The Novartis view on emerging drugs and novel targets for the treatment of chronic obstructive pulmonary disease

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**A B S T R A C T**

Chronic obstructive pulmonary disease (COPD) is a debilitating lung disease characterized by airflow limitation and chronic inflammation in the lungs. The mainstay of drug therapy for COPD is represented by long-acting bronchodilators, an important aspect of Novartis’ development program. Novel once-daily dosing bronchodilators, such as the long-acting muscarinic antagonist (LAMA) glycopyrronium and the LAMA/long-acting β2-agonist (LABA) fixed-dose combination QVA149, have been shown to provide significant benefits to patients with COPD in terms of improvement in lung function, exercise tolerance, health-related quality of life, symptoms and reduction in the rate of exacerbations. Despite the benefits provided by these new treatment options, prevention of disease progression and control of exacerbations in certain patient phenotypes remain key challenges in the treatment of COPD. In order to address these needs and gain new insights into the complexity of COPD, Novartis is, in addition to bronchodilator-only therapies, developing LABA/inhaled corticosteroids (ICS) combinations to target inflammation, such as QMF149, as well as non-steroid based anti-inflammatory agents against key novel targets. These commitments are central to the Novartis’ final goal of improving the standard of care in respiratory medicine and offering a better quality of life to patients with COPD.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating lung disease characterized by airflow limitation and associated with an enhanced inflammatory response to noxious particles and gases [1]. COPD is a multicomponent disease characterized by a range of pathological changes, which include mucus hypersecretion, airway narrowing and loss of alveoli in the lungs, and loss of lean body mass and cardiovascular effects at a systemic level [2].

Bronchodilators are the mainstay of pharmacological therapies for COPD. The recent revision to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategic document recommends long-acting inhaled bronchodilators as first-line maintenance therapy for COPD [1]. Treatment options include long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs), which could be used as monotherapy or in combination for patients whose symptoms are not effectively controlled by single bronchodilators. Inhaled glucocorticosteroids (ICS), which are associated with several side effects, including increased risk of pneumonia, osteoporosis and early onset of diabetes [3], are recommended only as add-on therapy in patients with severe and very severe COPD and frequent exacerbators that are not controlled by long-acting bronchodilators [1]. Given the importance of long-acting bronchodilators in the management of COPD as mono- or combination therapy, Novartis has made such agents a key part of its development program. As complex inhaler devices and a frequent dosing schedule may contribute to poor adherence [4,5], Novartis has focused its effort on trying to provide patients with new agents with a prolonged duration of action, which permits once-daily dosing, as well as fixed-dose combinations of bronchodilators and bronchodilators/ICS in a single, easy-to-use inhaler, with the aim of simplifying COPD management.

Despite the important benefits provided by new treatment options to patients with COPD, there are currently available therapies able to ensure full symptom control and more remains to be achieved to optimize quality of life. In addition, control and prevention of exacerbations continue to be major challenges that need to be further addressed in order to slow decline in lung function and disease progression, while potentially reducing mortality. Novartis is committed to addressing these unmet needs by

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developing innovative therapies aimed at improving the standard of care in respiratory medicine.

This review will summarize the therapeutic advances and benefits provided by new long-acting bronchodilators developed by Novartis as mono- or combination therapy, and discuss the most promising targets in COPD beyond bronchodilation.

2. Long-acting bronchodilators

2.1. Currently available long-acting bronchodilators for the treatment of COPD

Long-acting bronchodilators are the preferred option for maintenance treatment of COPD [1]. Two classes of long-acting inhaled bronchodilators are available—LABAs and LAMAs. LABAs directly induce bronchodilation by relaxing airway smooth muscle through stimulation of β2-receptors, whereas LAMAs prevent acetylcholine-induced bronchoconstriction by acting as competitive antagonists on muscarinic receptors [6].

Until recently, the twice-daily LABA salmeterol and formoterol were widely used maintenance bronchodilators. Indacaterol, the first once-daily LABA providing 24-hour bronchodilation, was developed by Novartis and has been available for use in patients with COPD since 2009. The efficacy of indacaterol in improving lung function has been demonstrated in four pivotal trials [7–10] and several supportive Phase III studies [11–13]. Indacaterol has also been shown to improve several important clinical outcomes; when compared with the twice-daily LABAs salmeterol and formoterol, indacaterol produced significantly superior improvements in dyspnea and reduced the use of rescue medication [7,10,12]. Several studies have also shown that indacaterol improves health status and exercise endurance time and reduces the frequency of COPD exacerbations compared with placebo [14–16]. In addition to improving several meaningful clinical outcomes, indacaterol, with its once-daily dosing, simplified the management of COPD, providing a significant advantage over previously available twice-daily LABAs.

Tiotropium was the first once-daily LAMA marketed for the treatment of COPD. Despite being effective in improving a range of important clinical outcomes [17–22], a study in patients with stable COPD has shown that tiotropium has a relative slow onset of action, taking up to 3 h to achieve optimal bronchodilation, in particular after the first administration [23].

