Addressing unmet needs in the treatment of COPD

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ABSTRACT The burden of chronic obstructive pulmonary disease (COPD) is considerable, both socially and economically. Central to COPD management is the use of long-acting bronchodilators, which provide patients with optimal bronchodilation and improvements in symptoms. The once-daily, long-acting β_2-agonist indacaterol, the long-acting muscarinic antagonist glycopyrronium, and the indacaterol/glycopyrronium fixed-dose combination QVA149 have all been shown to significantly improve lung function and patient-reported outcomes. The ability to take medication appropriately is important. Easy to use, low resistance devices may help patients take their medication and achieve good drug deposition. There is a need to optimise COPD management by treating the right patients with the right therapy at the right time during the course of their disease. Herein, we present a view on the current COPD management landscape and current unmet needs, and look to the future of COPD treatment and how patient care can be optimised.

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Introduction

Chronic obstructive pulmonary disease (COPD), a preventable and treatable disease characterised by persistent airflow limitation, is a major cause of morbidity and mortality worldwide [1]. COPD comprises a combination of small airways disease and emphysema, resulting from lung damage caused by the inhalation of noxious agents [1].

In many countries, COPD prevalence is directly related to the prevalence of tobacco smoking [2]. Whilst smoking rates are decreasing in most developed countries, tobacco consumption in developing countries is increasing [3], particularly in females [4]. Alternate risk factors to cigarette smoke include exposure to occupational dusts and chemicals, and indoor pollution from biomass fuels [1].

The economic and social burden of COPD is extensive and growing, owing to continued exposure to COPD risk factors and changes in global age demographics [5]. In China, for example, where COPD is ranked first among causes of disability [6], the annual direct economic burden of COPD accounted for approximately one-third of family income in rural areas [7]. Exacerbations account for the greatest proportion of COPD healthcare costs [1].

The frequency at which exacerbations occur differs between patients [8]. Heterogeneity in exacerbation frequency and other factors, such as the severity of airflow limitation, rate of lung function decline and

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presence of comorbidities, means individualised treatment may be desirable and effective for the management of patients with COPD [1, 8–10].

This review will present a view on the appropriate treatment of COPD, updated in light of recent therapeutic advances and the availability of new treatments. We will also explore the current unmet needs and the potential future of COPD management.

Rationale for early treatment

Multiple lines of evidence suggest that there is a substantial opportunity to clinically intervene early in COPD, before lung function is severely impaired. Air trapping after expiration (hyperinflation), a major component of COPD, is observed in patients from the early stages of the disease [1]. Hyperinflation impacts upon a patient's inspiratory capacity, increases functional residual capacity and limits exercise capability [1]. Similarly, *post hoc* analyses of data from the TORCH (Towards a Revolution in COPD Health), UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) and ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) studies found that pulmonary function decline is faster in the earlier stages of disease [10–13].

Early-stage COPD is also associated with symptomatic and health consequences, including dyspnoea [14], poor health status [15, 16] and lower activity levels [17–19], the latter of which may be linked to dynamic hyperinflation [20]. There is evidence that lung function, health status and dyspnoea in patients with mild-to-moderate COPD can be improved with single-agent pharmacotherapy [21–24]. Subgroup analyses of clinical trials suggest that pharmacotherapy may also reduce the rate in forced expiratory volume in 1 s (FEV_1) decline *versus* placebo in patients with early stages of the disease [11, 12, 25]. Therefore, we speculate that intervention with long-acting bronchodilators at an early stage in disease could prove beneficial and may improve patient-reported outcomes.

The diagnosis of COPD in the early stages is very low; COPD often remains undiagnosed until the disease has increased in severity [26]. Screening (performing spirometry in a specific population) and case-finding (identifying individuals who seek medical attention for specific respiratory symptoms) may help to improve the diagnosis of COPD before the disease becomes severe [27]. Whilst there is a scarcity of information regarding whether early diagnosis and treatment can preserve lung function and other outcomes in patients, it seems likely that early identification of the disease would result in the initiation of appropriate and beneficial treatment, potentially leading to a better long-term outcome [27].

COPD and asthma: differential diagnosis and overlap syndrome

The accurate identification and distinction of COPD from other respiratory diseases is vital. The differential diagnosis of COPD from asthma is imperative, owing to the differences in treatment strategies. Asthma is predominantly controlled using inhaled corticosteroids (ICS), with bronchodilators used mainly as reliever medication [28], whilst in COPD, bronchodilators are recommended as maintenance treatment at all stages, with ICS use limited to "high-risk" patients (patients with severe or very severe airflow limitation or a history of exacerbations) [1]. A major cause of misdiagnosis of COPD is the absence of routine spirometry [27]. Nevertheless, data from a recent Norwegian study suggest a recent improvement in COPD diagnosis, owing to an increase in spirometry use and the dissemination of guidelines for the identification of COPD [29].

