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The right treatment for the right patient: the Novartis view on COPD

Authors
Chris Compton[1], Francesco Patalano[2], Mark J. Fedele[3] & Danny McBryan[2]

[1]Novartis Horsham Research Centre, Horsham, RH12 5AB, UK.

[2]Novartis Pharma AG, Basel CH-4002, Switzerland.

[3]Novartis Pharmaceuticals Corporation, East Hanover, NJ 07936-1080, USA.

Chronic respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), kill more than four million people every year and affect the lives of hundreds of millions more[1]. Novartis is committed to providing innovative products and solutions to improve the quality of life of patients with chronic respiratory diseases. Foradil (formoterol), Onbrez/Arcapta (indacaterol), TOBI (tobramycin) and Xolair (omalizumab) are some of the results of this commitment. For the treatment of COPD, Novartis has several products in late-stage development. In this white paper, we present the Novartis view on the appropriate treatment of COPD and the importance of bronchodilation.

COPD is a preventable and treatable disease characterized by persistent and usually progressive airflow limitation that is associated with an enhanced chronic inflammatory response to noxious particles or gases in the lungs[2]. Dyspnoea, cough and sputum production are the characteristic symptoms of COPD; with the impact of symptoms on daily life usually being the factor that prompts patients to seek medical advice[2]. These symptoms, particularly dyspnoea, are often worst early in the day and have a considerable impact on the quality of life and activities of daily living of patients with COPD[3].

COPD is a major cause of morbidity and mortality, and is predicted to be the fourth leading cause of death by the year 2030[2]. Although it is often perceived as a disease of the elderly, approximately 50% of patients are estimated to be below 65 years of age[4]. COPD is associated with a huge economic burden due to direct healthcare costs and indirect costs related to loss of productivity[2]. Given the high prevalence and growing burden of COPD, and the immense impact of the disease on patients, healthcare systems and society at large, there is a pressing need for effective, easy to administer therapies.

There is considerable heterogeneity in clinical presentation and disease progression in COPD[5]. The identification and grouping of key features of COPD into clinically meaningful subgroups, or phenotypes, could potentially guide individualized and more effective therapy for COPD. At Novartis, we believe that it is imperative that the right treatment is offered to the right patient, at the right stage in the COPD disease process.