2.2. Glycopyrronium: a new long-acting muscarinic antagonist for the treatment of COPD

The once-daily LAMA glycopyrronium bromide (NVA237) has recently been approved as a once-daily treatment for COPD. Like other LAMAs, glycopyrronium acts as a competitive antagonist by binding to muscarinic type-1 (M1) and type-3 (M3) receptors in the bronchial smooth muscle, thereby preventing acetylcholine-induced bronchoconstriction [24]. Blockade of muscarinic type-2 (M2) receptors, which modulate cardiac sinus activity and contraction force in the heart [25], has the potential to cause cardiac side effects. It has been shown that glycopyrronium has a higher kinetic selectivity for M3 versus M2 receptors than tiotropium and a shorter residence time than tiotropium on M1 receptors, which are expressed in exocrine glands and central nervous system and are associated with anticholinergic adverse events such as dry mouth and gastrointestinal disturbances [26]. In preclinical studies, glycopyrronium displayed an improved in vivo therapeutic index, particularly for cardiovascular side effects, compared with tiotropium [27]. Notably, glycopyrronium also displayed a rapid onset of action in vitro, with a half-life (t1/2) of 6.1 ± 2.1 min for inhibition of methacholine-induced calcium release—approximately five times faster than that of tiotropium (t1/2 29.4 ± 4.2 min) [26]. Taken together, these results suggested potential for a more favorable tolerability profile and faster onset of action for glycopyrronium versus tiotropium, providing the rationale for further investigating glycopyrronium in clinical trials.

Phase II studies have shown that once-daily glycopyrronium (12.5–200 μg) is well tolerated and provides sustained 24-hour bronchodilation in patients with moderate-to-severe COPD [28–30]. The Phase III Glycopyrronium bromide in COPD airWays (GLOW) program further evaluated the efficacy and safety of 50 μg glycopyrronium once daily (50 μg refers to the quantity of the glycopyrronium moiety present in the capsule, which corresponds to a delivered dose of 44 μg) taken in the morning in patients with moderate-to-severe COPD. GLOW1 evaluated the efficacy, safety and tolerability of glycopyrronium compared with placebo over 26 weeks. GLOW2 evaluated the efficacy and safety of glycopyrronium compared with placebo and open-label (OL) tiotropium 18 μg once daily (as an active comparator) over 52 weeks and GLOW3 assessed the effects of glycopyrronium versus placebo on exercise tolerance.

2.2.1. Lung function

In GLOW1 FEV1 at Week 12 (primary endpoint) was significantly higher in patients receiving glycopyrronium compared with patients receiving placebo, with a least squares means (LSM) treatment differences versus placebo of 108 mL (p < 0.001; Fig. 1A) [31]. Similarly, in GLOW2 glycopyrronium significantly improved trough FEV1 at Week 12 (primary endpoint) versus placebo, with a LSM treatment difference of 97 mL (p < 0.001; Fig. 1B) [32]. The efficacy of glycopyrronium versus placebo in lung function improvement was similar to that of OL tiotropium (83 mL versus placebo p < 0.001; Fig. 1B). The bronchodilation achieved with glycopyrronium was sustained over 26 weeks (GLOW1) and 52 weeks (GLOW2) (Fig. 1A and B).

2.2.2. Onset of bronchodilation

In addition to being as effective as OL tiotropium in improving lung function, glycopyrronium displayed a rapid onset of action on Day 1. In GLOW1, a significant increase in FEV1 was already apparent shortly after the first dose on Day 1, with a difference in mean FEV1 of 93 mL at 5 min and 144 mL at 15 min versus placebo (p < 0.001). In GLOW2, the mean FEV1 treatment difference on Day 1 for glycopyrronium versus placebo was 87 mL at 5 min post-dose, while the difference for OL tiotropium versus placebo was 45 mL at 5 min (all p < 0.001). FEV1 was significantly higher at all measured timepoints from 5 min to 4 h post-dose compared with placebo (p < 0.001) and OL tiotropium (p < 0.01) (Fig. 2). In GLOW2 on Day 1 and at Week 26, glycopyrronium produced early bronchodilation following morning dosing, with significantly greater peak FEV1 and FEV1 area under the curve (AUC) from 0 to 4 h (AUC0–4 h) post-dose compared with tiotropium and placebo. The peak FEV1; LSM treatment difference for glycopyrronium-placebo and tiotropium-placebo was 200 and 152 mL (p < 0.001) at Day 1 and 177 and 127 mL at Week 26, respectively (p < 0.001); the treatment difference for glycopyrronium versus tiotropium was 47 mL (p < 0.001). The FEV1; AUC0–4 h LSM treatment difference for glycopyrronium-placebo and tiotropium-placebo was 197 mL and 141 mL at Day 1 and 177 and 127 mL at Week 26 (all p < 0.001); the treatment difference for glycopyrronium versus tiotropium was 56 and 50 mL at Day 1 and Week 26, respectively (p < 0.001 and p < 0.01).