Asthma–COPD overlap syndrome (ACOS) presents another diagnostic challenge, in which patients have evidence of an airflow obstruction that is not completely reversible and increased variability of airflow [30]. Recognition of the difficulties associated with the diagnosis and appropriate treatment of patients with ACOS is increasing, reflected by the inclusion of a chapter on the syndrome in the 2014 update of the Global Initiative for Asthma strategy document [31]. ACOS cannot be sufficiently distinguished from pure asthma or COPD through use of lung function tests alone and instead may require a combination of approaches, such as questionnaires, analysis of medical history and lung function assessments [27, 31]. ACOS reportedly accounts for 10–20% of obstructive airway disease [32–34] and is associated with increased risk of exacerbation and hospitalisation [35]. ACOS influences treatment options; patients with ACOS require treatment that controls both asthma and COPD, through use of an ICS and appropriate bronchodilator therapy [31].

Nonpharmacological interventions

Nonpharmacological approaches to COPD management, such as smoking cessation, pulmonary rehabilitation and preventive care (vaccination), have a considerable effect on disease outcomes and should be considered in individuals with COPD [1].

Smoking cessation exerts the greatest influence on COPD progression [1]. Studies in patients with COPD have demonstrated that stopping smoking reduces airway inflammation [36, 37], hyperresponsiveness [38, 39]

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and bronchial epithelial remodelling [40]. Pulmonary rehabilitation improves dyspnoea, exercise capacity and health status, and can also reduce COPD-related anxiety and depression and the number of hospitalisations [1, 41]. Pulmonary rehabilitation should be a core component of COPD management and should be associated with effective pharmacological therapy [1, 42]. Telehealth (the utilisation of telecommunication technology for the transfer of health-related services and information) and remote patient monitoring are ideally suited for patients with COPD, but the benefits need to be evaluated in larger, appropriately controlled clinical studies [43].

The central role of bronchodilation

Bronchodilators, which target bronchoconstriction and alter airway smooth muscle tone, are frequently described as the cornerstone of the management of COPD. The benefits associated with bronchodilator use include improved lung function, reduced dyspnoea, reduction of symptoms such as cough and mucus secretions, and increased exercise capacity, as well as a reduction in the incidence of exacerbations [1]. Improvements in these areas can improve a patient's health status and their ability to perform everyday activities [1].

Bronchodilators are recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) for use in the management of COPD at all stages of severity, from short-acting formulations for patients with mild COPD to combined long-acting therapies for patients with very severe COPD [1].

The role of ICS in COPD management

The long-term use of ICS is only recommended for some patients at high risk, such as those with severe-to-very severe airflow limitation and frequent exacerbations (two or more exacerbations per year) not sufficiently controlled with long-acting bronchodilators [1]. Recommendations for ICS use in patients with frequent exacerbations are largely based on the preventive effect ICS have on exacerbations, but they have also been shown to improve lung function and health status when used in combination with a long-acting β_2-agonist (LABA), compared with the individual components [44].

ICS are highly effective in the treatment of asthma, therefore, they are recommended for the treatment of ACOS. Patients with ACOS often have severe COPD according to the GOLD classification [33]. Effective bronchodilation, such as that provided by a dual bronchodilator, may be appropriate for these patients in addition to an ICS.

The side-effects associated with ICS use include an increased risk of pneumonia [45, 46], diabetes [47] and fractures [48]. For this reason, it is imperative to limit the use of ICS to patients with the appropriate indication. Reduced responsiveness to the anti-inflammatory effects of corticosteroids is also a major clinical challenge in the treatment of COPD. The response to ICS (even high doses) is poor in the majority of patients with COPD [49]. In accordance with the GOLD strategy, ICS plus LABA combinations should only be prescribed in patients who are at high risk of exacerbation [1]. In practice, however, ICS/LABAs are prescribed inappropriately in many patients with COPD, including those at low exacerbation risk [50–52].

GOLD recommendations and patient subgroups

According to GOLD, patients with COPD can be categorised through assessment of symptoms and exacerbation risk based on spirometry and exacerbation history (fig. 1a) [1]. Based on these assessments, patients can be classified as: low risk, less symptoms (group A); low risk, more symptoms (group B); high risk, less symptoms (group C); or high risk, more symptoms (group D) [1]. The recommended and alternative treatment choices according to GOLD groups are also listed in figure 1a.