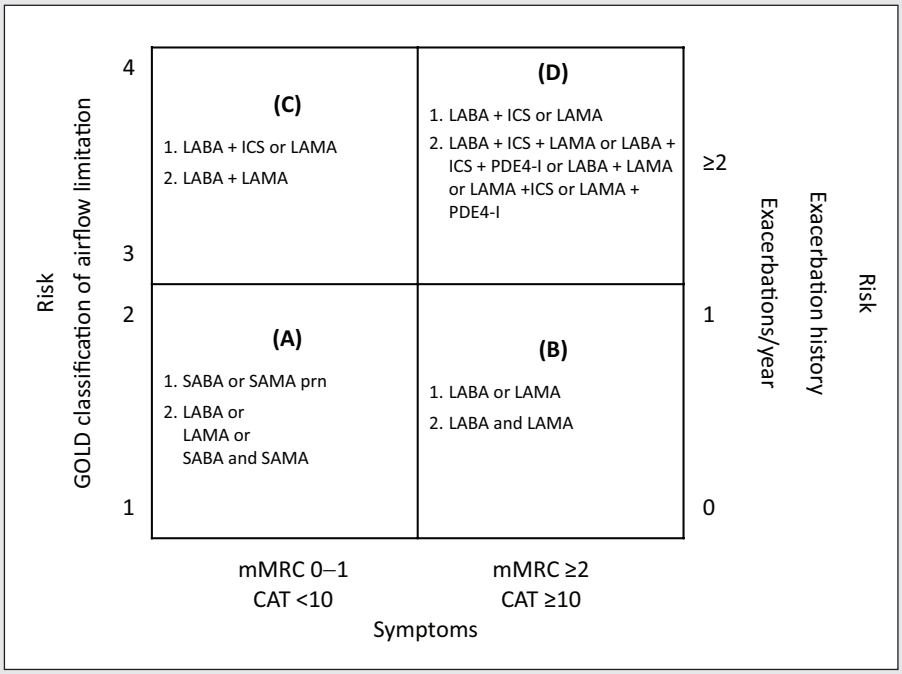

Figure 1 | GOLD 2011 classification of patients based on symptoms, spirometry and exacerbations, and recommendations for pharmacological management.
CAT, COPD assessment test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified medical research council; PDE4-I, phosphodiesterase-4 inhibitor; prn, as needed (pro re nata); SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist. Figure reproduced with permission from ref. 2.

Putting new paradigms into practice

Until recently, the classification of COPD severity in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was based solely on the degree of airflow limitation, with forced expiratory volume in 1 second (FEV_1) considered as the 'gold standard' for the diagnosis and assessment

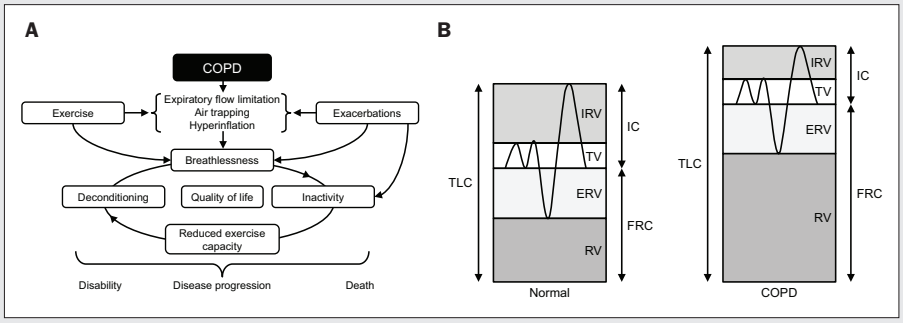

Figure 2 | Airflow limitation in COPD. a, The central role of airflow limitation leading to symptoms in COPD (reproduced with permission from ref. 9). **b,** Lung volume response to exercise: COPD versus normal (reproduced with permission from ref. 10). Residual volume (RV) and expiratory reserve volume (ERV), which together make up functional residual capacity (FRC), may increase in COPD. Although total lung capacity (TLC) usually increases in COPD, inspiratory capacity (IC) will decrease as a consequence of the increased FRC. IRV, inspiratory reserve volume; TV, tidal volume.

of COPD severity[2]. However, in recent years it has been increasingly recognized that the severity of airflow limitation alone is not sufficient to encapsulate the multiple clinical manifestations of this complex disease, or to predict an individual patient's prognosis or response to therapy. It is now recommended that the assessment and management of COPD should be based on a strategy incorporating severity of airflow limitation and symptoms, disease impact and the future risk of disease progression, particularly exacerbations. This illustrates a gradual shift in focus from the reactive, acute management of COPD to chronic care provision and prevention of disease complications and progression. It has also been suggested that COPD assessment should be matched to treatment objectives, a move towards individualized therapy in which treatment is tailored more closely to the patient's needs[2].

Optimal management for COPD patients should simultaneously address symptoms and any disability arising from the respiratory disease and the extra-pulmonary components of COPD. A holistic care model for COPD should include non-pharmacological interventions (smoking cessation therapy, promotion of a healthy lifestyle with maintenance of activity and regular exercise, vaccinations and pulmonary rehabilitation), optimal pharmacological interventions, assessment and appropriate management of comorbidities, and patient education for self management.

