisms in COPD. In particular, in order to improve dyspnea, respiratory function, exercise tolerance and overall quality of life, as well as to prevent COPD exacerbations, the most effective bronchodilators are long-acting β_2 -adrenergic agonists (LABAs) and long-acting muscarinic receptor antagonists (LAMAs). Indacaterol is the first LABA that can be used once daily, as it provides a prolonged bronchodilation, lasting at least 24 h [3, 4]. In addition, recent advances in the field of LAMA pharmacology have led to the current availability of glycopyrronium, which, similarly to indacaterol, induces a prolonged and very rapid bronchodilation [5, 6]. Since LABAs and LAMAs act via different mechanisms of action, when used together, they can exert synergistic bronchodilating effects [7]. This suggests that indacaterol and glycopyrronium can be used together to optimize and maximize bronchodilation in many COPD patients with severe air-

flow limitation, whose needs are not adequately met by monotherapy performed with a single (LABA or LAMA) bronchodilator. Therefore, the aim of this review is to provide an updated overview of the pharmacological mechanisms underlying the clinical and functional benefits that can be achieved in many COPD patients through the use of a new inhaled pharmaceutical combination consisting of the first coformulation of indacaterol and glycopyrronium.

Pathophysiology of Bronchoconstriction Induced by Cholinergic Mechanisms

Bronchoconstriction induced by cholinergic mechanisms is mainly mediated by activation of vagal nerve reflexes [8, 9]. In particular, stimulation of airway sensory nerve endings by noxious irritants, such as cigarette smoke and other airborne pollutants, triggers an orthodromic neurotransmission along the afferent parasympathetic branch of the autonomic nervous system, which originates from vagal ganglia such as the nodose ganglion. These sensory pathways project to the brain stem, where the majority of airway-innervating neurons are located within the commissural, ventrolateral and medial areas of the nucleus of the tractus solitarius [10, 11]. At this level, the nervous signal is integrated via multiple interneuronal connections and then reverberated through efferent preganglionic parasympathetic nerves, which synapse in local airway ganglia located within the bronchial walls where ACh is released. ACh then stimulates nicotinic and M_1 muscarinic receptors, which mediate ganglionic neurotransmission [12–14]. From these ganglia, short postganglionic vagal fibers originate which release large amounts of ACh at the level of end effectors of the respiratory tract, including mucous glands and, especially, airway smooth muscle (ASM) cells. Therefore, the baseline cholinergic bronchomotor tone of smokers with COPD is increased in proportion to the degree of disease severity [15]. ACh release from airway postganglionic parasympathetic nerve terminals can be inhibited by several different prejunctional receptors, including β_2 -ARs and M_2 muscarinic receptors (autoreceptors), whose stimulation thus implements a negative feedback in case of excessive activation of the peripheral cholinergic system [16]. In addition to being the main neurotransmitter released into the airways from postganglionic vagal nerve fibers, ACh is also secreted as a paracrine/autocrine mediator by nonneuronal cell sources such as inflammatory and bronchial epithelial cells [17]. Similar to the neuronal

release of ACh, also the nonneuronal secretion of ACh into the airways can be stimulated by cigarette smoke, and of course this mechanism significantly contributes to the COPD pathobiology.

Once released from neuronal and nonneuronal cells, ACh causes ASM contraction, mainly dependent on the stimulation of postjunctional M_3 muscarinic receptors (fig. 1). Via activation of these ASM receptors, ACh elicits a sharp increase in the intracellular concentration of cytosolic free calcium ions (Ca^{2+}) [18]. Indeed, the levels of cytosolic free Ca^{2+} increase up to 800–1,000 nmol/l (compared to baseline values ranging from 100 to 200 nmol/l). Such a remarkable and rapid Ca^{2+} rise is responsible for ASM tension development. This is mainly due to Ca^{2+} release from sarcoplasmic reticulum (SR) induced by inositol 1,4,5-trisphosphate (IP_3) [19]. IP_3 synthesis arises from stimulation of M_3 muscarinic receptors coupled to the Gq protein, which is responsible for the activation of the β_1 isoform of phospholipase C ($PLC-\beta_1$). The latter catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP_2), thus producing the two intracellular second messengers IP_3 and 1,2-diacylglycerol (DAG) (fig. 1) [20]. DAG activates protein kinase C (PKC), which enhances the sensitivity of the ASM contractile apparatus to Ca^{2+} . Furthermore, PKC phosphorylates the β -AR kinase, a serine-threonine kinase involved in the homologous and heterologous desensitization of β_2 -ARs [21]. Instead, IP_3 diffuses within the cytosol and binds to its specific receptor (IP_3R) located on SR, thereby mobilizing the IP_3 -sensitive pool of intracellular Ca^{2+} stores.