This rapid and early onset of bronchodilation of glycopyrronium compares favorably against tiotropium. The rapid onset of action of glycopyrronium could have important implications in COPD, as it may provide early relief of morning symptoms, a recognized issue for patients [33]. This may result in improvement in the ability to
perform morning activities [33]. It is interesting to note that an analysis investigating the impact of morning symptoms in patients receiving an ICS/LABA fixed-dose combination has recently shown that patients with morning symptoms had significantly more exacerbations in the previous twelve months than those without ($p = 0.005$) [34].

2.2.3. Symptoms and health-related quality of life

In both GLOW1 and GLOW2, glycopyrronium also significantly reduced symptoms such as breathlessness, one of the cardinal symptoms of COPD, as measured by the transition dyspnea index (TDI). In GLOW1, glycopyrronium significantly improved TDI focal score at Week 26, with a treatment difference of 1.04 versus placebo ($p < 0.001$), which exceeded the 1-point treatment difference considered as clinically important (Fig. 3A) [35]. In GLOW2, both glycopyrronium and tiotropium significantly improved TDI focal scores compared with placebo at Week 26 with treatment differences of 0.81 and 0.94, respectively (both $p = 0.002$) (Fig. 3B).

In both studies glycopyrronium improved health-related quality of life, as assessed by the St George's Respiratory Questionnaire (SGRQ). In GLOW1, the SGRQ total score was significantly better (lower) in patients receiving glycopyrronium compared with placebo ($p = 0.004$) at Week 26, with a treatment difference of $-2.81$. A significantly higher percentage of patients achieved a clinically meaningful improvement in SGRQ ($\geq 4$-point reduction) with glycopyrronium compared with placebo (OR 1.58, 95% CI: 1.14; $p = 0.006$). At Week 52 in GLOW2, SGRQ total score was significantly improved in patients receiving glycopyrronium and OL tiotropium versus placebo, with treatment differences of $-3.32$ ($p < 0.001$) and $-2.84$ ($p = 0.014$). A numerically higher proportion of patients receiving glycopyrronium or OL tiotropium achieved clinically meaningful improvements in SGRQ compared with placebo.

2.2.4. Exacerbations

Glycopyrronium significantly reduced the risk of a first moderate or severe exacerbation by 31% compared with placebo over 26 weeks in GLOW1 ($p = 0.023$) and by 34% over 52 weeks in GLOW2 ($p < 0.001$; Fig. 4). In the GLOW2 study, the risk reduction versus
placebo observed with glycopyrronium was similar to that for tiotropium (Fig. 4).

2.2.5. Exercise tolerance

In GLOW3, morning dosing of glycopyrronium improved exercise endurance time measured 1 h post-dose by 10% on Day 1 and 21% on Day 21 versus placebo \((p < 0.001; \text{ Fig. 5})\) [36]. This was accompanied by sustained reductions in lung hyperinflation, as indicated by significant improvements in inspiratory capacity (IC) at isotime (Fig. 5), which was also seen in the longer GLOW1 and GLOW2 studies. Glycopyrronium was also found to reduce exertional dyspnea versus placebo 1 h post-dose on Day 1 and Day 21 \((p < 0.05; \text{ Fig. 5})\) as measured by the Modified Borg Dyspnea score at isotime.

2.2.6. Safety

Pooled data of GLOW1 and GLOW2 demonstrated that glycopyrronium was well tolerated with a low frequency of cardiac and antimuscarinic side effects which was comparable to that of placebo and OL tiotropium. Antimuscarinic side effects, such as dry mouth, gastrointestinal disturbances, urinary retention and urinary tract infections, occurred with a low frequency in the glycopyrronium, placebo and tiotropium treatment groups. The percentage of patients with newly occurring or worsening clinically notable QTcF values (QT interval with Fridericia’s correction) was low across all treatment groups. The number of deaths reported in each group was low and similar across treatments, and none were considered to be related to study medication.

2.2.7. Glycopyrronium as an alternative choice to tiotropium

Overall, these results suggest that glycopyrronium is well tolerated and as effective as tiotropium in improving lung function, health status and exercise tolerance, and reducing dyspnea and risk of exacerbations in patients with COPD. Glycopyrronium, with its fast onset of action, represents a useful alternative to tiotropium.

3. Combination therapy in COPD

3.1. Combining long-acting bronchodilators

A single bronchodilator may not be optimal for COPD management especially for patients whose symptoms are not effectively controlled by monotherapy. As previously mentioned, the GOLD 2013 update recommends combination therapy with LAMA and LABA to optimize symptoms benefits [1].

Although the nature of interaction between cholinergic and adrenergic pathways in airway smooth muscle has not been fully understood, there is pharmacological evidence to suggest that the combination of muscarinic antagonists and \(\beta_2\)-agonists could have an additive effect on bronchodilation. The activation of \(\beta_2\)-receptors with a \(\beta_2\)-agonist reduces release of Ach by modulating cholinergic neurotransmission [37–39] thereby amplifying the bronchodilation produced by muscarinic antagonists [6]. \(\beta_2\)-receptors are abundant in the small airways [40], whereas M3 receptors are predominantly found in the lower trachea and bronchi [41]. Thus, the combination of \(\beta_2\)-agonists and muscarinic antagonists could result in a better coverage of the airways compared with monotherapy and provide maximal bronchodilation in all regions of the human lungs.