The GOLD 2011 strategy classifies patients with COPD into four groups — A, B, C or D — with a severity assessment based on a combination of symptoms, airflow limitation and exacerbations[2]. Bronchodilators are the foundation of pharmacological management of COPD and are recommended for all patients with COPD (groups A–D). For maintenance treatment of COPD (Fig.1) they are the preferred option, prescribed either alone or in combination with another bronchodilator or an inhaled corticosteroid (ICS). For patients in group A, who have mild-to-moderate disease and/or ≤1 exacerbation per year and fewer symptoms, short-acting bronchodilators are recommended to be used as needed, in conjunction with non-pharmacological interventions (for example, smoking cessation, maintenance of physical activity). Regular treatment with one or more long-acting bronchodilators, such as long-acting β_2-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs), is recommended as second choice for symptomatic patients in group A. LABAs and LAMAs are recommended as a first-choice pharmacological treatment for patients in groups B–D, in conjunction with non-pharmacological therapies such as pulmonary rehabilitation[2].

Regular treatment with ICS is recommended only for patients at high risk (groups C and D), defined by a history of frequent exacerbations (≥2 per year) and/or severe airflow limitation (FEV_1 <50% predicted). The effect of ICS in COPD is small, with their principle role being to reduce the risk of exacerbations. Furthermore, the use of ICS is associated with local and systemic side effects[6]. Despite the guideline recommendations, the limited therapeutic value and the risk of side effects, the use of ICS is widespread in patients with COPD , including those with newly diagnosed disease. At Novartis, we believe that in patients with moderate (group B) COPD, evidence suggests that ICS should not be used, and that LABA/LAMA combination therapy should be offered to those patients who remain symptomatic on bronchodilator monotherapy.

Airflow limitation in COPD

Chronic airflow limitation in patients with COPD is caused by a combination of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). The relative contribution of these conditions to airflow limitation in COPD varies from person to person[2].

The permanent parenchymal destruction seen in patients with COPD not only reduces gas exchange capacity owing to the destruction of alveoli, it also reduces the elastic recoil of the lungs. Combined with narrowed and poorly supported airways where airflow resistance is increased, this leads to a greater amount of air remaining in the lungs after expiration (that is, air trapping or hyperinflation) (Fig. 2)[8–10]. As a result, these patients use a large amount of energy to exhale, which contributes to fatigue. Superimposed on this static hyperinflation are further increases in lung volumes brought about by exercise or exacerbations. Hyperinflation reduces inspiratory capacity such that functional residual capacity increases, particularly during exercise (dynamic hyperinflation), resulting in dyspnoea and limitation of exercise capacity.

Although persistent and progressive expiratory flow limitation is the hallmark of COPD, it is hyperinflation that is responsible for the activity limitation and exertional dyspnoea that prevent patients engaging in their normal day-to-day activities. Patients become less active to avoid breathlessness, which causes physical deconditioning, leading to a downward spiral of dyspnoea and inactivity. Consequently, COPD leads to a significant reduction in patients' ability to exercise, with reductions in physical activity seen even in patients with mild disease (Fig. 3). Further decreases in activity occur as the severity of COPD worsens[11].

Treating airflow limitation with bronchodilators

Bronchodilators ameliorate airflow limitation by targeting bronchoconstriction and reducing air trapping. They bring about their effects by altering airway smooth muscle tone, improving the emptying of the lung, and acting on peripheral airways to decrease air trapping, thereby reducing lung volumes and improving symptoms and exercise capacity. There is a large body of evidence to support the key role that bronchodilators play in improving lung function, dyspnoea and exercise tolerance, preventing exacerbations and thus improving quality of life and ability to engage in activities of daily living in patients with COPD[2]. Evidence suggests that treatment with long-acting bronchodilators given once daily is more effective and provides the benefit of sustained bronchodilation throughout the day, without the peaks and troughs associated with twice-daily