The appropriate diagnosis and treatment of patients with COPD is still a fundamental aim of COPD management. Patients with COPD are frequently prescribed inappropriate medications according to their symptoms and risk level [50, 52, 53]. Both the over- and under-treatment of COPD have been observed, with misdiagnosis of COPD leading to inappropriate treatment of the condition, or no treatment at all [54–56]. Furthermore, an analysis of prescribing patterns in the UK demonstrated that a significant proportion of patients receiving treatment for COPD remain symptomatic [57].

Analysis of cohort data from four large studies [58–61] suggests that there is considerable variability between the prevalence of the four GOLD groups. Findings are influenced by the population involved. For example, the most prevalent group in the general population was found to be group A, whereas the most prevalent group in patients recruited from secondary and tertiary care was group D [62].

The analysis also found that there are distinct subgroups in the high-risk categories, as patients may be categorised by airflow limitation, exacerbations or both. The majority of patients in GOLD groups C and D were classified as such owing to severe or very severe airflow limitation, rather than exacerbation history (fig. 1b) [62]. Most patients were categorised as high risk due to a FEV_1 <50% predicted (70–78% and

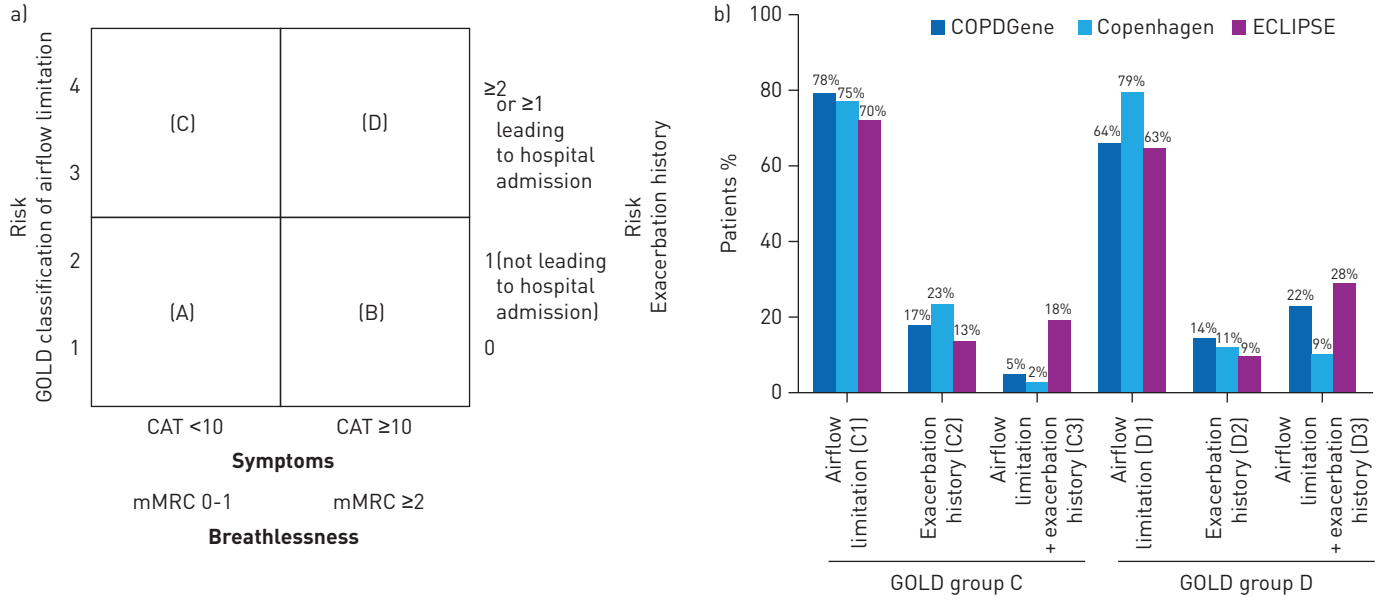

FIGURE 1 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification based on symptom and risk evaluation. a) GOLD model of symptom/risk evaluation of chronic obstructive pulmonary disease (COPD) and recommendations for the initial pharmacological treatment. In evaluating risk, the highest risk according to GOLD grade or exacerbation history should be selected. GOLD 1: forced expiratory volume in 1 s (FEV_1) $\geqslant$80% predicted; GOLD 2: FEV_1 50 – <80% pred; GOLD 3: FEV_1 30 – <50% pred; GOLD 4: FEV_1 <30% pred. The recommended first-choice treatments and alternative treatment choices for each GOLD group (in alphabetical order) are as follows. A: short-acting β_2-agonist (SABA) or short-acting muscarinic antagonist (SAMA) as needed; long-acting β_2-agonist (LABA) or long-acting muscarinic antagonist (LAMA) or SABA + SAMA. B: LABA or LAMA; LABA + LAMA. C: inhaled corticosteroid (ICS) + LABA or LAMA; LABA + LAMA, LABA + phosphodiesterase-4 (PDE4) inhibitor or LAMA and PDE4 inhibitor. D: ICS + LABA and/or LAMA; ICS + LABA + PDE4 inhibitor or LABA + LAMA or LAMA + PDE4 inhibitor. Other possible treatments are not shown but may be used alone or in combination with first or alternative choices. CAT: COPD Assessment Test; mMRC: modified Medical Research Council. Reproduced from [1] with permission from the publisher. b) The categorisation of patients in GOLD groups C and D based on FEV_1, history of exacerbations or both determinants. ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints. Reproduced from [62] with permission from the publisher.

63–79% for group C and D, respectively), whereas relatively few were categorised as high risk based on exacerbation history alone (13–23% and 9–14% for group C and D, respectively) [62].

Therefore, patients in both groups C and D may not benefit equally from different treatments, and tailoring treatment to their specific needs seems logical, thereby delivering a more personalised and targeted approach to COPD management. For example, severe airflow limitation may respond better to dual bronchodilation, while patients with a prior history of exacerbation (with or without airflow limitation) may respond better to the addition of an ICS.

