Improving the quality of life in patients with chronic obstructive pulmonary disease: focus on indacaterol

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Abstract: Chronic obstructive pulmonary disease (COPD) is a common disease in the general population and it places a considerable burden on patients, with the disease negatively affecting quality of life. In practice, patients with COPD generally seek medical attention because of symptoms, particularly breathlessness, and the resulting physical limitations, which affect the health-related quality of life (HR-QOL) in patients. The defining feature of COPD is airflow limitation that causes air trapping and increased hyperinflation as the ventilation rate increases during physical effort. Hyperinflation causes or worsens breathlessness as breathing becomes inefficient, with the end result being an avoidance of physical exertion and a cycle of increasing dyspnea caused by inactivity and deconditioning, with deleterious effects on HR-QOL. Current published guidelines for COPD state that the goals of pharmacologic therapy should be to control symptoms, improve health status and exercise tolerance, and reduce the frequency of COPD exacerbations. Effective and sustained bronchodilation has emerged as a key strategy for improving dyspnea and ability to exercise. As there is no cure for COPD, a major goal of treatment and of research into new therapies is to improve HR-QOL in COPD patients.

Conclusion: More recently, indacaterol, an inhaled ultra-long-acting β_2-agonist (24-hour action), has been approved in many countries at different doses (between 75 and 300 µg once daily) for treatment of patients with stable but symptomatic COPD. The aim of this review was to explore once-daily indacaterol clinical data as related to improvement in HR-QOL in COPD. Indacaterol studies have shown significant improvements in lung function of COPD patients, and these improvements have also translated into clinically meaningful improvements in patient symptoms and HR-QOL.

Keywords: airflow limitation, bronchodilation, long-acting β_2-agonist, COPD

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Introduction

Subjective indicators (based on self-rating) of quality of life (QOL) and health-related quality of life (HR-QOL) are increasingly incorporated in chronic obstructive pulmonary disease (COPD) because of the recognition of the importance of patient satisfaction and how patients with chronic disease feel, rather than how statistics imply these patients ought to feel. An American Lung Association survey states that half (51%) of all COPD patients say their condition limits their ability to work. The condition also limits COPD patients in normal physical exertion (70%), household chores (56%), social activities (53%), sleeping (50%), and family activities (46%).[1]

Although forced expiratory volume in 1 second (FEV_1) is a measurement of lung function, because COPD is a progressively worsening disease, improvement in lung function can be transitory and not always indicative of symptoms improvement.[2]

It appears that improvements in patient-centered outcomes such as dyspnea and health status may better reflect the effectiveness of the particular pharmacotherapy.[3,4] The concept of HR-QOL and its determinants in clinical trials have evolved to encompass those aspects of QOL that can be clearly shown to affect health, either physical or mental.[5] In relation to health, health status is increasingly referred to as QOL, and, in order to narrow down the term's operationalization in research studies, QOL is increasingly referred to as HR-QOL. Similar to subjective health status, HR-QOL is patient based; however, HR-QOL focuses more on the impact of a perceived health state on the patient's ability to live a fulfilling life.[6]

The traditional approach to the diagnosis, staging, and treatment of COPD was based primarily on the percentage of predicted FEV_1 and the rate of decline in FEV_1. Previous recommendations for management of COPD were based solely on spirometric category. FEV_1, while an important marker, is far from being the only measure available to characterize patients with COPD. In light of considerable cumulative evidence that the level of FEV_1 is a poor descriptor of the disease status, Global Initiative for Chronic Obstructive Lung Disease guidelines[7] have incorporated a strategy that considers both disease impact (determined mainly by symptoms burden and activity limitations) and future risk of disease progression (especially of exacerbations).[7] Since the health status of patients with COPD is reported to be only weakly associated with spirometric values such as FEV_1, measures of HR-QOL are increasingly used for evaluating the efficacy of bronchodilator medications in patients with COPD. Dyspnea, a key symptom in COPD, has been found to be strongly negatively associated with health status and to have the highest correlations with health status questionnaires.[8–10] However, dyspnea is a subjective measure that poorly correlates with objective assessments of lung function, exercise capacity, and other outcomes. The other significant factors that determine QOL/health status in COPD patients are mood disorders (anxiety and depression) and exercise tolerance are all directly related to the disease – such as dyspnea and other symptoms – this will automatically result in these strong associations.[11]