IP_3R is an agonist-operated Ca^{2+} channel characterized by a homotetrameric structure consisting of four subunits, each having a molecular weight of about 260 kDa [22]. The fast and marked elevation of the cytosolic Ca^{2+} concentration induced by IP_3 is responsible for the sequential occupancy of the four Ca^{2+} -binding sites of calmodulin (fig. 1). The Ca^{2+} -calmodulin complex then opens and activates the enzymatic domain of myosin light-chain kinase (MLCK), which phosphorylates a specific amino acid residue (serine 19) of the regulatory 20-kDa myosin light-chain (MLC_{20}) subunit of myosin. MLC_{20} phosphorylation is indeed essential to trigger crossbridge cycling, i.e. the movement of myosin heads along actin filaments (fig. 1). Hence, the contractile model of ASM is consistent with a sliding filament mechanism in which actomyosin crossbridges, powered by ATP hydrolysis catalyzed by the intrinsic ATPase activity of myosin, are responsible for tension development [23, 24].

Fig. 1. ASM contraction induced by ACh. The interaction of ACh with the M₃ muscarinic receptor induces the sequential activation of the coupling Gq protein and of PLC-β, which cleaves PIP₂ into two intracellular second messengers: IP₃ and DAG. IP₃ binds to its receptor localized in the SR, thereby mobilizing the Ca²⁺, which binds to calmodulin, thus inducing the activation of MLCK. MLCK phosphorylates MLC, thereby promoting the subsequent

actin-myosin interaction which is responsible for muscle contraction. Bronchoconstriction ends following MLC dephosphorylation, catalyzed by MLC phosphatase (MLCP). MLCP is inhibited by CPI (C kinase-potentiated phosphatase inhibitor)-17, undergoing phosphorylation-dependent activation mediated by PKC, which in turn is activated by DAG.

Glycopyrronium – Mechanism of Action, Clinical and Functional Effects

The bronchoconstrictive effect of ACh can be inhibited by inhaled anticholinergic drugs, which act through a competitive antagonism of muscarinic receptors located in both proximal and distal airways [25]. Glycopyrronium bromide, also known as NVA237, is a powerful once-daily inhaled anticholinergic characterized by a high kinetic selectivity for M₃ versus M₂ muscarinic receptors (fig. 2)

[26, 27]. Glycopyrronium exerts a long-lasting bronchodilation associated with a very fast onset of action, due to the rapid occupancy of muscarinic receptors. Such an immediate blockade of ASM M₃ muscarinic receptors is thus responsible for a prompt decrease in cytosolic Ca²⁺ levels, paralleled by a rapid inhibition of bronchoconstriction elicited by cholinergic agents [27]. The advantageous bronchodilating patterns of glycopyrronium explain its excellent therapeutic profile, emerging from several clinical trials. In particular, the GLOW1 and GLOW2 studies