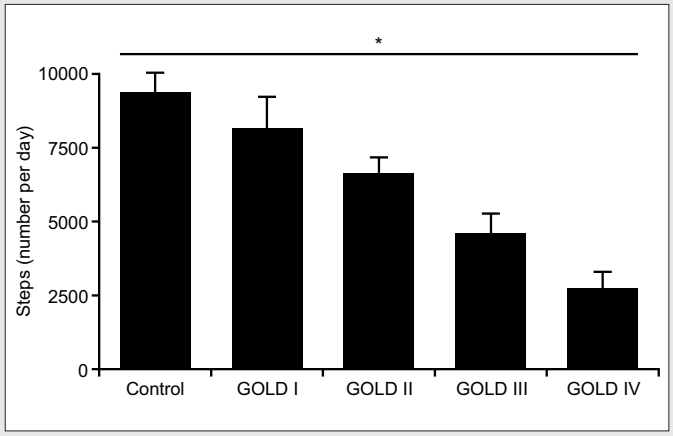

Figure 3 | Physical activity levels as COPD progresses. The number of steps in matched, healthy control subjects and patients with mild (GOLD I) to very severe (GOLD IV) COPD (GOLD 2010 criteria). Asterisk indicates statistical significance of the analysis of covariance (ANOVA) linear trend. Figure reproduced with permission from ref. 11.

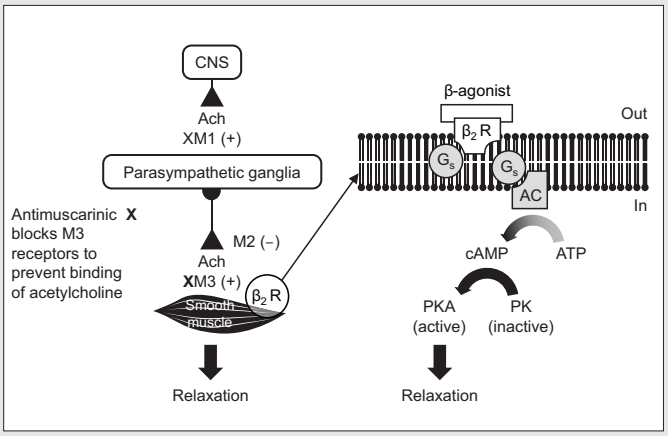

Figure 4 | Direct and indirect smooth muscle relaxation. Ach, acetylcholine; AC, adenylyl cyclase; β_2R, β_2 receptor; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; Gs, stimulatory G-protein; M, muscarinic receptor; PK(A), protein kinase (A). Figure reproduced with permission from ref. 17.

therapy[12]. Once-daily treatment is also more convenient than treatment with short-acting bronchodilators, which need more frequent daily dosing regimens. This has the potential to increase adherence to therapy[13].

Novartis has focused its efforts on developing novel bronchodilators with an improved duration of action, allowing for once-daily dosing, and developing fixed-dose combinations of bronchodilators in a single inhaler. Our research and development teams believe that this will help simplify treatment regimens and foster patient adherence, thus providing improved patient outcomes. Consequently, considerable resources have been devoted to the development of long-acting bronchodilators, both LABA and LAMA, and a fixed-dose LABA/LAMA combination for delivery in a single-device platform known as the Concept 1 device (approved for prescribing as the Breezhaler® device or the Neohaler® device).

Indacaterol (Onbrez® and Arcapta®), the first once-daily LABA providing 24-hour bronchodilation, was developed by Novartis and is available for use in patients with COPD. The development of a once-daily LABA provides a significant advantage compared with previously available options (salmeterol and formoterol), which require twice-daily administration. The efficacy and safety of indacaterol in patients with COPD has been established in several randomized studies[14]. Indacaterol received European regulatory approval in 2009, and has been launched in many countries worldwide, including in the European Union (EU; as Onbrez®) and the USA (as Arcapta®).

