A role of indacaterol in chronic obstructive pulmonary disease management: a turning point or crossroads?

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J Thorac Dis 2013;5(4):378-380. doi: 10.3978/j.issn.2072-1439.2013.07.24

Chronic obstructive pulmonary disease (COPD) is very different today, in both magnitude and makeup, than a mere two decades ago. COPD is rapidly becoming one of the world's most serious health issues affecting millions of people. About one on four adults age 35 and over can be expected to develop COPD. While it is estimated that around 210 million people worldwide have COPD (1), it is likely that only about half of these have been diagnosed (2). Many patients with COPD remain undiagnosed even when the disease causes severe disability (3). The consequences of COPD have a devastating impact on the individual, their family and the society. 2011 COPD exposed report estimates that 26% of people aged between 45 and 67 who were not at work gave-up working because of COPD (2). The prevalence of COPD in women is increasing, as is hospitalization for COPD (4). The defining feature of COPD is airflow limitation that causes air trapping and increased hyperinflation as the ventilation rate increases during physical effort. Significant airflow obstruction may be present before the individual is symptomatic. In the past COPD was often characterized in terms of two more specific diagnoses: chronic bronchitis and emphysema (5). This "umbrella" definition of COPD acknowledged that chronic bronchitis and emphysema were associated with cigarette smoking and airway obstruction, and that they often coexisted, but implied that both were "irreversible" and resistant to treatment. Although the definition of COPD is now more elaborate than in the past, the presence of persistent airflow obstruction is still a defining feature of COPD and a target of the improved pharmacologic management. Irreversible airflow limitation is caused by airway remodeling, resulting from small airway fibrosis and narrowing, and a loss of elastic recoil, a consequence of alveolar destruction. The reversible component reflects ongoing airway smooth muscle contraction, airway inflammation, and mucus secretion, which also contribute to airflow limitation and hyperinflation. The increasing availability of effective treatments makes early intervention increasingly important. Current published guidelines for COPD state that the goal of pharmacologic management should be to control symptoms, improve health status and exercise tolerance, and reduce frequency of COPD exacerbations (6). American Thoracic Society (ATS), European Respiratory Society (ERS) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment guidelines all place bronchodilators as the foundation of pharmacological management of COPD. Long-acting bronchodilators have been shown to improve multiple clinical outcomes in COPD including lung function, symptoms, dyspnea, quality of life, and exacerbations. In patients with moderate to very severe respiratory impairment adding regular treatment with one or more long-acting bronchodilators, is recommended. (long-acting 2-agonists, LABA; long-acting muscarinic antagonists, LAMA) Yet compliance and adherence to the treatment plans historically have been poor. Medications regimens for patients with COPD are particularly vulnerable to adherence problems because of the chronic nature of the disease, the use of multiple medications or polypharmacy, and the periods of symptoms remission. Until recently, the once-daily anticholinergic tiotropium and the twice-daily 2-agonists salmeterol and formoterol were the most widely used maintenance medications. More recently, indacaterol, an inhaled ultra-long acting 2-agonists (24-hour action), has been approved in many countries at different doses (between 75 and 300 mcg) for treatment of patients with stable but symptomatic COPD. Indacaterol was first introduced throughout the European Union in 2009 at doses of 150 and 300 mcg doses. In July 2011, indacaterol was also approved for use in the United States, but at a lower once-daily dose of 75 mcg. Indacaterol thus has become the first effective once-daily LABA that is widely approved for use in stable COPD management.

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Submitted Jul 10, 2013. Accepted for publication Jul 11, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