Comprehensive assessment of the effects of COPD requires a battery of instruments that tap not only the disease-specific effects but also the overall burden of the disease on everyday functioning and emotional well-being. Health status as a concept of high complexity is assessed indirectly and requires the application of specially designed questionnaires. The most widely used instruments in studies addressing effects of pharmacologic treatment of COPD on HR-QOL are the Baseline Dyspnea Index (BDI) and the Transitional Dyspnea Index (TDI) for measuring breathlessness and the St George Respiratory Questionnaire (SGRQ) to assess the effects of bronchodilators on health status in COPD.[12] The SGRQ is universally administered in COPD trials to measure improvements in HR-QOL. The use of an as-needed short-acting rescue inhaler (eg, salbutamol) has also become a quasi-standard measurement of symptom control in COPD trials. Additional outcomes of interest in clinical practice for management of COPD patients include mortality, hospitalizations, pneumonia, medication tolerability, and symptoms (especially exacerbations).

Indacaterol

The current standard of care for COPD patients is usually stepwise and is generally guided by disease severity. Current guidelines recommend treatment with one or more long-acting bronchodilators for patients with moderate or more severe disease.[7] In clinical practice, bronchodilators are used for symptomatic relief in COPD patients with all stages of severity and on the basis of long-term improvements that can be achieved in clinical outcomes such as dyspnea, health status, and exacerbations. Indacaterol is the first ultra-long-acting β_2-agonist (LABA) approved that has a 24-hour bronchodilatory effect, allowing for once-daily administration.

Indacaterol was first introduced throughout the European Union in 2009 at doses of 150 and 300 µg doses. In July 2011, indacaterol was also approved for use in the United States, but at a lower once-daily dose of 75 µg. The US Food and Drug Administration (FDA) approval of indacaterol was based on six phase III, randomized, double-blind trials: INLIGHT 1, INLIGHT 2, INVOLVE, INHANCE, INTENSITY, INSIST, and INDORSE (an extension of INHANCE).[13–19] The designs of the six studies, plus the extension, are summarized in Table 1. Inclusion criteria were similar through each trial; patients were over 40 years old, with moderate to severe COPD and with at least a 10-pack-year smoking history. Short-acting β_2-agonist (SABA) rescue medication and inhaled corticosteroids were permitted throughout all trials. A new drug application for indacaterol was submitted to the FDA in 2009; however, the drug was not approved at that time because a meaningful difference in efficacy between the proposed doses of 150 and 300 µg and a lower dose of 75 µg could not be discerned and because of concerns regarding safety with higher doses. To better delineate dose response at a lower dosage, the FDA requested

Table 1 Pivotal trials of 12 weeks in duration or longer

Reference	Study	Severity of COPD	Study duration (weeks)	Treatment arms
Feldman et al[13]	B2346, INLIGHT1	Moderate to severe	12	IND 150 µg (n = 211) Placebo (n = 205)
Kornmann et al[14]	B2336, INLIGHT2	Moderate to severe	26	IND 150 µg (n = 330) SAL 50 µg BID (n = 334) Placebo (n = 335)
Dahl et al[15]	B2334, INVOLVE	Moderate to severe	52	IND 300 (n = 437) or 600 µg (n = 428) FOR 12 µg BID (n = 435) Placebo (n = 432)
Donohue et al[16]	B2335S, INHANCE	Moderate to severe	26	IND 150 (n = 416) or 300 µg (n = 416) Placebo (n = 418) Open-label TIO 18 µg (n = 415)
Buhl et al[17]	B2350, INTENSITY	Moderate to severe	12	IND 150 µg (n = 794) TIO 18 µg (n = 799)
Korn et al[18]	B2349, INSIST	Moderate to severe	12	IND 150 µg (n = 559) SAL 50 µg BID (n = 562)
Chapman et al[19]	Study 2335SE, INDORSE (extension of INHANCE)	Moderate to severe	Additional 26 (total 52)	IND 150 or 300 µg Placebo (n = 415)

Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; FOR, formoterol; IND, indacaterol; SAL, salmeterol; TIO, tiotropium.

the study in patients with asthma, a condition that is more responsive to bronchodilators than COPD. In addition to dose-ranging studies in asthma, the sponsor provided a second dose-ranging trial in patients with COPD and separate 12-week confirmatory trials using the 75 and 150 µg doses. In both the asthma and the COPD dose-ranging studies, there was no clear separation between 75 and 150 µg doses in the FEV_1 time profile. As for the noncomparative confirmatory trials, both 75 and 150 µg doses had significantly higher trough FEV_1 values than placebo. Because these studies did not directly compare the two doses, it is difficult to conclude whether the 150 µg dose is more effective than the 75 µg dose.[20–22] As a result, the FDA supported approval of the 75 µg dose, based on the FDA's own overall risk-benefit assessment. The primary efficacy outcome reported in all six studies was the difference in least squares mean trough FEV_1 at 24 hours after 12 weeks of treatment. FEV_1 is an important measurement in diagnosing and staging COPD. It is also commonly used in COPD clinical trials because it is an objective, reproducible measurement of lung function.