LABA/LAMA combinations have been shown to improve lung function (formoterol plus tiotropium [42–44]; tiotropium plus indacaterol [45]), symptoms and reduce the need for daytime rescue medication compared with monotherapy (formoterol plus tiotropium [42–44]). Safety data from all these studies have suggested that combination therapy does not increase the risk of side effects compared with monotherapy. In addition to providing greater bronchodilation, fixed-dose combinations of LABAs and LAMAs may simplify treatment and potentially lead to increased adherence, particularly for patients with several comorbidities who are likely to be taking other medications.

Although several LABA/LAMA combinations are currently under investigation [46], QVA149, which contains a fixed-dosed combination of indacaterol (110 \(\mu\)g) and glycopyrronium (50 \(\mu\)g), is the once-daily dual bronchodilator in the most advanced stage of development. In a Phase II study, QVA149 had a rapid onset of
action and significantly increased 24-hours post-dose FEV$_1$ compared with placebo and indacaterol alone on Day 1 and Day 7 [47]. In a study primarily designed to assess cardiovascular safety, QVA149 was tolerated with an adverse event (AE) rate similar to that of placebo [48].

QVA149 is undergoing investigation in the ongoing IGNITE clinical trial program, one of the largest Phase IIIa program in COPD involving more than 7000 patients with moderate-to-severe COPD [49]. The IGNITE program is evaluating the safety and efficacy of QVA149 on lung function, rate of exacerbations, exercise endurance and dyspnea, versus indacaterol, glycopyrronium, tiotropium, salmeterol/fluticasone (SFC) and placebo.

SHINE, a 26-week, double-blind, parallel-group study was designed to compare QVA149 with placebo, indacaterol 150 μg, glycopyrronium 50 μg and Ol tiotropium 18 μg in 2144 patients with moderate-to-severe COPD [50]. QVA149 significantly improved trough FEV$_1$ at Week 26 (primary endpoint) compared with placebo and all active treatments (mean difference versus placebo, indacaterol, glycopyrronium and tiotropium: 200, 70, 90 and 80 mL, respectively; all \(p < 0.001\); Table 1). QVA149 provided 24-hour bronchodilation with a rapid onset of action from Day 1, as shown by significantly higher FEV$_1$ and FEV$_1$ AUC$_{0-4}$h compared with placebo and all the active comparators (all \(p < 0.01\); Table 1). At Week 26, TDI focal score was significantly improved with QVA149 compared with placebo (LSM difference −3.01; \(p < 0.01\)) and tiotropium (LSM difference −2.13; \(p < 0.05\); Table 1).

In the ILLUMINATE study, QVA149 was compared with the LABA/ICS combination of twice-daily SFC in terms of efficacy, safety, and tolerability in patients with moderate-to-severe COPD and no history of exacerbations in the previous year [51]. This particular patient population was chosen to provide new evidence to support the recommended approach of treating patients with moderate-to-severe COPD with bronchodilators, while reserving ICS for patients with severe disease and high risk of exacerbation. Despite this recommendation, the side effects associated with their use, and their relative narrow approved indications in many countries, combination inhalers containing ICS are often prescribed to patients with more moderate disease [52]. The results of this study highlighted the potential benefits of dual bronchodilation over LABA/ICS combination in patients with moderate-to-severe COPD. FEV$_1$ AUC from 0 to 12 h (AUC$_{0-12}$h) was significantly higher with QVA149 versus SFC at Day 1 and Weeks 12 and 26 (primary endpoint) (LSM difference: 70, 120 and 140, respectively; \(p < 0.001\); Fig. 6). Serial spirometry showed significantly higher and clinically meaningful improvements in FEV$_1$ with QVA149 versus SFC at all timepoints from 0 to 12 h at Day 1 and Weeks 12 and 26 (treatment mean: 2.16 versus 1.41; \(p = 0.003\)) and reduced the use of rescue medication.

In the BRIGHT study, QVA149 also improved exercise tolerance versus placebo in patients with moderate-to-severe COPD [53].
SPARK, which is also part of the IGNITE program and involved 2224 patients over a period of 64 weeks, showed that QVA149 reduced the risk of moderate/severe exacerbations by 12% compared with glycopyrronium (primary endpoint; \( p < 0.05 \)) and the risk of all (mild, moderate and severe) exacerbations versus both glycopyrronium and tiotropium (\( p = 0.001 \) and \( p < 0.01 \), respectively) [54]. Overall, these studies demonstrated that QVA149 provides a significant advantage versus LABA and LAMA monotherapy in terms of improvement in lung function, relief from symptoms and reduction in the number of exacerbations. In addition, there were incremental benefits in lung function, dyspnea and rescue medication use compared to LABA/ICS combination therapy in patients without history of an exacerbation in the previous year, therefore highlighting the importance of dual bronchodilation in moderate-to-severe COPD.