showed that glycopyrronium provides a rapid and sustained FEV₁ (forced expiratory volume in 1 s) increase already detectable within 5 min of administration [6, 28]. These effects are associated with significant improvements of the transition dyspnea index (TDI) and health-related quality of life, as assessed by St. George's Respiratory Questionnaire (SGRQ). Furthermore, the GLOW1 and GLOW2 studies demonstrated that glycopyrronium is able to significantly reduce the risk of moderate and severe exacerbations of COPD. The protective effect exerted by glycopyrronium against COPD exacerbations is also mainly due to its bronchodilating action. Indeed, the degree of baseline airflow limitation is predictive of exacerbation severity [29]. Therefore, it can be argued that a severe bronchial obstruction predisposes to recurrent COPD exacerbations, which in turn promote a further worsening of airflow limitation, thus implementing a deleterious and self-perpetuating vicious circle that can be interrupted by an effective and persistent bronchodilation. In addition, the GLOW3 trial showed that, when compared to placebo, glycopyrronium can induce a significant improvement in exercise endurance and exertional dyspnea, as assessed by the modified Borg scale [30]. These effects are associated with a parallel reduction in dynamic lung hyperinflation, documented by a significant increase in inspiratory capacity. It is thus reasonable to assume that glycopyrronium is able to exert its bronchodilating action also at the level of small airways, thereby facilitating lung emptying and counteracting air trapping, which is one of the most important factors limiting physical activity in COPD. In addition, the prolonged reduction in lung hyperinflation secondary to the decreased airway resistance, afforded by the regular use of glycopyrronium, can also contribute to prevent disease exacerbations. In fact, the improvement of lung hyperinflation is correlated with positive effects on the frequency and severity of COPD exacerbations, probably due to a better resetting of lung function dynamics elicited by long-acting bronchodilators [31].

The high degree of kinetic selectivity for M₃ over M₂ muscarinic receptors displayed by glycopyrronium (fig. 2) greatly contributes to its excellent pharmacological profile concerning both efficacy and safety. Indeed, glycopyrronium rapidly dissociates from M₂ muscarinic receptors, which within the airways inhibit the release of ACh from postganglionic parasympathetic nerve terminals [16]. Moreover, cardiac M₂ muscarinic receptors modulate atrial pacemaker activity, atrioventricular conduction and ventricular electromechanical coupling [32]. A persistent blockade of M₂ muscarinic receptors could thus attenuate bronchodilation primarily due to M₃ re-

ceptor antagonism as well as increase the risk of unwanted cardiovascular side effects including tachycardia and arrhythmias. Therefore, by largely preserving M₂ muscarinic receptor function, glycopyrronium maximizes bronchodilation and is also characterized by a very good pattern of cardiovascular safety [5, 6].

Indacaterol – Mechanism of Action and Clinical and Functional Effects

All β_2 -AR agonists, including indacaterol, induce bronchodilation by relaxing ASM regardless of the nature and multitude of constricting stimuli, thus acting as functional antagonists of bronchoconstriction. These drugs occupy and activate β_2 -ARs, which are coupled to the stimulatory G protein (Gs), which is in turn responsible for the stimulation of adenylyl cyclase (AC) and the subsequent increase in the intracellular concentration of the second messenger cyclic AMP (cAMP) (fig. 2) [33]. The latter activates cAMP-dependent protein kinase A, which phosphorylates several targets within the cell [34], thereby leading to the inhibition of MLCK and activation of MLCK phosphatase, which result in ASM relaxation. In addition, β_2 -adrenergic agonists promote Ca²⁺ sequestration inside the intracellular stores, and, by facilitating the opening of large-conductance Ca²⁺-activated K⁺ channels, these drugs induce the repolarization of the ASM cell membrane [34].

Indacaterol is a powerful β_2 -adrenergic agonist able to induce a very rapid and prolonged bronchodilation which lasts for about 24 h (fig. 2) [35]. This drug has an intense intrinsic activity at the level of β_2 -ARs, and its bronchodilating action does not elicit significant tachyphylaxis [34]. Unlike salmeterol, indacaterol does not alter the fluidity of the cell membrane, and its long-lasting bronchodilating effect is due to a high affinity of the lipophilic tail of the molecule for the so-called lipid rafts [36]. These consist of microdomains rich in cholesterol and sphingolipids that function as aggregation sites for β_2 -ARs within the cell membrane, thus also facilitating their connection with the signaling pathway, including Gs and AC. The rapid onset of the bronchodilating action of indacaterol depends on its hydrophilic head, which interacts with the β_2 -AR hydrophilic pocket surrounded by the seven hydrophobic transmembrane domains of this G protein-coupled receptor.