Tailored treatment based on clinical phenotypes may also prove beneficial. Phenotypic characteristics that impact upon treatment decisions include the presence of chronic bronchitis, ACOS, frequent exacerbations and the presence of comorbidities. These may have therapeutic implications [63], and their recognition may help to facilitate the appropriate and effective management of patients [63].

Therapeutic agents in the COPD portfolio

The long-acting bronchodilators indacaterol, glycopyrronium and the combination of both in a fixed-dose combination (QVA149) have been shown to significantly improve lung function and patient-reported outcomes in patients with COPD.

Indacaterol

Indacaterol maleate was the first once-daily LABA to be approved for the treatment of COPD and is currently approved and marketed in more than 100 countries around the world.

Indacaterol significantly improved lung function, health status, dyspnoea, rescue medication use, exercise endurance time and rate of exacerbations *versus* placebo [64, 65]. Indacaterol has also demonstrated superior bronchodilation and clinical efficacy compared with the twice-daily LABAs salmeterol [66] and formoterol [67], and is at least as effective in improving lung function and symptoms as tiotropium [68, 69].

In the recent 26-week phase IV study INSTEAD, patients with moderate COPD and no exacerbations in the previous year (approximating to GOLD group B) were switched from the ICS/LABA salmeterol/fluticasone

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propionate combination (SFC) to once-daily indacaterol [70]. Indacaterol demonstrated non-inferiority to SFC in lung function at week 12 in the studied population [70]. Other outcomes such as dyspnoea and health status were also similar between the two treatments after 12 and 26 weeks, suggesting that ICS can be removed in these patients without loss of efficacy over the 26 weeks following withdrawal, provided appropriate bronchodilator therapy is maintained [70].

Glycopyrronium

Glycopyrronium bromide is a once-daily long-acting muscarinic antagonist (LAMA) approved for use in COPD treatment in the European Union, Japan and over 60 other countries. Significant improvements have been observed with glycopyrronium *versus* placebo in lung function and clinical end-points, such as health status, dyspnoea, rescue medication use, daily symptoms, exercise endurance time and rate of exacerbations in three major clinical trials [23, 71–73].

Glycopyrronium has also demonstrated comparable efficacy and safety to blinded and open-label tiotropium, with a faster onset-of-action [72]. In the GLOW (GLycopyrronium Bromide in COPD Airways) 2 and GLOW5 studies, glycopyrronium provided comparable efficacy and safety to tiotropium, including similar improvements in lung function, dyspnoea, health status, rescue medication use and rate of exacerbations [72, 74]. Additionally, glycopyrronium demonstrated rapid and early onset of bronchodilation from day 1, comparing favourably with tiotropium [72, 74].

Triple therapy (the combination of a LABA/LAMA with an ICS, or an ICS/LABA with a LAMA) is a treatment option for patients in GOLD group D. The improvements in lung function and clinical end-points observed with glycopyrronium [71–74] suggest that the LAMA may be a suitable candidate for use in a loose triple combination with an ICS/LABA. To study the efficacy of glycopyrronium in this approach, the GLISTEN trial investigated the efficacy (non-inferiority) of glycopyrronium compared with blinded tiotropium when added to twice-daily SFC [75]. Data from this study are expected to be presented later this year.