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Least squares mean treatment difference</th>
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<tr>
<td><strong>Day 1</strong></td>
<td></td>
</tr>
<tr>
<td>Trough FEV(_1) (mL)(^+)</td>
<td>QVA149–PBO 190a 80a 80a 80a</td>
</tr>
<tr>
<td>FEV(<em>1) AUC(</em>{0-4,h}) (mL)</td>
<td>QVA149–IND 60a 30a 80a 80a</td>
</tr>
<tr>
<td>FEV(<em>1) AUC(</em>{0-24,h}) (mL)</td>
<td>QVA149–NVA237 30a 27a 80a 80a</td>
</tr>
<tr>
<td>FEV(<em>1) AUC(</em>{0-24,h}) (mL)</td>
<td>QVA149–TIO 27a 80a 80a 80a</td>
</tr>
<tr>
<td><strong>Week 26</strong></td>
<td></td>
</tr>
<tr>
<td>Trough FEV(_1) (mL)(^+)</td>
<td>QVA149–PBO 200a 70a 90a 80a</td>
</tr>
<tr>
<td>FEV(<em>1) AUC(</em>{0-4,h}) (mL)</td>
<td>QVA149–IND 110a 100a 100a 80a</td>
</tr>
<tr>
<td>FEV(<em>1) AUC(</em>{0-24,h}) (mL)</td>
<td>QVA149–NVA237 110a 110a 110a 80a</td>
</tr>
<tr>
<td>Peak FEV(_1) (L) (0–4 h)</td>
<td>QVA149–TIO 130a 130a 130a 130a</td>
</tr>
<tr>
<td>St George's Respiratory Questionnaire</td>
<td>−3.01b −1.09 −1.18 −2.13c</td>
</tr>
<tr>
<td>transition dyspnea index focal score</td>
<td>−0.96a −0.30c −0.66c −0.54c</td>
</tr>
<tr>
<td>rescue medication use</td>
<td>−0.96a −0.30c −0.66c −0.54c</td>
</tr>
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\(+\) End of Day 1; \( ^{+} \) \( p < 0.001 \); \( ^{b} \) \( p < 0.01 \); \( ^{c} \) \( p < 0.05 \). FEV\(_1\) – forced expiratory capacity in 1 s; AUC\(_{0-4\,h}\) – area under the curve from 0 to 4 h; AUC\(_{0-24\,h}\) – area under the curve from 0 to 24 h.

#### 3.3. ICS/LABA combinations

The use of ICS plus LABA therapy is recommended in patients with severe COPD and high risk of exacerbation [1]. In contrast to their effectiveness in controlling the underlying chronic inflammation in asthma, the efficacy of ICS in COPD is less well established and the debate over their clinical use continues. Evidence from a number of clinical trials suggest that ICS as monotherapy failed to prevent disease progression in patients with COPD [55–57]. Several long-term clinical studies have shown that high-dose ICS had no effect on the annual decline of FEV\(_1\) [55,57]. A meta-analysis of six long-term studies, involving 3571 patients with COPD, also failed to show any effect on the rate of FEV\(_1\) decline [55,56]. The limited efficacy of ICS treatment in COPD could be explained by its inability to suppress inflammation in lungs and airways due to an active resistance mechanism [58].

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**Fig. 6.** Improvement in lung function with QVA149 versus SFC: the ILLUMINATE study [51]. Data are LSM ± SE; FEV\(_1\) – forced expiratory volume in 1 s; \( ^{**} p < 0.001 \) for comparisons between QVA149 and SFC; AUC\(_{0-2\,h}\) – area under the plasma concentration–time curve from 0 to 12 h; LSM – least squares means; SE – standard error; SFC – salmeterol/fluticasone. *n* numbers shown represent patient number per treatment group at each timepoint.
Despite their limited efficacy in COPD as monotherapy, ICS have shown a greater clinical effect when used in combination with long-acting bronchodilators. The TORCH (Towards a Revolution in COPD Health) study compared all-cause mortality among patients with COPD between SFC, fluticasone propionate, salmeterol, and placebo [59]. Although not effective in reducing mortality, SFC provided greater symptom control, improvement in pulmonary function and reduction in exacerbations, compared with either of the individual components [59]. A post hoc analysis of the results of this study showed a small but significant reduction in the annual rate of FEV₁ decline by SFC compared with placebo in severe patients [60], suggesting that the use of ICS/LABA combination could potentially have a positive impact on disease progression. Moreover, ICS/LABA combinations appear to have anti-inflammatory effects not seen with ICS alone [61]. ICS have also been shown to enhance the bronchodilator effect of LABAs [62], suggesting that additional pro-contractile agents, the release of which could be mediated by the activation of pro-inflammatory pathways, may contribute to the airflow limitation observed in COPD. Even though the molecular mechanism of such a synergistic effect is yet fully understood, it is now acknowledged that the pathways activated by ICS and LABAs interact at several different levels [63].

In the light of these findings, it is interesting to note that the bronchodilator effect of LABAs with adjunctive ICS therapy is a valuable option for patients with more severe COPD and frequent exacerbations. In order to meet the treatment needs of these patients, Novartis is investing significant resources in developing QMF149, a new ICS/LABA combination.