Administered once daily by inhalation route (150 or 300 μ g) to patients with COPD, indacaterol induces an immediate and long-lasting bronchodilation [37, 38]. Fur-

Fig. 2. Dual bronchodilation induced by coformulation of indacaterol/glycopyrronium. Indacaterol induces a long-lasting (about 24 h) relaxation of ASM via a prolonged activation of β_2 -ARs, coupled through the Gs to AC, which catalyzes the synthesis of the intracellular second messenger cAMP. The bronchodilation induced by indacaterol is greatly enhanced by glycopyrronium, which, similarly to the above LABA, provides a persistent bron-

chodilation due to the prolonged competitive blockade of M_3 muscarinic receptors. Indeed, glycopyrronium dissociates very slowly from these receptors, whereas it quickly detaches from M_2 muscarinic receptors. Although the latter may partially contribute to bronchoconstriction via inactivation of AC mediated by the inhibitory G protein (Gi), they are primarily responsible for the prejunctional inhibition of ACh release.

thermore, indacaterol is very effective for the regular maintenance treatment of COPD, thus providing a persistent improvement in trough FEV₁ for the entire duration of several trials that have been carried out over 52 weeks [3, 4, 39]. This drug also reduces the need to use short-acting rescue bronchodilators. Compared to placebo, indacaterol is also able to significantly decrease the incidence and frequency of COPD exacerbations [4]. In patients with COPD, indacaterol improves dyspnea and exercise tolerance [3, 40]; these effects are mostly due to a decrease in lung hyperinflation, as indacaterol is able to reduce residual volume and to increase inspiratory capacity [40, 41]. Therefore, indacaterol greatly improves health status and quality of life, as assessed by SGRQ [3, 4]. Finally, all clinical studies have shown that indacaterol is characterized by a very good safety and tolerability profile [35].

The Pharmacological Basis of Dual Bronchodilation Induced by the New Coformulation of Indacaterol/Glycopyrronium

In patients with COPD characterized by a marked air-flow limitation, in whom treatment with a single long-acting bronchodilator (LABA or LAMA) does not provide an adequate control of respiratory symptoms, a LABA/LAMA combination therapy can be used. Five complementary and cooperative effects of indacaterol and glycopyrronium are responsible for their synergism of action, based on reciprocal potentiation resulting in a maximization of bronchodilation.

(1) Indacaterol induces a direct bronchodilating effect mediated by β_2 -AR stimulation. The rapid and sustained increase in the intracellular concentration of cAMP elic-

ited by indacaterol (fig. 2) is responsible for the very effective functional antagonism of ASM contraction. Therefore, the integration of this mechanism of action with the postjunctional competitive antagonism of muscarinic receptors, i.e. at the level of the ASM cell membrane, makes it possible for indacaterol and glycopyrronium, when inhaled simultaneously, to maximize the resultant bronchodilation in COPD patients [7].

(2) Glycopyrronium inhibits ACh-dependent bronchoconstriction. The immediate, selective and prolonged blockade of M_3 muscarinic receptors allows glycopyrronium to optimize the competitive receptor antagonism of bronchoconstriction induced by ACh (fig. 2) [27], the main bronchoconstrictive mediator involved in the pathogenesis of the airflow limitation occurring in COPD.

(3) Indacaterol inactivates the signaling cascade underlying bronchoconstriction, thus enhancing the bronchodilating action of glycopyrronium. β_2 -Adrenergic agonists, such as indacaterol, inhibit the activation of the Gq protein coupled to M_3 muscarinic receptors. This mechanism is mediated by transcriptional stimulation of the expression of the regulator of G-protein signaling 2, which specifically inhibits the activation of Gq protein [42].

(4) Glycopyrronium prevents β_2 -AR desensitization, thus enhancing the bronchodilating action of indacaterol. By blocking M_3 muscarinic receptors, glycopyrronium inhibits receptor coupling to the signal transduction pathway, leading to the sequential activation of Gq and PLC, which is in turn responsible for the synthesis of DAG, the intracellular second messenger that activates PKC [24]. PKC can phosphorylate both the β_2 -AR and Gs protein, thereby uncoupling two key components of the signaling pathway underlying the bronchodilating action of β_2 -adrenergic agonists (fig. 2) [43].

