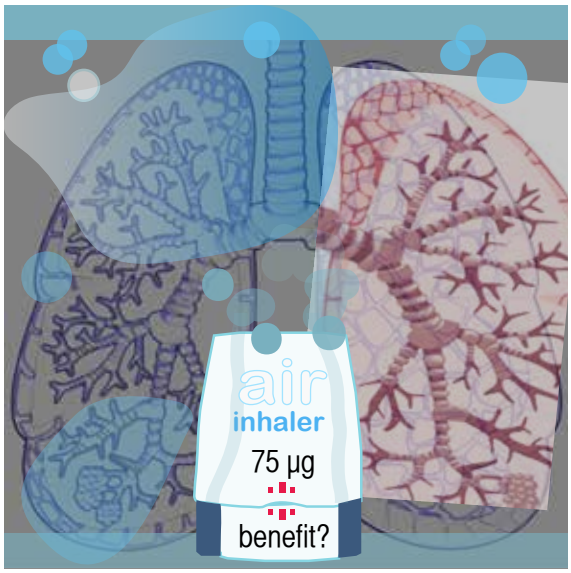
therapeutics letter
September - October 2016

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Indacaterol for chronic obstructive pulmonary disease



Chronic obstructive pulmonary disease (COPD) is an inflammatory condition characterized by irreversible airflow obstruction. It is caused by exposure to noxious particles or gases, with exposure to cigarette smoke the most common cause. Several classes of drugs can be prescribed: short and long-acting beta$_2$ (β2) agonist, short and long-acting anti muscarinic, inhaled corticosteroids and phosphodiesterase-4 inhibitors. **We are conducting a class review of all long-acting beta$_2$ (β2) agonist (LABA) drugs and indacaterol is the first of this series.** All drugs to treat COPD are licensed by regulatory authorities based on short duration randomized trials showing an improvement in a surrogate marker, Forced Expiratory Volume in 1 second (FEV$_1$). This surrogate marker does not reflect the main concerns of patients with COPD, preventing acute moderate to severe exacerbations, improving quality of life and reducing symptoms such as shortness of breath.[1] The approved doses, brand names and year of approval by three regulatory agencies are shown in Table 1.

Objective

To determine the clinical efficacy of inhaled indacaterol as compared to placebo in adult patients with COPD.

Type of studies: Randomized placebo controlled parallel group clinical trials.

Type of participants: Adult patients with clinical diagnosis of COPD.

Type of interventions: Indacaterol at various doses (once or twice daily) compared to placebo control group.

Type of outcomes: Total mortality; total serious adverse events; number of patients with one or more acute moderate to severe exacerbation; quality of life measured by Saint George Respiratory Questionnaire (SGRQ) total score; time to first exacerbation; improvement in symptoms such as dyspnea measured by Transient Dyspnea Index (TDI score), need for rescue medications; total adverse events; total withdrawals, withdrawals due to adverse effects and COPD related health care utilization.

Search Strategy

We searched for all relevant RCT reports in Medline, Embase, CENTRAL, EBSCO CINAHL, ClinicalTrials.gov, Drugs@FDA, EMA public assessment reports and manufacturer's website.

Data Collection and Analysis

Two independent reviewers selected the studies and extracted the data. We conducted a meta-analysis to compare the incidence of outcomes between indacaterol and placebo and presented the results as relative risks (RR) with 95% confidence intervals (CI) for dichotomous outcomes and as weighted mean difference (WMD) for continuous outcomes. We assessed risk of bias for each trial using the Cochrane risk of bias tool.

Results

We identified 12 RCTs[2-11] that met the inclusion criteria, comprising 6,947 adult patients with stable COPD. Patients with concurrent respiratory disease, including asthma, were excluded. Patients could continue using inhaled corticosteroids at the stable dose throughout the studies. Oral corticosteroids were not allowed. Salbutamol/albuterol could

Table 1. Indacaterol dose and year of approval for COPD

Regulatory Agency	Brand Name	Approved Dose	Year Approved
European Medicines Agency (EMA)	Onbrez Breezhaler	150 and 300 µg daily	2009
US Food and Drug Administration (FDA)	Arcapta Neohaler	75 µg daily	2011
Health Canada	Onbrez Breezhaler	75 µg daily	2012