Currently, the only LAMA approved for maintenance therapy in COPD is tiotropium (Spiriva®); however, once-daily glycopyrronium (in development at Novartis as NVA237), was filed for approval in several regions and countries, including the EU and Japan, in 2011. Phase III studies have demonstrated similar efficacy and safety compared with open-label tiotropium, with improvements in several outcomes — including lung function, dyspnoea, risk of exacerbations, exercise tolerance and health status — in patients with moderate-to-severe COPD[15,16]. Glycopyrronium, taken in the morning, also demonstrated a rapid onset of action with either statistically or numerically greater bronchodilation than open-label tiotropium in the critical first 4 hours after inhalation. Glycopyrronium has therefore shown potential as a useful alternative choice to tiotropium for the management of patients with moderate-to-severe COPD.

With indacaterol as an established LABA for the treatment of COPD, combination products with indacaterol are in development at Novartis. QVA149 is being developed as a once-daily, fixed-dose combination of indacaterol and glycopyrronium, providing bronchodilation through two different mechanisms; QMF149 is being developed as a once-daily, fixed-dose combination of indacaterol and mometasone (an ICS) for patients with severe COPD and frequent exacerbations.

The potential benefits of dual bronchodilation

Targeting a single bronchodilatory pathway may be insufficient to maximize bronchodilation[2]. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease the risk of side effects compared with increasing the dose of a single bronchodilator[2]. LABAs and LAMAs work on complimentary pathways to provide bronchodilation; with the combination, bronchodilation can be achieved directly, by the stimulation of β_2-adrenergic receptors with LABAs, and indirectly, by the inhibition of acetylcholine-induced bronchoconstriction with LAMAs (Fig. 4)[17]. Several studies have demonstrated significantly superior improvements in bronchodilation with free LABA/LAMA combinations compared with either therapy used alone[2]. Fixed-dose combinations of LABAs and LAMAs have the added potential benefit of improving adherence to therapy. As many patients with COPD have several comorbidities for which they are likely to be taking other medications, simplifying COPD treatment may improve compliance.

Several fixed-dose LABA/LAMA combinations are under development, including Novartis' QVA149. This once-daily, fixed-dose combination of the LABA indacaterol and the LAMA glycopyrronium is currently being investigated in the phase III IGNITE programme, involving more than 7,000 patients. The studies in this programme are evaluating the efficacy and safety of QVA149 versus indacaterol, glycopyrronium, tiotropium, salmeterol/fluticasone and placebo. Their major aim is to clarify further whether dual bronchodilation translates into improvements in outcomes for patients with COPD, and to evaluate the potential benefits of combining two long-acting bronchodilators in a single inhaler for the treatment of COPD.

Long-acting bronchodilators in early COPD

In the early stages of the disease, dyspnoea may occur upon exertion. During increased

activity, the lungs fail to accommodate the additional demand, and the patient experiences dyspnoea. Interventions aimed at an early stage of the disease may help improve the capacity for physical activity, and thus slow the rate of symptom progression[8]. Significant decreases in activity are seen even in patients with mild COPD[11], and can affect their productivity and quality of life.

In post-hoc analyses of data from the large, long-term studies Towards a Revolution in COPD Health (TORCH) and Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT), it was shown that initiation of maintenance treatment with long-acting bronchodilators in patients early in the course of the disease can result in greater improvements in lung function, exacerbations, quality of life and mortality, compared with control[18].

Maintenance pharmacotherapy with long-acting bronchodilators may be particularly effective in patients in GOLD group A with moderate airflow limitation. The current GOLD guidelines recommend that these patients should be offered short-acting bronchodilators (as needed) as a first choice. If their symptoms persist or deteriorate, they should then be categorized as GOLD group B and be offered long-acting bronchodilators as first-choice treatment. However, based on the evidence from TORCH and UPLIFT, patients in group A may benefit from long-acting bronchodilator therapy, LABAs or LAMAs, upon diagnosis. Early intervention with long-acting bronchodilators at this stage may help relieve breathlessness, and maintain or improve the capacity for physical activity and exercise.

The role of ICS

The use of ICS in COPD remains a matter for debate. In contrast to the universal acceptance of anti-inflammatory agents in the treatment of persistent asthma, the efficacy of ICS is less well-established in COPD.