3.4. QMF149 (indacaterol/mometasone)

QMF149, administered via the Breezhaler® device, is a once-daily ICS/LABA fixed-dose combination of mometasone furoate and indacaterol currently in development at Novartis for the maintenance treatment of asthma and COPD. Although in early stages of clinical development for the treatment of COPD, QMF149 with its once-daily dosing has the potential to provide important benefits over the two currently available twice-daily ICS/LABA fixed-dose combinations fluticasone propionate/salmeterol and budesonide/formoterol. In addition, evening dosing is expected to ensure peak efficacy of QMF149 during early morning hours when lung function and symptoms are worst [33].

This new ICS/LABA combination could also represent an advance in therapy as it combines the efficacy and rapid onset of action of the established LABA indacaterol with the anti-inflammatory activity of mometasone furoate. Mometasone furoate, alone or in combination with formoterol, is licensed for the treatment of asthma and COPD, where it has been shown to have a favorable safety and tolerability profile [64–66]. In a 52-week, placebo-controlled clinical trial in patients with COPD, mometasone furoate significantly increased FEV₁ from baseline and reduced the risk of exacerbations [67]. The study demonstrated comparable AE rates between mometasone furoate and placebo groups, with a low incidence of pneumonia, a side effect associated with some ICS/LABA combinations [68].

The efficacy and safety of QMF149 via the Twischhaler® device was assessed in a randomized, double-blind, active-comparator (mometasone furoate) study in patients with persistent asthma [69,70]. QMF149 significantly improved trough FEV₁ and reduced the risk of a serious exacerbation versus mometasone furoate with an incidence of AEs comparable to that of mometasone furoate alone. The efficacy and safety of QMF149 (150 µg/160 µg once-daily) compared with salmeterol xinafoate/fluticasone propionate (50 µg/500 µg twice-daily) will be investigated in a randomized, double-blind, 12-week parallel group study in patients with moderate-to-very severe COPD [71]. The Twischhaler® device has been replaced by the Breezhaler® device, which is able to ensure a higher lung delivery [72], in the QMF149 development program.

3.5. The Breezhaler® device: a common platform for the delivery of Novartis COPD pipeline products

As inhalation is the preferred route of administration in COPD, the characteristics of inhalation devices play a vital role in ensuring an effective management of this disease. An ideal inhaler for use in COPD should be easy to use and provide optimal and consistent drug delivery over a wide range of inspiratory flow rates. The internal resistance of the inhaler determines the effort patients have to make to achieve adequate inspiratory flows for effective and reproducible dose delivery [73,74]. This is particularly relevant in light of the results of recent studies showing that older patients and those with severe COPD have difficulty generating sufficient inspiratory flow for correct use of dry-powder inhalers [75,76]. In order to overcome these limitations, Novartis has chosen to deliver all its COPD products by a low-resistance single-dose, dry-powder inhaler known as the Breezhaler® device. Studies with the Breezhaler® device have shown that it delivers a consistent dose of indacaterol, irrespective of disease severity and is easy to use and well accepted by patients [77,78].

In addition to the characteristics mentioned above, an ideal inhaler for use in COPD should also generate optimal particle size for lung delivery and retention at the required site. The aerodynamic size of drug particles generated by inhalers is one of the most important factors in defining the distribution and deposition of drug within the lung, with a particle size of less than 4.7 µm in diameter generally considered optimal for deposition in the bronchi and alveoli [79]. A high fine particle fraction (FPF), defined as fraction of particles of less than 4.7 µm in diameter, indicates that a significant proportion of the inhaled dose is likely to reach the pulmonary region [80]. A recent in vitro study has also revealed that the Breezhaler® device delivers a high FPF across a wide range of inspiratory flows, further suggesting that it may be suitable for patients with COPD of different severities, including severe COPD [81].

The Breezhaler® device also offers continuity across the Novartis COPD portfolio, as it will be used to deliver glycopyrronium, QVA149 and QMF149. This will simplify the management of COPD, as patients will not need to learn the use and handling of a new device when switching from one inhaled treatment to another.

4. Emerging anti-inflammatory strategy for COPD

4.1. Role of inflammation in COPD

Inflammation in the lungs leads to the airway structural changes and associated airflow limitation characteristic of COPD (Fig. 7) [82]. Macrophages and epithelial cells in the respiratory tract are activated by inhaled irritants, such as cigarette smoke, occupational dust and environmental pollution, to release inflammatory mediators, including tumor necrosis factor (TNF)-α and other CXC chemokines, which in turn attract different types of inflammatory cells to the airways [82]. Neutrophils produce proteases, which are potent stimulants of mucus secretion [83], and are believed to be associated with chronic bronchitis, one of the main features of COPD. T-lymphocytes, which have the capacity to cause cytolsis and apoptosis of alveolar epithelial cells [84], contributes to the emphysema associated with COPD [85]. Macrophages not only orchestrate the inflammatory response in COPD, but can also cause emphysema by producing elastolytic enzymes, such as matrix metalloproteinase 9 (MMP-9) [86], able to break down connective tissue in the lung parenchyma.
Evidence from a number of studies has shown that COPD is intimately linked to inflammation, both locally and systemically. The number of inflammatory cells in bronchial biopsies and induced sputum has been correlated with COPD disease severity and rate of decline in lung function and health status [87–89]. Inflammatory cells and mediators have also been shown to increase during an exacerbation [90–92], suggesting that treatments that suppress inflammation in COPD could potentially reduce exacerbations. In addition, several studies have shown that serum biomarkers of inflammation including TNF-α and MMP-9 are increased in patients with COPD and correlate with the degree of airflow obstruction as well as with important clinical outcomes including mortality [93–95]. This may account for the observation that patients with COPD also present with systemic symptoms and comorbid conditions, including muscle weakness, weight loss, cardiovascular disease, osteoporosis, hypertension, depression, cognitive decline [96,97].