Mailing Address: Therapeutics Initiative
The University of British Columbia
Department of Anesthesiology, Pharmacology & Therapeutics
2176 Health Sciences Mall
Vancouver, BC Canada V6T 1Z3

Tel.: 604 822 0700
Fax: 604 822 0701
E-mail: info@ti.ubc.ca
www.ti.ubc.ca

ISSN 2369-8683 (Print)
ISSN 2369-8691 (Online)

Table 2. Indacaterol outcome data

Outcome in Published Literature	Participants (Studies)	RR or WMD (95% CI)
Mortality	6,913 (11)	0.47 (0.21 to 1.07)
Total serious adverse events	6,908 (11)	1.00 (0.83 to 1.19)
Participants experiencing one or more exacerbation of any severity	3,255 (3)	0.84 (0.74 to 0.95)
WMD in SGRQ score	5,183 (10)	-3.46 (-4.31 to -2.62)
≥ 4-point difference in SGRQ score	1,566 (3)	1.28 (1.15 to 1.42)
Need for rescue medication	2,192 (5)	-0.80 (-0.99 to -0.61)
Total adverse events	6,905 (11)	1.04 (0.99 to 1.09)
Withdrawals due to adverse effects	6,911 (11)	0.80 (0.66 to 0.98)
Total withdrawals	6,912 (11)	0.66 (0.60 to 0.73)

be used for rescue as needed. No other bronchodilators were permitted. Duration of trials ranged from 12 weeks (8 trials) to 26 weeks (3 trials). Only one trial was 52 weeks in duration. Indacaterol doses included 27.5 μg twice daily, 75 μg, 150 μg, 300 μg and 600 μg once daily. Four RCTs included more than one dose of indacaterol.[3-6] Subgroup analysis showed no significant differences between various doses so results for all outcomes are presented as overall RR or WMD with 95% CI (see Table 2). The number of patients with one or more acute moderate to severe exacerbations, time to first exacerbation and COPD-related health care utilization outcomes were not reported in any study.

Risk of bias

All studies were judged individually and overall to be at high or unclear risk of bias[12] (see Figure in Revman file on website).

Dose ranging efficacy

No significant difference in any outcome measure was noted between the lowest dose 27.5 μg bid and 600 μg once daily. Comparing two different doses within the same study showed no significant difference in any outcome measure between 300 and 150 μg or 600 and 300 μg dose.

Clinical Implications

A systematic review of all available evidence showed no statistically significant difference in mortality, total serious adverse events and total adverse events. Lower incidence of total withdrawals and withdrawal due to adverse effects in the indacaterol group was due to perceived lack of efficacy in the placebo group, which likely reflects loss of blinding. For all other outcomes, the small but statistically significant reduction in patients experiencing one or more exacerbation of any severity; quality of life scores and reduced need for rescue medication are based on a subset of total randomised patients and represents very low quality evidence which may not be real, or at best is an exaggeration of the real benefit.[13]

Other systematic reviews

In contrast to our review, a Cochrane review[14] published in 2015 judged the overall risk of bias to be minimal and thus they were more positive about the efficacy of indacaterol. A non-Cochrane systematic review[15] rated the overall quality of included studies as mediocre with poor reporting of methodological details. They concluded that indacaterol at dosage < 150 μg improved FEV_1, SGRQ and TDI score in patients with moderate to severe stable COPD, but at a dose of 300 μg indacaterol did not prevent exacerbations at 1 year.

Conclusions

- The only single product dose of inhaled indacaterol approved in Canada is 75 μg.
- Doses of indacaterol higher than 75 μg were not significantly different in any clinically meaningful outcome measure as compared to lower doses.
- **There are no proven clinically meaningful benefits in terms of reduction in mortality or total serious adverse events for indacaterol in patients with COPD.**
- Because the overall evidence is graded as of very low quality, it is unclear whether indacaterol causes a clinically meaningful reduction in acute exacerbations, improvement in quality of life, dyspnea or reduced need for rescue medications.
- **For any new class of drugs for COPD, evidence of a reduction in clinically relevant outcomes should be required for licensing.**

References

Complete list of references and additional details from the review are posted at: **www.ti.ubc.ca/letter102**

The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

The Therapeutics Initiative is funded by the BC Ministry of Health through a grant to the University of BC. The Therapeutics Initiative provides evidence-based advice about drug therapy, and is not responsible for formulating or adjudicating provincial drug policies.