Guidelines recommend the use of ICS in COPD based on their preventive effect on exacerbations[2]. The GOLD 2011 strategy document recommends that regular treatment with ICS be reserved for patients with severe or very severe airflow limitation and/or ≥2 exacerbations per year (GOLD groups C and D). Much of the data in favour of the use of ICS in COPD comes from early studies, which demonstrated that patients with more severe COPD and a history of recurrent exacerbations benefit from their use. Furthermore, dose–response with ICS has never been fully characterized in COPD, and they are often used in relatively high doses. Therapy with ICS is associated with local adverse effects such as oral candidiasis, hoarseness and skin bruising, and may increase the risk of pneumonia and reduce bone density[2,6]. Given that patients with COPD are often of advanced years, and are likely to have several comorbidities, such as cardiovascular disease, diabetes, osteoporosis, anxiety and depression (and may be taking several medications for them), they have a heightened susceptibility to the adverse effects of ICS treatment. Evidence suggests that there may be value in adding ICS to bronchodilator treatment in patients categorized as belonging to GOLD groups C and D. Indeed, QMF149, a fixed-dose LABA/ICS combination in development at Novartis, would potentially be appropriate for this very group of patients with severe to very severe airflow limitation and frequent exacerbations.

Despite this lack of evidence and the recommendations of global guidelines, ICS and fixed-dose combinations containing ICS are used in a great many patients with COPD, including a large proportion of those with newly diagnosed disease[7]. Many patients seen in primary care have moderate disease, and do not experience frequent exacerbations, and are therefore not appropriate recipients of ICS. Indiscriminate use of ICS-based therapies in COPD not only exposes patients to unnecessary risk, it may also be wasteful of healthcare resources owing to their cost and side effects. Novartis supports the guideline approach of treating patients with mild-to-moderate disease using bronchodilators, while reserving ICS for more severe disease associated with frequent exacerbations. To this end, we designed the ILLUMINATE study, part of the phase III IGNITE programme, to evaluate the efficacy and safety of dual bronchodilation with once-daily QVA149 versus the LABA/ICS combination of salmeterol/fluticasone in patients with moderate to severe COPD and no history of exacerbations in the previous year. Results from this study will provide evidence for the potential of LABA/LAMA combinations compared to LABA/ICS in patients with symptomatic COPD but without frequent exacerbations.

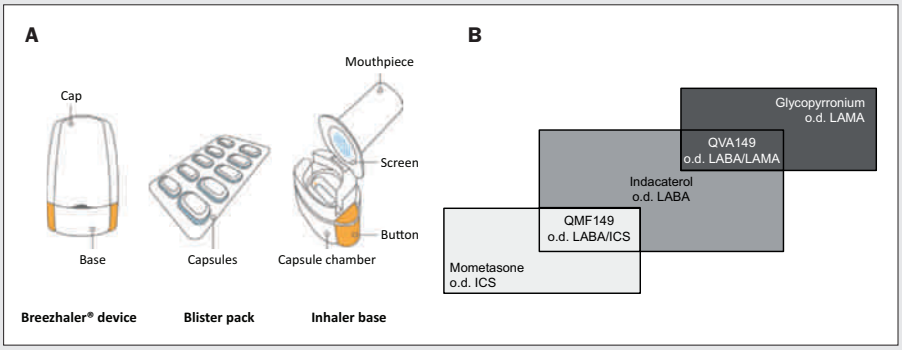

Figure 5 | Meeting the evolving needs of patients with COPD. a, The Breezhaler® (and Neohaler™) device. **b**, Novartis' once-daily COPD portfolio. ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; o.d., once daily.

The pharmacological management of COPD may have evolved from the drugs used for the treatment of asthma, but the treatment models for the two diseases are markedly different. In asthma, the use of ICS is the foundation of treatment for all but the mildest cases, whereas in COPD their role is limited. A correct differential diagnosis is therefore imperative to distinguish cases of COPD from those of asthma and choose the appropriate treatment strategy.