The secondary outcome of interest to the FDA was the change from baseline in the SGRQ score. The FDA based approval of indacaterol on these two outcomes only. Because the FDA and the sponsor could not reach an agreement on the definition of "exacerbation," this important outcome was not included in the FDA approval process.[22] Because dyspnea is the key symptom of COPD and the need for rescue medication use is driven by dyspnea episodes, the data from the clinical development of indacaterol (eg, comparisons with active controls or scores on the BDI and the TDI) may have been weighed differently by the European Medicines Agency.[21] Doses equal to or greater than 150 µg daily make up the majority of the available clinical data. Only 449 patients were exposed to the FDA-approved dose of 75 µg daily for up to 3 months.

Indacaterol data for health status/HR-QOL

The author has reviewed clinical evidence from the six indacaterol COPD studies mentioned earlier.[13–19] The studies compared indacaterol with placebo, and inhaled tiotropium, salmeterol, or formoterol monotherapy. Indacaterol, along with all other bronchodilators, showed a statistically significant reduction in dyspnea compared with placebo. Importantly, improvements in lung function have translated into correspondingly beneficial effects on patient-reported outcomes, such as dyspnea, number of days with poor control, and clinically meaningful improvements in HR-QOL, particularly when comparisons are made with placebo.[23]

Breathlessness

The TDI was used to assess relief of dyspnea. The BDI and the TDI are validated clinical ratings that describe symptoms at a single point in time (eg, baseline) and measure changes in breathlessness from this baseline state over time, using a seven-point scale from −3 (major deterioration) to +3 (major improvement). TDI ratings are obtained in the course of an interview conducted by an experienced observer, with the
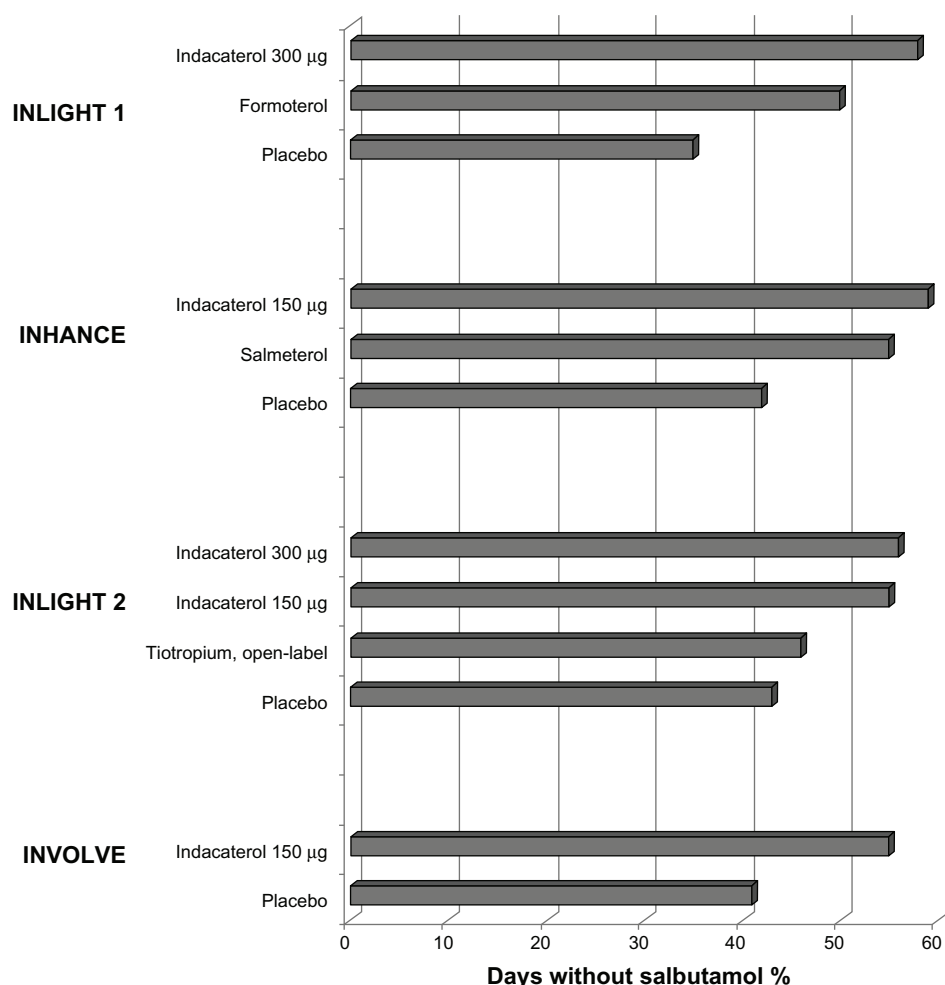
observer asking open-ended questions about the patient's experience of breathlessness during everyday activities that are then translated into numerical values. A change of one point is considered to be the minimum clinically important difference (MCID).[24,25]