Dual bronchodilation: a new treatment option in the management of COPD

Administering LABAs and LAMAs concurrently can significantly improve lung function, dyspnoea and patient symptom scores compared with treatment with a single bronchodilator [76, 77]. The scientific rationale behind the additive effects observed when combining bronchodilators includes the different mechanisms of action of β_2-agonists and muscarinic antagonists (fig. 2), and the potential intracellular interactions between these pathways [78]. LABAs directly induce bronchodilation through stimulation of β_2-adrenergic receptors, whereas LAMAs indirectly cause bronchodilation through inhibition of acetylcholine-induced bronchoconstriction [78].

Administering bronchodilators in fixed-dose combinations in a single inhaler may prove beneficial when compared with multiple inhalers in terms of patient compliance to treatment programmes. The use of a single inhaler has been associated with higher treatment persistence and increased adherence rates compared with the use of multiple inhalers; this is likely to be associated with patient difficulties in correct inhaler use, compounded by the addition of a second device [79].

The once-daily fixed-dose LABA/LAMA combination QVA149 combines indacaterol and glycopyrronium in a single inhaler. The efficacy and safety of QVA149 were investigated in the IGNITE (indacaterol and glycopyrronium bromide clinical studies) programme, which comprises 11 studies, eight of which were completed in 2012.

QVA149 has been shown to improve lung function and patient-reported outcomes compared with the mono-components and open label tiotropium. In the 26-week SHINE study, lung function and rescue medication use were significantly improved with QVA149 *versus* indacaterol, glycopyrronium, tiotropium and placebo (fig. 3) [80]. QVA149 also significantly improved dyspnoea and health status *versus* placebo and tiotropium [80].

The impact of QVA149 on patient-reported dyspnoea was investigated in the BLAZE study. In this 6-week, three-period crossover trial, transitional dyspnoea index (TDI) self-administered computerised total score was significantly improved with QVA149 compared with placebo and blinded tiotropium [81]. Improvements were also observed with QVA149 in lung function and rescue medication use *versus* placebo and tiotropium [81].

The comparative efficacy of QVA149 *versus* SFC in patients with symptomatic COPD and no moderate or severe exacerbations in the previous year (approximating to GOLD group B) was investigated in the 26-week ILLUMINATE study [82]. The results of ILLUMINATE demonstrated that QVA149 was superior to SFC in this patient population. QVA149 significantly improved lung function compared with SFC [82]. QVA149 also significantly improved TDI total score and significantly reduced rescue medication use *versus*

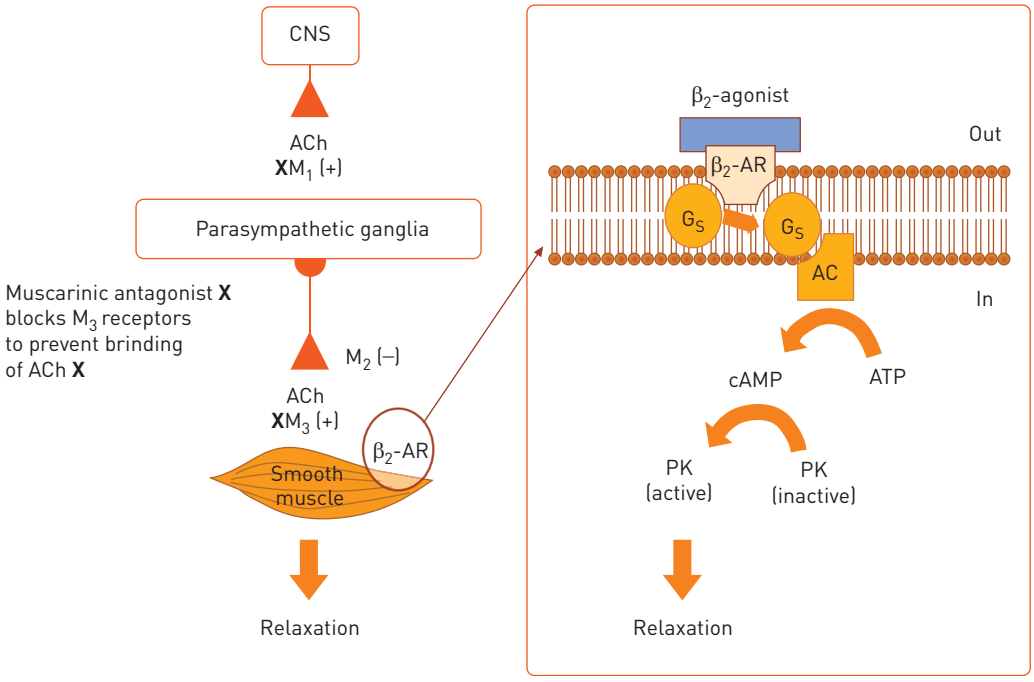

FIGURE 2 Direct and indirect relaxation of smooth muscle: mechanisms of action of β_2-agonists and muscarinic antagonists. CNS: central nervous system; ACh: acetylcholine; β_2-AR: β_2-adrenergic receptor; M_x: muscarinic receptor type x; G_s: stimulatory G-protein; AC: adenylyl cyclase; PK: protein kinase. Reproduced from [78] with permission from the publisher.