(5) Indacaterol inhibits the prejunctional release of ACh, thus further enhancing the bronchodilating action of glycopyrronium. The positive interactions occurring between indacaterol and glycopyrronium also extend to the prejunctional site, i.e. at the level of vagal postganglionic nerve endings. Prejunctional inhibition of ACh release is indeed mediated by indacaterol-dependent β_2 -AR activation as well as by stimulation of M_2 muscarinic autoreceptors [7]. The function of prejunctional M_2 autoreceptors is largely preserved by glycopyrronium, which dissociates very rapidly from these receptors, whereas this drug blocks for a long time the postjunctional M_3 muscarinic receptors (fig. 2), which are mainly responsible for bronchoconstriction and mucus hypersecretion.

Another aspect of the reciprocal potentiation of the pharmacological effects of indacaterol and glycopyrroni-

um could also relate to the combination of the inhibitory actions exerted by both LABA and LAMA on the lung fibroblast expression of endothelin-1 [44]. This peptide, characterized by powerful bronchoconstrictive and fibroproliferative activities, is indeed also implicated in the development of peribronchiolar fibrosis, which significantly contributes to airflow limitation in subjects with COPD. Moreover, within the airways of these patients, LABA and LAMA may jointly inhibit neutrophil adhesion to bronchial epithelial cells, which is induced by transforming growth factor- β_1 [45]. Therefore, this recent experimental evidence suggests that the positive interactions between indacaterol and glycopyrronium could also be related to the potential anti-inflammatory actions of these two drugs. However, such an interesting hypothesis requires adequate confirmation, which can only be obtained by appropriate controlled clinical studies including large numbers of patients with COPD.

Clinical and Functional Effects of the Coformulation of Indacaterol/Glycopyrronium

Based on the above-discussed pharmacological considerations, adequate evaluations have been made with regard to the correct dosage of the coformulation of indacaterol/glycopyrronium, as it is not a simple preformed association. Indeed, the coformulation of indacaterol/glycopyrronium was based on the inhaled powder of glycopyrronium, to which indacaterol was added via complex procedures of micronization and adjustment of excipient concentrations. During the early phases of development, a greater mass of fine particles as well as a higher fraction of fine particles of indacaterol maleate were indeed obtained. Consequently, the dosage of indacaterol, but not that of glycopyrronium, has been reduced [46]. Therefore, the dosage of indacaterol in the coformulation with glycopyrronium is 110 μg , a lower amount with respect to the dosage of 150 μg available as monotherapy with indacaterol alone. Each capsule thus contains 143 μg of indacaterol maleate, equivalent to 110 μg of indacaterol, and 63 μg of glycopyrronium bromide, equivalent to 50 μg of glycopyrronium. Each delivered dose (the dose released by inhaler mouthpiece) contains 110 μg of indacaterol maleate, equivalent to 85 μg of indacaterol, and 54 μg of glycopyrronium bromide, equivalent to 43 μg of glycopyrronium. This reduction in indacaterol dose did not have any clinical consequence, as shown by the BEACON trial, which confirmed the synergism of the coformulation. In this study, the indacaterol/

glycopyrronium coformulation, delivered together by a single inhaler, was compared to the extemporaneous combination of the two drugs, each one delivered by a distinct inhaler. The primary endpoint was to evaluate the respiratory function (trough FEV₁), and the results have confirmed the lack of any statistically and clinically significant difference between the two coformulated doses and those independently delivered by two inhalers [47]. Several clinical trials have shown the remarkable effectiveness of the bronchodilation arising from the combined inhalation of indacaterol and glycopyrronium after a single administration with a Breezhaler dry powder inhaler device.