The availability of a once-daily inhaled 2-agonist for the maintenance treatment of COPD somehow marks a trend in the recent therapeutic developments in COPD, indicating a shift from short-acting bronchodilators with multiple dosing per day to reduced dosing frequency and prolonged duration of action, including once-daily treatment (7). Circadian variation in lung function is a normal process that also occurs in obstructive airway diseases, including COPD, and results in the lowest forced expiratory volume in one second (FEV_1) levels in the early hours of the morning. The early morning is also the time of day when symptoms are worse or the worst, and shortness of breath is often limiting for the patient's routine and daily activities in life (8). Clinical studies demonstrated that indacaterol produces rapid (within 5 minutes) and sustained (for at least 24 hours) bronchodilation in patients with various degrees of airflow obstruction. Until recently, it was thought that the speed of action was not an important issue in the treatment of patients with a chronic disease such as COPD. However, several studies now suggest that the faster the drug acts, the faster the improvement experienced by the patient, and this may have an impact on morning symptoms (9). Indacaterol provides a level of bronchodilation that is at least similar to tiotropium and greater than the twice-daily agents, formoterol and salmeterol. The bronchodilator effect of indacaterol was also demonstrated in terms of its improvement of Forced Vital Capacity (FVC). Effects on FVC generally reflect effects on FEV_1 but can also be useful in patients with COPD, specifically those with hyperinflation, to identify a therapeutic response in the absence of effects on FEV_1. This reduction in hyperinflation may represent an important mechanism through which indacaterol reduces symptoms in COPD (8). 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 health-related quality of life (HR-QOL) (10). Further, it was shown that longer-term beneficial effects of indacaterol were not dependent on age, concomitant inhaled corticosteroids (ICS) use, and baseline bronchodilator reversibility. It is suspected that many patients taking ICS do not need them (11). While there is no evidence of harm from treatment with LABA in COPD, there is increasing evidence that the use of ICSs contributes to increased incidence of pneumonia (12). With this in mind, ICS-free long-acting bronchodilator therapy such as indacaterol is appropriate in many patients with stable COPD. ICSs need not be added unless the patient manifests frequent (two in the last year) exacerbations of their disease. Beyond guidelines, 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. Most of the indacaterol clinical trials have included broadly similar proportions of patients with moderate and severe COPD. Of interest the two indacaterol doses used in most trials (150 and 300 mcg) were not significantly different from each other and were, variously, significantly more effective than formoterol, salmeterol, and at least as effective as tiotropium. Decramer *et al.* (13) have conducted post-hoc analysis of pooled clinical study data to investigate efficacy and safety of indacaterol compared with placebo and other long-acting bronchodilators (formoterol, salmeterol, open-label tiotropium) in patient subgroups defined by COPD severity (GOLD stage II or III) and ICS use at baseline. Indacaterol 150 mcg was judged to be most the most effective treatment for those patients with GOLD stage II disease, not only as bronchodilator but also in terms of improvement in dyspnea and health status. However, in the GOLD stage III it was the 300 mcg dose of indacaterol that appeared to have the best overall profile of efficacy, and was significantly more effective than the 150 mcg dose in its effect of dyspnea (13). It is estimated that in clinical practice approximately 50% of patients with COPD are diagnosed at moderate disease. (GOLD stage II); and 30% at severe or very severe disease (GOLD stage III or IV, respectively) (14). Unfortunately, COPD is a progressive disease and often more therapies, with different mechanisms of action, are added in order to control symptoms and improve HR-QOL. Since 2009, a year when sponsor Novartis first introduced indacaterol, a growing body of evidence shows that LAMA and LABA co-administration is more effective than either drug class along in managing stable COPD to improve lung function, symptoms and health status. Two studies investigating the approach of dual bronchodilation using indacaterol (150 mcg) and tiotropium, compared with tiotropium alone, produced a significantly greater improvement in lung function than the tiotropium alone in patients with COPD (15). Novartis also recently added an investigational long-acting muscarinic antagonist, glycopyrronium bromide (QVA 149), developed as once-daily inhaled maintenance therapy for the treatment of COPD. The results of phase III clinical data demonstrated the efficacy of dual bronchodilation with indacaterol and glycopyrronium and showed a superior effect on lung function and patient-reported outcomes versus all comparators used as monotherapy (placebo, indacaterol alone, glycopyrronium alone, and tiotropium) (16). COPD is a highly complex, multi-component, heterogeneous disease. Relief of symptoms