Interviewer blinding to patients' clinical status is necessary to prevent assessment bias. Mahler et al[26] demonstrated for the first time that dyspnea ratings (including the TDI) were significantly related to the stage of disease severity based on the percentage of predicted FEV_1. Indacaterol significantly improved dyspnea (measured by the TDI) compared with placebo.[14–16] In general, indacaterol appeared to have greater effects on most COPD symptoms than open-label tiotropium, formoterol, or salmeterol, although differences between indacaterol and active comparators were not consistently statistically significant. Indacaterol subjects showed a 43% greater likelihood than tiotropium subjects of experiencing an MCID in the TDI of one point or higher (62% of indacaterol patients versus 52% of tiotropium patients).[27] Tiotropium was

used as an open-label comparator, thus introducing bias and limiting results interpretation. Nevertheless, when indacaterol was compared with tiotropium in blinded fashion in a study published by Buhl et al,[17] indacaterol yielded greater improvements in TDI and SGRQ total scores than tiotropium.

Percentage of days with no rescue medication

The use of salbutamol because of severity and/or frequency of COPD symptoms experienced by the patients serves as an indirect measure of how effective the study treatments are in controlling these symptoms. The percentage of days with no rescue medication was significantly higher in the indacaterol groups than in the active comparator groups in four studies (Figure 1).[13–16] Indacaterol (both 150 and 300 μg doses) and formoterol recipients had significantly more days with no use of rescue medication than open-label tiotropium recipients in pooled analyses of 3-month[28] and 6-month data.[29] In addition

Figure 1 Effect of treatment on use of as-needed salbutamol, averaged over the period of the studies, as percentage of days without use of salbutamol.

to the four large (n > 400) placebo-controlled long-term indacaterol studies (Figure 1), significantly more patients receiving indacaterol had less need for a rescue inhaler (salbutamol) than salmeterol recipients over 12 weeks in the INSIST (Indacaterol: investigating superiority vs salmeterol) study.[18]

Use of an as-needed rescue inhaler (salbutamol)

Use of an as-needed short-acting rescue inhaler (salbutamol) has become a standard measure of symptom control in COPD trials. Rodrigo et al have conducted post hoc analysis of the five pivotal indacaterol studies.[13–16,18] When compared with placebo, indacaterol significantly reduced the number of puffs per day of the rescue inhaler. Patients in the indacaterol group used less as-needed salbutamol, when compared with twice-daily LABA treatment, with a decrease of approximately one and a half puffs per day from baseline, although probably without clinical significance.[23] Although use of a SABA in COPD during treatment with a LABA is recommended as needed, its effectiveness is unclear. To the best of the author's knowledge, no clinical data have been reported to date about the effects of acute SABA administration on top of regular use of indacaterol in COPD treatment. The design of all phase III indacaterol COPD studies has included only stable patients. La Piana et al's[30] observational study, using a SABA on top of formoterol in patients with stable COPD, did not demonstrate improvement in FEV_1 or peak expiratory flow after either acute or chronic treatment with formoterol. However, the authors concluded that the results of the study suggest a SABA was still effective in possibly reducing air trapping, as was demonstrated by the increase in forced vital capacity in the study.[30]

