EDITORIAL

New once-daily, long-acting inhaled β_2-agonist: what role will it play in the treatment of chronic obstructive pulmonary disease?

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Chronic obstructive pulmonary disease (COPD) is a progressive, life-threatening respiratory disease that affects 210 million people worldwide including up to 82 million in Europe. Over the last decade, major clinical trials have allowed us to better refine our approach to clinical management and to solidify best practice with evidence-based medicine.

Bronchodilators remain the cornerstone of symptomatic treatment for all COPD severity stages when administered on a regular basis to prevent or reduce symptoms and exacerbations.[1-3] Many national and international guidelines suggest using either a long-acting β_2-agonist (LABA) or long-acting antimuscarinic (LAMA) to treat COPD. Because both are effective and convenient, no guidance has been given on which one to choose if short-acting agents fail to improve dyspnea.[4] The COPD marketplace has also undergone a rapid evolution over the last decade with early adoption of these long-acting bronchodilators, i.e., monotherapy with tiotropium (LAMA), salmeterol, or formoterol (LABA), or alternatively with inhaled corticosteroids (ICS) as ICS/LABA combination therapy. In practice, most patients with symptomatic disease associated with recurrent exacerbations are currently promptly established on triple therapy (LAMA along with ICS/LABA combination inhaler). Currently available inhaled LABAs, such as salmeterol and formoterol, only provide bronchodilation for approximately 12 hours at recommended doses, and hence they are administered twice daily when prescribed alone or as part of a combination inhaler with ICS.

In September 2009, a new LABA medication for COPD, indacaterol (QAB149), from Novartis, Basel, Switzerland, received positive opinion in Europe from the Committee for Medicinal Products for Human Use supporting regulatory approval of the drug in the European Economic Area (EEA) as a once-daily therapy. Two doses (150 and 300 μg) are currently being launched in many European markets with other regulatory authorities following suit. In October 2009, the United States Food and Drug Administration, after reviewing the data, requested additional information on the dosing proposed for indacaterol before further considering approval.

Indacaterol is a novel once-daily, inhaled, ultra LABA (uLABA) that provides rapid and sustained 24-hour improvement in airflow and hyperinflation in patients with COPD. Clinical trials of up to a year's duration have confirmed the suitability of indacaterol for once-daily dosing, along with a favorable overall safety and tolerability profile for the maintenance treatment of COPD, at least in the European market.[5,6]

Indacaterol (Onbrez) via the Breezhaler delivery system has an onset of action within 5 minutes and a duration of bronchodilation of at least 24 hours. In doses of 150 and 300 μg (the approved European dosage regimens), it has sustained benefits over 6 to 12 months with respect to both bronchodilation and patient-reported outcomes.

Dahl et al.[5] described a large randomized controlled trial that compared 2 doses of indacaterol (300 and 600 μg) given once daily vs. formoterol 12 μg twice daily and placebo and reported data on efficacy, safety, and tolerability. The indacaterol regimens were statistically better than formoterol in the pulmonary function outcomes. It is interesting that the superiority in lung function over formoterol did not translate into a significant difference in clinical outcomes, i.e., the St George's Respiratory Questionnaire, time to first exacerbation, days of poor control.

Also it is important to further consider safety and tolerability. Randomized controlled trials

are designed to assess efficacy, not safety, but it is reassuring to know that even when the 600 μg dose of indacaterol was studied (twice the maximum dose currently approved in Europe), no worrying signals or safety concerns were apparent, particularly with relation to tachycardia or evidence of electrocardiogram changes in indacaterol-treated patients.

Intriguingly, trials of indacaterol have also described a phenomenon that seems to be highly prevalent but of unknown mechanism, i.e., cough around the time of inhalation. When investigators were asked in the Dahl trial to record any instances of cough occurring within 5 minutes of drug administration during clinic visits, regardless of whether they considered it an adverse event, cough was observed in 19.1% of patients in both indacaterol groups, 0.8% of the formoterol group, and 1.8% of the placebo group.[4] The cough typically started within 15 seconds of inhaling indacaterol, had a median duration of 12 seconds or less, and was not associated with bronchospasm. Interestingly, the presence of this cough was not associated with any increase in discontinuation rates.[5] Some may comment that the cough could have been sufficient to unblind study participants. It also will be interesting to see how this nuisance symptom is perceived or described in postmarketing pharmacovigilance in day-to-day practice.

Donahue et al.[6] have reported a dose ranging indacaterol study vs. placebo, formoterol and open-label tiotropium, which showed benefits at some doses comparable with those seen in a tiotropium comparator group. Once again benefits in lung function did not translate into clinically significant improvements over open-label tiotropium.

Currently, after reviewing the evidence we are left with a conundrum. We do not have clinical trials that translate the consistent improvement in lung function parameters seen with indacaterol into benefit in clinical outcomes in a way that might significantly alter the current content of the guidelines.

One other aspect that needs to be highlighted is the inhaler delivery system for indacaterol. Novartis is not new to the LABA market having their own version of formoterol (Foradil) that uses the Aerolizer, a dry powder delivery device. Little is known about the characteristics of this inhaler device, and to most patients and clinicians it was neither liked, nor widely prescribed, compared with formoterol (Oxeze) from AstraZeneca available in the Turbuhaler device. The new Breezhaler delivery system for indacaterol appears to be very similar with only slight modification to the previous Aerolizer device. Little, if any, further peer-reviewed information is available. Use of inhaler devices is not intuitive, and outside specialist practice family doctors, pharmacists, and patients will need careful instruction on how to use another inhaler device. Independent studies on patient technique and preference are required, as are good patient instruction information in written and visual formats.

Primary care physicians (PCPs), who prescribe most of the medications for COPD, may not see the introduction of indacaterol as a major step forward in COPD management after review of the currently available literature. Currently, PCPs seem comfortable with the available products, and in certain countries, i.e., Canada, they are quite reluctant to prescribe monotherapy with LABA, due to the concern of masking of inflammation in undiagnosed asthma, although this has not been reported in COPD.[7] Updates in current COPD guidelines, which are developed to aid nonspecialists in therapeutic choices, may be more dynamically affected with the concurrent licensing and availability of an oral PDE4 inhibitor with proposed anti-inflammatory activity.[8] Indacaterol is most likely to be positioned within guideline updates as a once-a-day alternative to the currently available LABA bronchodilator products. The current care gap in COPD bronchodilator pharmacotherapy is not for a uLABA, such as indacaterol, but for a lack of availability of a LABA/LAMA combination inhaler, which would satisfy both the convenience aspect of one inhaler plus once-daily dosing.

In order to change perception and prescription habits, it will be important to complement the release of indacaterol with large prospective clinical trials similar in size and duration to TORCH and UPLIFT to further establish and solidify the role of this uLABA with respect to both long-term efficacy and safety in COPD.[9,10]

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