Given the central role played by inflammation in COPD, targeting relevant pathways is key to developing innovative therapies, in particular to slow disease progression and better control exacerbations. In order to achieve these goals, the identification of novel anti-inflammatory drugs is vital, as inflammation in COPD is resistant to the effect of ICS monotherapy [58]. In this review we will focus on phosphodiesterase-4 (PDE4) inhibitors, chemokine antagonists and p38 mitogen-activated protein kinase (MAPK) inhibitors, which represent the most promising classes of anti-inflammatory drugs currently in development for the treatment of COPD.

4.2. PDE4 inhibitors

PDE4 is a specific phosphodiesterase predominantly expressed by inflammatory cells, including those important to the pathogenesis of COPD, which makes it an attractive target for the development of new drugs [98]. PDE4 inhibitors are effective anti-inflammatory agents in animal models and have been shown to reduce markers of inflammation in COPD [99,100].

Roflumilast is an oral PDE4 inhibitor approved in the EU and in the US for patients with severe COPD and a history of exacerbations [101]. The efficacy and safety of roflumilast alone or in combination with a long-acting bronchodilator (tiotropium or salmeterol) were investigated in four long-term, large clinical trials [102–105]. Although in all these studies roflumilast significantly improved post-bronchodilator FEV1 compared with placebo, its effect on exacerbations was inconclusive. Two post-hoc, pooled analysis of trials involving patients with COPD, revealed that roflumilast reduced exacerbation frequency in a subset of COPD patients with chronic bronchitis, particularly in those taking concomitant ICS [103,106]. Based on the results of these analyses, the effect of roflumilast plus an ICS/LABA fixed-dose combination on exacerbations will be investigated in a 1-year randomized, double-blind, placebo-controlled Phase III/IV study [107].

Several inhaled PDE4 inhibitors are currently in development to maximize efficacy and reduce side effects associated with oral administration [108]. GSK256066 demonstrated potent and long-lasting anti-inflammatory effects in animal models of pulmonary inflammation, with a low rate of gastrointestinal side effects [109]. A Phase II trial in COPD patients has recently been completed but no data are currently available [110]. Despite the potential of GSK256066, failures in clinical trials have been reported for other inhibitors in development such as tofimilast [111].

PDE3 is important in mediating airway smooth muscle relaxation, as confirmed by the observation that PDE3 inhibitors cause bronchodilatation in subjects with asthma [112]. Combined PDE3/4 inhibitors, such as RPL554, could therefore have the ability to relax airway smooth muscle and suppress inflammation and are currently under investigation for the treatment of COPD. RPL554 has been shown to exhibit a broad range of both bronchoprotective and anti-inflammatory activities in animal models [113]. The results of a Phase II clinical trial in COPD patients have recently become available and showed that a single dose of nebulized RPL554 produced a rapid bronchodilator response, with increase in FEV1 significantly greater than that obtained with placebo and equivalent to that achieved with the active comparator salbutamol [114]. In addition, RPL554 was well tolerated and did not cause any significant adverse effects.

New approaches in development to target PDE enzymes also include oligonucleotide therapy, which aims at reducing protein expression levels by targeting messenger RNA [115]. Several oligonucleotides are currently in late preclinical or clinical stage development for the treatment of COPD.

4.3. Chemokine antagonists

Expression of several chemokines is increased in patients with COPD; this has generated a lot of interest in developing small-molecule chemokine receptor antagonists [116,117]. Chemokines secreted by activated macrophages play a pivotal role in inflammation as they recruit neutrophils and monocytes to the lungs, thereby amplifying the inflammatory response [82]. CX chemokine receptor 2 (CXCR2) is expressed by monocytes and neutrophils and mediates the activity of secreted chemokines such as CXCL1, CXCL5, CXCL7 and CXCL8 [82]. Interestingly, CXCR2 has been found to be up regulated in bronchial biopsies of patients with COPD with severe exacerbations [118]. Two oral CXCR2 inhibitors, SCH527123 and SB656933, are in early clinical development. Studies in healthy volunteers have demonstrated that both inhibitors caused attenuation of ozone-induced neutrophil recruitment to the lungs and displayed good tolerability profiles [119,120]. Moreover, SB656933 had also an effect on peripheral blood neutrophils and inhibited agonist (CXCL-1)-mediated expression of the integrin CD11d, which enables transmigration of circulating neutrophils into the lung parenchyma [120]. A clinical trial in patients with asthma has recently shown that SCH527123 was well tolerated and effective in reducing sputum neutrophils [121]. A study evaluating the safety
and dose ranging of SCH527123 in patients with moderate-to-severe COPD has been completed although data are not currently available [122].