HR-QOL

Health status as a concept of high complexity is assessed indirectly and requires the application of specially designed questionnaires. The SGRQ has been widely used in clinical trials as a secondary end point to assess the effects of bronchodilators on health status in COPD and it has been demonstrated to be valid, reliable, and responsive among patients with COPD.[31] The SGRQ is completed by the patient and has 50 questions covering three areas – symptoms, activity, and disease effects – summed to provide a total score of between zero (best) and 100 (worst). The instrument is time-consuming to implement and is therefore of limited applicability in day-to-day clinical practice. The SGRQ covers domains of symptoms (frequency and severity of

respiratory symptoms), activity (effects on and adjustment of everyday activities), and psychosocial impact, from which a total score with a possible maximum of 100 points is calculated. A zero score indicates no impairment of QOL. The threshold for a MCID is a four-unit decrease in total SGRQ score. For example, a change of this size would occur in a patient who reports that he or she no longer takes so long to wash or dress, can walk up stairs without stopping, and is able to leave the house for shopping or entertainment.[32,33] The SGRQ was used to assess HR-QOL in three studies.[14–16] Significant improvements in HR-QOL were seen with indacaterol as compared with placebo, evidenced by statistically significantly lower (ie, better) mean SGRQ total scores at end-of-study assessments. Clinically important improvements (four points or greater) versus placebo were observed for indacaterol recipients.

Exercise endurance and lung hyperinflation

Limitation in exercise capacity represents an important feature of COPD and is one of the main factors that negatively affect the QOL in patients.[34] Reduced exercise capacity is considered to be a consequence of airflow obstruction primarily because of dynamic hyperinflation occurring during exercise.[35] Limited physical activity of patients with COPD, although a result of the disease, at the same time promotes worsening and progression of the disease and further decline in the patient's HR-QOL. Consequently, exercise testing is increasingly being used in the functional and HR-QOL assessment of COPD patients and their response to bronchodilators. The possible methods of assessment of exercise capacity are field tests (6-minute and shuttle walking tests) and cardiopulmonary exercise testing (CPET).

CPET is considered the gold standard for studying a patient's level of exercise limitation and its causes. O'Donnell et al[36] undertook a study designed to assess the effect of indacaterol 300 µg once daily (dose not approved in the United States) on exercise endurance in patients with moderate to severe COPD using CPET.[36] Indacaterol provided clinically meaningful improvements in exercise endurance with sustained reductions in lung hyperinflation both at rest and at the end of exercise. The authors postulated that the overall improvement in exercise capacity achieved with indacaterol at 300 µg once daily in the study may be an explanation for the improved health status (assessed using the SGRQ) seen with indacaterol in long-term studies.[15,16]

Mroz et al's[37] study of 34 patients with COPD used the 6-minute walking distance test to assess the impact

of indacaterol add-on therapy on lung function, exercise tolerance, and QOL. This 3-month study showed that the patients' QOL changed favorably in the indacaterol treatment arm, even though the FEV_1 did not change significantly in the indacaterol group.[37]

Exacerbations of COPD

Exacerbations of COPD indicate clinical instability and progression of the disease and are associated with reduced health status, physical and physiologic deterioration, and an increased risk of morbidity and mortality.[38,39] The prevention or reduction of exacerbations thus constitutes a major treatment goal. Although exacerbations are an important problem in COPD and a target of intervention, there is no universally standardized tool for assessing the frequency, severity, and duration of exacerbations. Health care databases and patient-based verification by interview, or prospectively from diary cards completed by patients, are the tools available for recording exacerbation rates during trials. Seasonal variations in exacerbation frequency usually require long-term studies of at least 1 year in duration.[40] Analysis of time to first COPD exacerbation at 6 months has shown a reduced risk relative to placebo for indacaterol 150 µg. Similarly, the rate of exacerbation relative to placebo has been shown to be lower for indacaterol 150 µg but not for indacaterol 300 µg or tiotropium.[16] Subjects with moderate to severe COPD who completed the 26-week INHANCE study were eligible for enrollment in an extension of the trial, during which double-blind treatment with indacaterol, 150 or 300 µg once daily, or placebo was continued for a further 26 weeks.[19] Indacaterol treatment over this 12-month extension was accompanied by significant reductions in COPD exacerbations. However, indacaterol trials were not designed to measure exacerbations as the primary outcome, and all studies have only included stable patients without history of frequent exacerbations.