SFC, and provided similar improvements to SFC in health status [82]. These data indicate that in symptomatic patients, QVA149 is an alternative treatment option to SFC.

In the recently completed 26-week LANTERN study, QVA149 demonstrated superiority to twice-daily SFC in lung function improvement in patients with or without a history of exacerbations [83]. Further data from this study are expected to be presented later this year.

In addition to improving symptoms and health status, reducing the frequency of exacerbations is an important treatment goal in the management of COPD. Data from the 64-week SPARK study indicated that QVA149 can reduce exacerbations compared with LAMA monotherapy in patients with a high risk of exacerbation (GOLD groups C and D). QVA149 significantly reduced the rate of moderate or severe exacerbations *versus* glycopyrronium by 12%, the primary outcome of the study (fig. 4) [84]. The rate of all (mild, moderate and severe) exacerbations was also significantly reduced with QVA149 *versus* glycopyrronium (15%) and open label tiotropium (14%) [84]. In addition to providing benefits in terms of exacerbation rate, QVA149 significantly improved trough FEV_1, health status, patient symptom scores (including the percentage of nights with no night-time awakenings, percentage of days with no daytime symptoms and daily total symptom score), daily rescue medication use and the percentage of days without use of rescue medication compared with glycopyrronium and open label tiotropium [84–86].

No new safety issues were identified with QVA149 compared with its mono-components in the IGNITE trials, and the overall adverse event profile of QVA149 was noted to be similar to that of placebo and of the active comparators glycopyrronium, indacaterol, tiotropium and SFC [84, 87, 88].

The totality of these data demonstrates the benefits of dual bronchodilation compared with monotherapy across a range of clinical outcomes in patients with COPD, with positive effects on lung function and clinical outcomes also observed with QVA149 compared with established treatments, *i.e.* tiotropium and SFC.

Further data on the efficacy and safety of QVA149 will become available from trials in the IGNITE programme that are currently ongoing. These include the 52-week FLAME study, a non-inferiority trial comparing the effect of QVA149 on the rate of exacerbations *versus* SFC in patients with one or more moderate exacerbations in the previous year [89], and RADIATE (formerly GLISTEN), a long-term safety study that will compare QVA149 with blinded tiotropium and placebo over 52 weeks [90].

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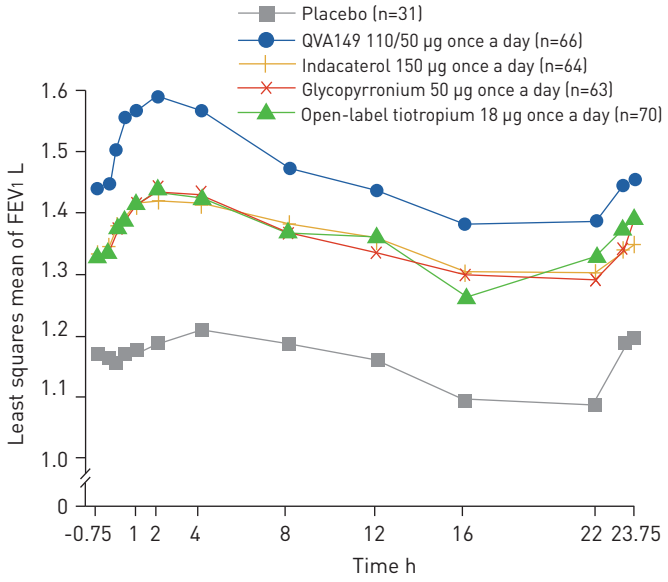

FIGURE 3 Serial spirometry on week 26 in the SHINE study. Serial spirometry was conducted in a subset of 294 patients. n: number per treatment group in the serial spirometry subset of the full analysis set; FEV1: forced expiratory volume in 1 s. Reproduced from [80] with permission from the publisher.

Indacaterol, glycopyrronium and QVA149 are all administered *via* the same device, a single-dose, capsule, dry-powder inhaler. Trials indicate that the device has a low airflow resistance and the dose is delivered consistently, irrespective of disease severity [91, 92].