The importance of inhaler devices

Inhalation is the preferred route of administration for drugs used to alleviate the symptoms of COPD[2]. It is recognized that compared with drugs taken orally, more of the drug is delivered directly to the required site of action and can take effect more quickly following inhaled dosing, while causing fewer adverse effects. When selecting a device for delivering inhaled drugs, several factors should be considered. These include its efficiency and the ability of the patients to handle the selected device correctly[19]. The use of a uniform device when several drugs are to be inhaled may also be advantageous. It is therefore desirable that the medications prescribed to a patient are delivered through the same or similar efficient devices.

The Breezhaler® (Neohaler® in the USA) device is a single-dose, dry-powder inhaler (Fig. 5a) specifically developed to have low airflow resistance, to ensure that patients with severe lung conditions are able to use the device effectively. Experience so far suggests that the device is liked and well accepted by physicians and patients with COPD[19]. It has been designed with the needs of patients as the primary consideration, with features such as low airflow resistance,

reliable feedback and ease of use. A simple mechanism, with low effort required to pierce the capsule, and a practical design makes the device easy to use for patients with COPD. A combination of unique feedback features enable patients to see, hear and feel with confidence that their dose is correctly taken. Additionally, the device offers continuity across the Novartis COPD portfolio, as it offers a common platform for the delivery of indacaterol, glycopyrronium, QVA149 and QMF149 (Fig. 5b). This will simplify the transition from one inhaled treatment to another, so that patients will not need to learn and become accustomed to the use and handling of a new device.

The future of COPD management

Efforts have been ongoing in recent years to characterize better the different phenotypes of the syndrome of COPD and develop a new classification and terminology for COPD. This could clarify the underlying pathophysiology, natural history and response to treatment of the different phenotypes. Identifying the specific features of the different phenotypes of COPD will assist with identification of new drug targets and allow the implementation of a more personalized treatment, in which the characteristics of the patients, together with the severity of their disease, will be key determining factors in choosing the best treatment option — the right treatment for the right patient.

COPD is a chronic inflammatory disorder, and a key question is whether novel anti-inflammatory agents can prevent or slow the decline in lung function characteristic of COPD. The loss of airway function in COPD is related to the destruction of alveoli, which results in a reduction in elasticity associated with increased protease activity (emphysema), and/or obstruction and fibrosis of the small airways due to inflammation and mucus hypersecretion (chronic bronchitis)[20]. By reducing the severity of the inflammation and tissue remodelling, lung function could be improved and the progression of COPD could be slowed. Emerging therapies for COPD include novel anti-inflammatory agents that target lung inflammation via several strategies. These include inhibitors of cell signalling, protease inhibitors, cytokine and chemokine antagonists and histone deacetylase 2 modifiers[20].

Novartis is committed to developing new therapies for the treatment of COPD. Indeed, we have an innovative pipeline of COPD products that offers the potential to manage and treat the disease in a multimodal manner.

Summary

It is estimated that approximately 210 million people worldwide have moderate or severe COPD[1]; however, the prevalence may be underestimated as a result of a failure to recognize and accurately diagnose the disease in all affected individuals[2]. Considering the existing burden of COPD and the estimated future projections, there is an urgent need to develop further efficacious, safe and convenient therapies for COPD.

Recognizing the central role of bronchodilators, we have demonstrated our commitment to the development of effective, once-daily therapies for the management of COPD, with the LABA indacaterol, the LAMA glycopyrronium, the LABA/LAMA combination QVA149 and the LABA/ICS combination QMF149. Furthermore, we have invested considerable resources in developing the Breezhaler® device — the single-device platform for the delivery of all the products under the Novartis COPD portfolio.

At Novartis, we believe that it is crucial to provide the right treatment to the right patient at the right time. It is our vision and goal to adhere to this philosophy, and develop innovative treatments that improve the lives of patients with COPD.

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