Discussion

The understanding of the merits and limitations of current methods for assessing physiological and clinical outcomes of COPD is crucial for the interpretation and design of clinical trials. Unfortunately, in contrast to spirometric category, there is no gold standard for measuring health status/HR-QOL, physical capacity for activities of daily living, and exacerbations, as none of the available methods is optimal in all regards.[39] Nevertheless, there is considerable evidence that HR-QOL is a valid and important measure

of the disease's effect and activity.[11] Therefore, it is fundamental that the study question be answerable by the study design. Since the relationship between spirometry, symptoms, and health status appears to be poor, measures of lung physiology alone may not adequately describe both the social impact of COPD and the effectiveness of therapeutic interventions.[7]

Indacaterol is a novel inhaled ultra-LABA providing 24-hour bronchodilation on once-daily dosing and is now approved in many countries for the management of patients with COPD. Indacaterol studies have shown significant improvements in lung function that, importantly, have translated into correspondingly beneficial effects on patient-reported outcomes such as dyspnea, number of days with poor control, and clinically meaningful improvements in HR-QOL as measured by the SGRQ, particularly when comparisons are made with placebo. Dyspnea is the primary reason for patients seeking medical care, and its measure may provide an insight into the practical effects of treatment on everyday life, reflecting whether or not patients perceive an improvement in this primary symptom of COPD. Results showed the sustained bronchodilator effect of indacaterol was accompanied by significant improvements in dyspnea and health status/HR-QOL when compared with placebo.[23] Indacaterol was statistically superior to twice-daily LABAs (salmeterol and formoterol) in terms of exceeding the MCID in dyspnea BDI and TDI measurements. Indacaterol was also shown to be at least as effective as tiotropium in improving dyspnea and health status scores in indacaterol studies that included patients with mostly moderate to severe COPD.[17,23]

An important finding in phase III studies is that treatment with indacaterol showed in disease control, since sustained bronchodilation provided by indacaterol was associated with a 40% increase in rescue-free days compared with placebo. This meaningful reduction in salbutamol use for symptom relief characterized all indacaterol studies, suggesting that patients were experiencing fewer symptoms.[41] The beneficial effects of indacaterol on breathlessness and health status suggest that the overall results of the indacaterol trials provide a useful guide to the level of efficacy that may be expected in milder patients who may be seen predominantly in a primary care patient population.[27]

Additionally, a new pooled analysis from three randomized studies (INVOLVE, INHANCE, and INLIGHT 2) in the indacaterol clinical trial program, INERGIZE, presented at the annual 2012 European Respiratory Society Congress in Vienna, Austria, showed that indacaterol 300 µg was superior

to tiotropium in improving breathlessness in COPD patients who had more severe breathlessness symptoms on entry to the studies.[42] Unfortunately, COPD is a progressive disease and often more therapies, with different mechanisms of action, are added in order to control symptoms and improve QOL. Recently, two studies investigating the approach of dual bronchodilation using indacaterol (150 μg) and tiotropium, compared with tiotropium alone, produced a significantly greater improvement in lung function than the tiotropium alone in patients with COPD.[43] Sponsor Novartis introduced indacaterol in 2009. Novartis also added an investigational long-acting muscarinic antagonist, glycopyrronium bromide (NVA237), developed as once-daily inhaled maintenance therapy for the treatment of COPD. The results of phase III IGNITE data presented at the 2012 European Respiratory Society Congress demonstrated the efficacy of dual bronchodilation with indacaterol and glycopyrronium bromide (QVA149) and showed a superior effect on lung function and patient-reported outcomes versus all comparators used as monotherapy (placebo, indacaterol alone, glycopyrronium bromide alone, and tiotropium). QVA149 improved breathlessness as measured by the TDI, increased HR-QOL as measured by the SGRQ, and reduced rescue medication use.[44] These results provide further support to current guidelines, which recommend use of one or more bronchodilators of different classes for treating moderate to severe disease.[7] Additional studies assessing the impact of indacaterol and/or combination therapies such as a long-acting muscarinic antagonist and a LABA on COPD exacerbations, using a standardized definition of an exacerbation, are clearly needed.

Conclusion

Indacaterol is the first ultra-long-acting β_2-agonist (LABA) approved that has a 24-hour bronchodilatory effect. Indacaterol studies have shown significant improvements in lung function that, importantly, have translated into correspondingly beneficial effects on patient-reported outcomes such as dyspnea, number of days with poor control, and clinically meaningful improvements in HR-QOL. Recent studies also suggest that dual bronchodilation with indacaterol in combination with long-acting muscarinic antagonists provide an additive impact on improving HR-QOL in patients with moderate to severe COPD with important implication for COPD management.

Disclosure

The author reports no conflicts of interest in this work.

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