The aim of the ENLIGHTEN study was to verify the safety and effectiveness of the coformulation of indacaterol 110 µg/glycopyrronium 50 µg (QVA149), administered once daily [48]. This double-blind, randomized and placebo-controlled trial was carried out for 52 weeks in 339 patients with moderate-to-severe COPD who exhibited postbronchodilator FEV₁ measurements ranging from 30 to 80% of predicted values. From a quantitative as well as qualitative point of view, QVA149 and placebo elicited similar patterns of unwanted side effects, mainly characterized by mild-to-moderate severity [49]. QVA149 significantly improved lung function, thus steadily increasing FEV₁ throughout the whole study period. Furthermore, QVA149 was remarkably more effective than placebo in decreasing both respiratory symptoms and the need of using short-acting rescue bronchodilators.

The main objective of the SPARK trial, performed in 362 centers located in 27 countries, was to evaluate the efficacy of the indacaterol/glycopyrronium coformulation by comparing it over 64 weeks to either glycopyrronium or tiotropium with regard to the prevention of COPD exacerbations [48]. In particular, 2,224 patients with severe or very severe COPD were enrolled, presenting a postbronchodilator FEV₁ <50% of the predicted value and having experienced at least one exacerbation in the year prior to enrollment. Therefore, following a double-blind, randomized design, 741 subjects were assigned to treatment with indacaterol/glycopyrronium, 741 to monotherapy with glycopyrronium (50 µg daily with the Breezhaler device) and 742 to monotherapy with tiotropium (18 µg daily with the HandiHaler device). The results showed that QVA149 was able to significantly reduce the overall rate of all COPD exacerbations (mild, moderate and severe), at rates of 15 and 14% when compared to glycopyrronium and tiotropium, respectively [48]. With respect to the latter two drugs, QVA149 also induced a persistently and significantly greater increase

in trough FEV₁. Moreover, QVA149 was also more effective than either glycopyrronium or tiotropium in improving the global health status, as assessed by SGRQ. In addition, no significant differences between the three treatment groups were detected with regard to the incidence of unwanted side effects.

In the SHINE study, 2,144 patients with moderate-to-severe COPD (postbronchodilator FEV₁ ranging from 30 to 80% of predicted values) were randomly divided into five groups receiving a once-daily administration of the following treatments for 26 weeks: (1) QVA149, i.e. indacaterol 110 µg/glycopyrronium 50 µg (n = 475); (2) indacaterol 150 µg (n = 477); (3) glycopyrronium 50 µg (n = 475); (4) tiotropium 18 µg (n = 483), and (5) placebo (n = 234) [50]. With the exception of the group of patients undergoing treatment with tiotropium, who used the HandiHaler dry powder inhaler, all other groups used the Breezhaler as a dry powder device. The majority of patients were male (75.4%), and had not experienced exacerbations during the year prior to enrollment (74.6%). Before starting the various treatments, there were no significant spirometric differences between the five groups. The results of spirometries performed at week 26 of treatment showed that indacaterol/glycopyrronium, when compared to monotherapies with either indacaterol, glycopyrronium, tiotropium or placebo, induced significantly greater increases in trough FEV₁ and peak expiratory flow [50]. With respect to placebo, tiotropium and glycopyrronium at week 12, as well as in comparison to tiotropium and placebo at week 26, indacaterol/glycopyrronium induced a greater improvement in dyspnea, as assessed by TDI. At the end of the study, the overall health status, evaluated through the SGRQ score, resulted to be also significantly improved in the group treated with indacaterol/glycopyrronium when compared to the groups treated with either tiotropium or placebo. Furthermore, a significant decrease in the consumption of as-needed short-acting bronchodilators, used as rescue medications, was detected in the group treated with indacaterol/glycopyrronium when compared to the other four groups. With regard to the safety and tolerability profiles, no significant differences were found between the five groups in the number and severity of unwanted side effects [50].