CX chemokine receptor 3 (CXCR-3) and CX3C chemokine receptor 1 (CX3CRI), which respectively mediate the recruitment of T-lymphocytes and leukocytes in small airways and lung parenchyma, are also under investigation as new molecular targets in COPD [123,124].

4.4. p38 MAPK inhibitors

The p38 MAPK family comprises four different isoforms (α, β, γ and δ) that are activated in response to cellular stress [125]. The p38 MAPK pathway, which is activated in macrophages, CD8 lymphocytes and bronchial epithelial cells in patients with COPD [126,127], regulates the expression of inflammatory cytokines including CXCL8, TNF-α and MMPs, and therefore plays a key role in inflammation [128,129]. In particular, p38α, the most important isoform in the inflammatory response in COPD, is directly involved in the migration of neutrophils and eosinophils into the lungs [129-131]. Evidence suggests that inhibition of p38 MAPK kinase pathway could potentially have therapeutic benefits on many aspects of COPD, in addition to reducing the inflammatory response that contributes to the pathogenesis of this disease. p38 MAPK family mediates airway smooth muscle contraction and may also contribute directly to the airflow limitation observed in COPD [132-134]. Additionally, p38 MAPK activation has been shown to contribute to corticosteroid insensitivity [135] and may play an important role in mediating the effect of respiratory viruses, the most common cause of exacerbations, on airways cells such as macrophages and respiratory epithelium [136-138].

A number of small-molecule inhibitors of p38 MAPK have now been developed. Although several oral p38 MAPK inhibitors have been associated with liver toxicity, mainly due to off-target effects [136], two novel compounds had encouraging efficacy and safety profiles in short-term studies in COPD. A single oral dose of the p38α-selective inhibitor dimapimod (SB681323) reduced the levels of phosphorylated heat shock protein 27 (p-HSP27), a marker of p38 MAPK activation, and TNF-α in whole blood derived from patients with COPD [139]. A reduction in sputum neutrophils, accompanied by an improvement in FVC but not in FEV1, was also reported in a 4-week treatment using this compound [140]. In a 6-week study different doses of PHT97804, another inhibitor of p38α, significantly increased FEV1 with concomitant improvement in dyspnea score and IC [141]. The efficacy, safety and tolerability of the oral Novartis inhibitor BCT197 are under evaluation in a randomized, double-blind, placebo-controlled study in patients with an acute COPD exacerbation [142].

Inhaled p38 inhibitors, are currently under development for the treatment of COPD, with the aim of improving efficacy and further reducing systemic effects [143].

5. The future of COPD management: tailoring therapies to phenotypes

It has now been recognized that COPD is a complex disease characterized by multiple clinical manifestations with pulmonary as well as extrapulmonary components [144]. Despite novel therapies significantly improving the standard of care in COPD in recent years, a better understanding of the complexity of this disease at molecular, cellular and clinical level is still needed to guide the choice of therapy more effectively and allow patients to gain full benefits from new treatments.

Efforts have been ongoing in recent years to better characterize the different phenotypes of COPD. In this context, a phenotype is defined as ‘a single or combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes’ [145].

Novartis is committed to identifying novel phenotypes in COPD and is actively involved in several collaborations including COPDGene, COPD MAP, SPIROMICS and the COPD Foundation Biomarker Qualification Consortium with the aim of identifying underlying genetic factors, new clinical outcomes and biomarker in COPD. This will allow the classification of patients into distinct subgroups and potentially drive the development of individualized therapy, which could be matched more closely to patients’ needs, as well as helping to further clarify the underlying pathophysiology of COPD.

6. Conclusions

Long-acting bronchodilators remain the cornerstone of the management of symptomatic COPD. Given their importance in the COPD treatment algorithm, Novartis has focused considerable effort on developing novel once-daily dosing agents such as the LABA indacaterol, the LAMA glycopyrronium and the LAMA/LABA fixed-dose combination QVA149, which have been shown to provide significant benefits to patients with COPD in terms of improvement in lung function, exercise tolerance, health-related quality of life, symptoms and reduction in the rate of exacerbations. The new Novartis’ ICS/LABA combination QMF149, which is in early clinical development, offers potential as a new treatment option for patients at high risk of exacerbations. In order to ensure continuity across the COPD Novartis portfolio, Novartis has further invested significant resources in developing the low-resistance, dry-powder inhaler Breezhaler® device, which represents a common platform for the delivery of all the COPD products.

Despite these recent advances in the treatment of COPD, there is still a pressing medical need to develop new therapies targeted at preventing disease progression and reducing mortality and exacerbations. In this context, targeting inflammation represents the most promising approach; Novartis is fully committed to developing novel anti-inflammatory drugs able to address different aspects of the pathophysiology of COPD. Novartis is also actively involved in several collaborations with the aim of gaining new insights into the complexity of COPD and identifying novel COPD phenotypes. This commitment is central to the achievement of Novartis’ final goal: developing innovative therapies in COPD to improve patients’ lives.

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