Considerations for future trial design

When considering the future of COPD treatment and the role of dual bronchodilators in this landscape, we acknowledge that gaps remain in our knowledge.

To date, SPARK is the only trial to have studied the effect of a LABA/LAMA on exacerbations as the primary end-point. Further studies investigating the effect of dual bronchodilation on exacerbations are needed. The FLAME study will compare the effect of QVA149 *versus* SFC on exacerbations in patients with moderate-to-very severe COPD and a recent history of exacerbations. There is also a need for trials comparing the efficacy and safety of a LABA/LAMA compared with LABA/LAMA/ICS triple therapy in patients with COPD.

Greater understanding is needed around the appropriate treatment of patients in GOLD groups C and D in lung function and exacerbation subgroups. Further knowledge on the appropriate treatment of ACOS is also required; current thinking is based around the responsiveness of asthma and COPD to ICS and bronchodilators, respectively [31]. There are currently no dedicated studies in ACOS that investigate the most appropriate treatment for these patients.

Another potential area for further study is the role of COPD therapies on the progression of the disease. Are there benefits of aggressive early intervention when lung function decline is at its greatest? What are the benefits of "step-related" treatments compared with initial "optimal bronchodilation"? Furthermore, what are the benefits of combining nonpharmacological treatment approaches and bronchodilators, compared with either alone?

Consideration should be given on how the benefits of therapies are measured in the future. Are the current tools appropriate for capturing whether patient needs have been addressed? In many clinical trials, the well-established concept of a minimum clinically important difference (MCID) is used to indicate whether an intervention has provided the minimum level of perceived benefit. However, MCIDs are commonly derived from average estimates from studying groups of patients and may not reflect the benefits perceived by individuals. Additionally, MCIDs, which are usually determined in the context of placebo-controlled studies, may not be sufficiently sensitive for comparing active treatments, where measured treatment effects may be small. In this case, responder analyses describing the percentage of patients who experience an improvement at or above the MCID may help to assess the minimum worthwhile incremental advantage of one active treatment regimen over another [93].

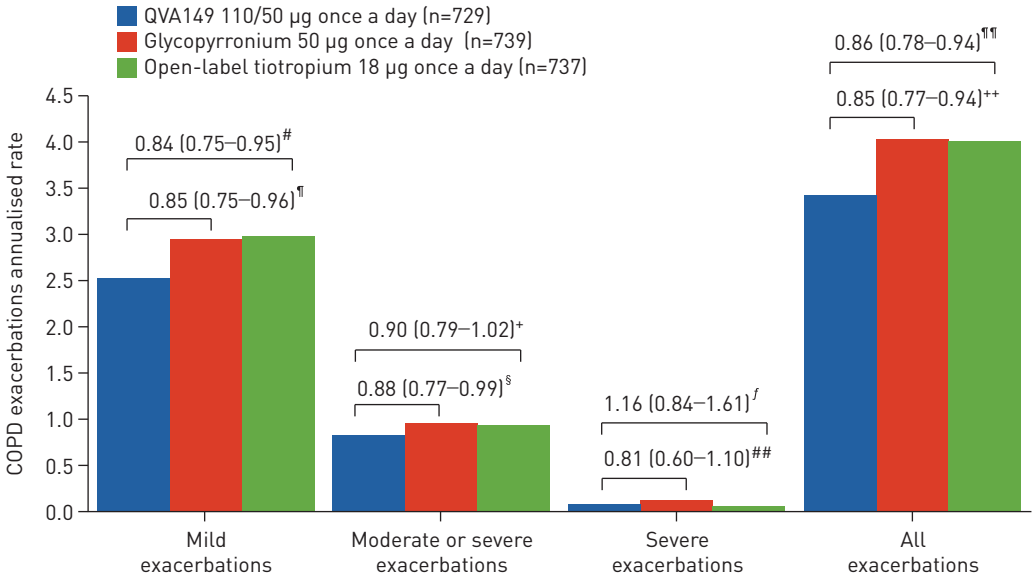

FIGURE 4 Annualised rate of chronic obstructive pulmonary disease (COPD) exacerbations over 64–76 weeks in the SPARK study by treatment group. Data are presented as rate reduction (95% CI). #: p=0.0052; ¶: p=0.0072; +: p=0.096; §: p=0.038; f: p=0.36; ##: p=0.18; ¶¶: p=0.0017; ++: p=0.0012. Reproduced from [84] with permission from the publisher.