The aim of the multicenter, double-blind, randomized ILLUMINATE trial was to assess the effectiveness of QVA149 in comparison to the fixed LABA/inhaled corticosteroid combination consisting of salmeterol 50 µg plus fluticasone propionate 500 µg (SFC), delivered twice daily via the Diskus dry powder inhaler [51]. In particular, this study lasted 26 weeks and included 523 current or

ex-smokers with moderate-to-severe COPD (age ≥ 40 years) who had no disease exacerbation during the year prior to their enrollment. Airflow limitation was characterized by a postbronchodilator FEV₁ ranging from 40 to 80% of predicted values. The results of this study showed that indacaterol/glycopyrronium, when compared to SFC, induced a significantly higher FEV₁ increase, already detectable during the first study day as well as at weeks 12 and 26 [51]. Moreover, a recent meta-analysis has shown that the coformulation of indacaterol/glycopyrronium delays the onset of the next exacerbation by 35% [52]. Indacaterol/glycopyrronium was significantly more effective than SFC in decreasing the use of as-needed short-acting bronchodilators as well as in improving dyspnea, as assessed by TDI. No significant differences were found between the two treatments with regard to both health status, as assessed by SGRQ, and the incidence of unwanted side effects [51]. However, with regard to the use of LABA/inhaled corticosteroid associations, previous trials have shown a high increase in the risk of pneumonia [16, 53], which was not found with the use of the indacaterol/glycopyrronium coformulation.

Based on the above study results, it can thus be assumed that a dual bronchodilating treatment, performed through the use of an inhaled pharmaceutical formulation capable of simultaneously delivering indacaterol and glycopyrronium, is characterized by a greater therapeutic effectiveness when compared to monotherapies consisting of either drug administered alone. Therefore, this experimental evidence confirms the pharmacologic rationale underlying the synergistic potentiation of the bronchodilating actions exerted by different drugs such as LABA and LAMA, which act via distinct mechanisms of action. This improvement in therapeutic efficacy can be achieved without increasing the incidence of adverse events. This suggests that the coformulation of indacaterol/glycopyrronium can be utilized to optimize and maximize bronchodilation in many COPD patients who do not experience an adequate improvement of airflow limitation by using a single bronchodilator. Furthermore, at least in those COPD patients who do not exhibit frequent disease exacerbations, also when compared to SFC, the coformulation of indacaterol/glycopyrronium appears to be characterized by a better therapeutic efficacy [51].

Finally, the combined use of indacaterol and glycopyrronium is furthered by the inhalation device used. In fact, the Breezhaler dry powder inhaler shows a low airflow resistance that allows the activation of the device with a relatively weak inspiratory effort [54]. This feature is very important because the Breezhaler can thus be easily used

even by patients with the most severe forms of COPD, which of course includes the main candidates for the dual LABA/LAMA combined therapy. In fact, the magnitude of the peak inspiratory flow decreases gradually as the disease severity increases. However, since the Breezhaler can be activated by a relatively low inspiratory flow, its use is markedly suitable for almost all patients with COPD, also including those characterized by the most severe degrees of respiratory functional impairment. In addition, the Breezhaler has other remarkable advantages, especially related to auditory, gustatory and visual perceptions, which make it possible for the patient to be sure of having properly inhaled the drug medications. Indeed, the release of a drug-fixed dose by the Breezhaler is associated with an audible hum in the inhalation chamber, the sensation of a sweet taste due to the presence of lactose, and the appreciation of powder emptying due to the transparency of the capsule inserted into the inhaler. All these features of the Breezhaler, associated with the advantage of once-daily administration, guarantee a high degree of compliance by the patient, with a consequent considerable increase in the adherence to prescribed inhaled therapy [55].

Concluding Remarks

The pharmacologic coformulation of indacaterol/glycopyrronium makes it possible to open a new chapter in COPD management. It is indeed the first LAMA/LABA coformulation available in a single inhaler for once-daily administration, thus currently representing the most advanced bronchodilator therapy. In fact, by exploiting the complementarity and integration of the different mechanisms of action activated by LABA and LAMA, respectively, it is possible to implement a synergism of action leading to an optimization and maximization of bronchodilation. This results in greater improvements in subjective symptoms, lung function and overall quality of life, associated with relevant delays in the onset of COPD exacerbations. In addition, the enhancement of airway stabilization and the long-term persistence of airway patency (pharmacologic 'airway stenting') associated with a more effective prevention of COPD exacerbations are likely to slow the rate of disease progression as well as to concomitantly reduce mortality.

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