and prevention of exacerbations are two of the main goals of COPD management. To achieve these goals, therapy in COPD was guided broadly by the severity of airflow limitations. Yet the airflow limitation (FEV_1) is poorly related to the degree of breathlessness, health status and number of exacerbations reported (17). In light of considerable cumulative evidence that the level of FEV_1 is a poor descriptor of the disease status, 2011 GOLD guidelines 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) What is now evident is that management of COPD should be individualized according to the symptoms and impairments that patients are experiencing, which may change over the course of the disease. {GOLD 2013} The persistent increase in airflow obstruction that characterizes COPD is best addressed by improving lung function throughout the 24-hour a day. Data from indacaterol trials indicate superior bronchodilation and clinical efficacy over twice-daily LABA and at least equipotent bronchodilation as once-daily tiotropium. 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 quality of life (18). At present, the majority of COPD patients are treated in primary care, and approximately 80% have mild to moderate disease (19). As a result, general practioners often find themselves at a crossroads in the care of COPD patients. Current evidence indicates that indacaterol is suitable, safe and effective for use as first-line monotherapy for management of stable COPD patients with moderate to severe disease and beyond that does not require an ICS as per GOLD guidelines (20). It is advisable that patients with severe and very severe COPD, and particularly those who remain symptomatic or have repeated COPD exacerbations have a consultation with an expert-pulmonologist.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. World Health Organization. Chronic obstructive pulmonary disease (COPD). Fact sheet No. 315. Available online: http://www.who.int/mediacentre/factsheets/fs315/en, accessed November, 2012.
2. Fletcher M, Van der Molen T, Barnes N, et al. COPD: The New Work Place Epidemic. Available online: http://www.educationforhealth.org/data/files/COPD_report_sept11.pdf, accessed July, 2013.
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.
4. Han MK, Postma D, Mannino DM, et al. Gender and chronic obstructive pulmonary disease: why it matters. Am J Respir Crit Care Med 2007;176:1179-84.
5. Fishman AP. One hundred years of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;171:941-8.
6. Global Initiative for Chronic Obstructive Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Revised 2013. Available online: http://www.goldcopd.org/guidelinesglobal-strategy-for-diagnosis-management.pdf, last accessed July, 2013.
7. Beeh KM, Beier J. Indacaterol: a new once daily long-acting beta2 agonist. Int J Chron Obstruct Pulmon Dis 2009;4:37-41.
8. Bleecker ER, Siler T, Owen R, et al. Bronchodilator efficacy and safety of indacaterol 150 μg once daily in patients with COPD: an analysis of pooled data. Int J Chron Obstruct Pulmon Dis 2011;6:431-8.
9. Lopez-Campos JL, Calero C, Quintana-Gallego E. Symptom variability in COPD: a narrative review. Int J Chron Obstruct Pulmon Dis 2013;8:231-8.
10. Rodrigo GJ, Neffen H. Comparison of indacaterol with tiotropium or twice-daily long-acting β-agonists for stable COPD: a systematic review. Chest 2012;142:1104-10.
11. Barnes PJ. Glucocorticosteroids: current and future directions. Br J Pharmacol 2011;163:29-43.
12. Yawn BP, Li Y, Tian H, et al. Inhaled corticosteroid use in patients with chronic obstructive pulmonary disease and the risk of pneumonia: a retrospective claims data analysis. Int J Chron Obstruct Pulmon Dis 2013;8:295-304.
13. Decramer M, Dahl R, Kornmann O, et al. Effects of long-acting bronchodilators in COPD patients according to COPD severity and ICS use. Respir Med 2013;107:223-32.
14. Mapel DW, Dalal AA, Blanchette CM, et al. Severity of COPD at initial spirometry-confirmed diagnosis: data from medical charts and administrative claims. Int J Chron Obstruct Pulmon Dis 2011;6:573-81.
15. Mahler DA, D'Urzo A, Bateman ED, et al. Concurrent use of indacaterol plus tiotropium in patients with COPD provides superior bronchodilation compared with tiotropium alone: a randomised, double-blind comparison. Thorax 2012;67:781-8.
16. Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. ERJ Express 2013. Available online: http://erj.ersjournals.com/content/early/2013/05/30/09031936.00200212.full.pdf, last assessed July, 2013.
17. Agusti A, Calverley PM, Celli B, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res 2010;11:122.
18. Feldman GJ. Improving the quality of life in patients with chronic obstructive pulmonary disease: focus on indacaterol. Int J Chron Obstruct Pulmon Dis 2013;8:89-96.
19. Kruis AL, van Adrichem J, Erkelens MR, et al. Sustained effects of integrated COPD management on health status and exercise capacity in primary care patients. Int J Chron Obstruct Pulmon Dis 2010;5:407-13.
20. Ribeiro M, Chapman KR. Comparative efficacy of indacaterol in chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2012;7:145-52.

Cite this article as: Feldman GJ, Edin A. A role of indacaterol in chronic obstructive pulmonary disease management: a turning point or crossroads? J Thorac Dis 2013;5(4):378-380. doi: 10.3978/j.issn.2072-1439.2013.07.24