The future of COPD treatment

Triple therapy (the combination of a LABA/LAMA with an ICS, or an ICS/LABA with a LAMA) in a single fixed-dose combination is a valuable future development in the treatment of COPD. In the GOLD 2014 strategy document, triple therapy is a treatment option for patients in group D [1]. The combination of dual bronchodilation and the anti-inflammatory capabilities of an ICS may also make triple therapy an ideal treatment for patients with ACOS to manage both the COPD and asthma components of the disease. The use of triple therapy should be reserved for patients in need of an ICS and not used broadly.

The development of triple therapies may be aided through the development of muscarinic antagonist-β_2-agonist molecules, agents that combine muscarinic antagonism and β_2-agonism in a single molecule [94]. However, issues with dosing flexibility may limit the usefulness of muscarinic antagonist β_2-agonist molecules [94].

The escalation and de-escalation of therapy in COPD is a matter of importance: when should physicians switch, step up or step down treatments in their patient? The GOLD strategy provides guidance on treatment following the initial assessment of the patient. However, there are no available data regarding how frequently patients should be reassessed and when patients should be moved on to different therapies. In addition, evidence suggests that a high proportion of patients with GOLD grade 2 airflow limitation are still symptomatic (defined as modified Medical Research Council dyspnoea scale $\geqslant$2 or COPD Assessment Test $\geqslant$10) despite receiving treatment [57]. How should treatment be modified in these patients?

There may also be a need to de-escalate treatment in certain patients. The prescription of ICS-containing regimens in patients who do not require an ICS according to recommendations is common. In these patients, can ICS be withdrawn safely? Some data suggest that ICS withdrawal may result in deterioration of lung function [95] and reduce the time to exacerbation [96]. However, preliminary data from the INSTEAD study, in which patients with moderate COPD and no exacerbations in the previous year were switched from SFC to indacaterol, indicate non-inferiority in lung function at week 12 with indacaterol compared with SFC, and similar symptomatic benefits in terms of dyspnoea and health status at weeks 12 and 26 [70]. Similarly, in OPTIMO (Real-Life Study on the Appropriateness of Treatment In Moderate COPD Patients), withdrawal of ICS in patients with moderate airflow limitation and <2 exacerbations per year was not associated with any deterioration in lung function and symptoms or increase in exacerbations during 6 months, if regular treatment with a long-acting bronchodilator was maintained [97]. There is a need for further studies into the effects of ICS withdrawal in patients with COPD and the stepping down of treatment.

The future of COPD management may involve new anti-inflammatory strategies, some directed at COPD-specific targets, reflecting the central role that inflammation plays in COPD. Novel nonsteroid-based anti-inflammatory agents include phosphodiesterase-4 inhibitors, chemokine antagonists and p38 mitogen-activated protein kinase inhibitors. While it is readily acknowledged that COPD is an inflammatory disease,

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the benefit of effective anti-inflammatory therapy has been difficult to demonstrate. Therefore, more knowledge is needed regarding pharmacologically targeting the inflammatory pathways within COPD.

In the coming years, the management of COPD may evolve to reflect the need for individualised treatment. COPD is a complex, multicomponent disease in which heterogeneity exists in a range of factors, including lung function decline, exacerbation frequency and the contribution of emphysema and small airways disease to airflow limitation [1, 8–10, 98]. Addressing this heterogeneity is an unmet need in COPD management. Identifying phenotypes of COPD relating to these differences could result in more personalised treatments for patients, with consideration for disease severity and the presence of comorbidities. COPDGene (Genetic Epidemiology of COPD [99]), COPDMAP [100], SPIROMICS [101], the Innovative Medicines Initiative PROactive project and the COPD Biomarker Qualification Consortium are collaborative studies that aim to increase the understanding of these phenotypes. The identification of underlying genetic factors and biomarkers in COPD through these collaborations will permit the classification of patients into subgroups and potentially the advancement toward personalised therapy.

Conclusion

COPD is under-diagnosed and under-treated, with treatments prescribed contrary to guidelines in patients according to their symptoms and risk level. There are unmet needs in the treatment of COPD, such as exacerbation and symptom control, improving health status and slowing the decline of lung function and disease progression. There is considerable evidence that bronchodilators provide lung function improvements, as well as clinical benefits in patients with COPD. The bronchodilators indacaterol, glycopyrronium and the LABA/LAMA combination QVA149 (all delivered by the same low-resistance inhaler) have a prolonged duration of action, enabling once-daily dosing. The once-daily administration of fixed-dose combinations of bronchodilators in a single inhaler may improve the convenience for patients and adherence to treatment. Gaining new insights into the pathophysiology of COPD and identifying novel targets for therapy, to optimise treatment and ultimately improve the lives of patients, is an important target in the management of COPD.

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