therapeutics letter
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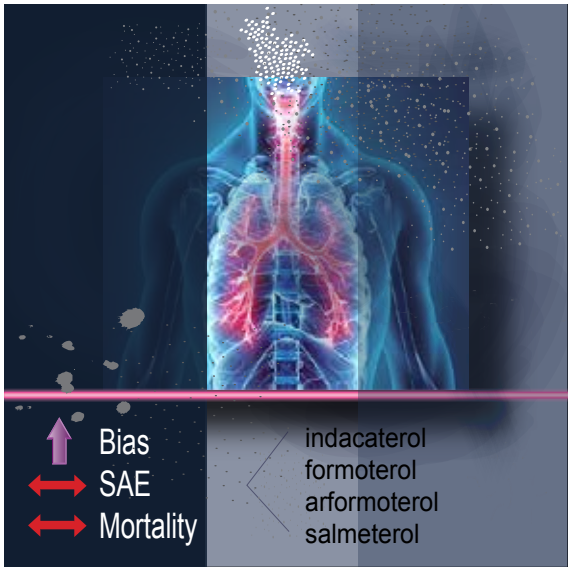
THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Inhaled long acting β2 agonists for COPD



In Therapeutics Letter #102[1] we reviewed the inhaled long acting β2 agonist (LABA) indacaterol for chronic obstructive pulmonary disease (COPD). We concluded "There are no proven clinically meaningful benefits in terms of reduction in mortality or total serious adverse events…" for this indication based on 12 trials in 6,947 patients. In this Letter we report systematic reviews of 3 other inhaled LABA drugs licensed for COPD: formoterol, arformoterol and salmeterol.

Objective

To determine the clinical efficacy of inhaled formoterol, arformoterol and salmeterol as compared to placebo for chronic maintenance treatment in adult patients with COPD. Since COPD causes important morbidity and mortality, we rank these outcomes as most important. Another potential benefit of inhaled LABA would be meaningful improvement in disabling symptoms of COPD.

Methods

Inclusion criteria: randomized placebo controlled parallel group clinical trials (RCTs) with clinically important outcomes. We used standard Cochrane methods for search strategy, data collection and analysis.[1]

Results

Since arformoterol is an R-R enantiomer of racemic formoterol, we combined their analyses. We identified 22 RCTs[2-21] for formoterol and 2 RCTs[22-23] for arformoterol (N = 13,958), and 17 RCTs[23-39] for salmeterol (N = 10,115). These trials excluded patients with other concurrent respiratory diseases, including asthma. Patients were allowed to continue using the following at stable doses throughout the studies: inhaled or oral corticosteroids, inhaled short or long acting antimuscarinic drugs, phosphodiesterase-4 inhibitors and short acting salbutamol for rescue therapy. Most participants were men with the mean age ranging from 60 to 67 years.

Twice daily dose ranges were: formoterol 4.5 to 24 µg, arformoterol 15 to 50 µg, salmeterol 42 to 100 µg. Most data were available for formoterol 9 to 12 µg twice daily and salmeterol 50 µg twice daily.

Duration of formoterol trials ranged from 4-26 weeks (14 RCTs) to 48-52 weeks (8 RCTs). Arformoterol trials ranged from 12 to 52 weeks (2 RCTs). Salmeterol trials ranged from 4-24 weeks (14 RCTs) to 52 weeks (2 RCTs), with a single much longer trial lasting 156 weeks.[27] The trials identified no clinically meaningful dose related differences, so we present results combining all doses (See Table 1).

Risk of bias

We assessed risk of bias for each trial using the Cochrane risk of bias tool.[40] We judged most studies to be at high or unclear risk of bias due to selection, performance, detection, attrition, selective reporting and source of funding biases (see risk of bias graphs on our website). Many authors were in potential conflict of interest by serving as consultants on the advisory boards of, and/or receiving unrestricted research grants and speaking fees from the manufacturers of the drug under study.

TORCH trial[27]

This multi-country trial contributed the most weight to the salmeterol review. We judged it to be at high risk of bias arising from attrition, selective reporting and source of funding. It did not specifically define a COPD exacerbation. Severity of exacerbation was based on treatment received (inhaled corticosteroid or antibiotic), which varied significantly between different countries and centers. The investigators reported no significant difference in number of participants experiencing 1 or more moderate to severe exacerbation: RR 1.01 (0.96, 1.06) or severe exacerbation requiring hospitalisation: RR 0.95 (0.84, 1.07). The authors also reported no difference between the salmeterol and placebo groups in the number of patients with unscheduled health care contacts (emergency room visits, outpatient clinic visits and hospital admissions).[41]

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Table 1: Outcome data

Outcomes in published literature	Formoterol and Arformoterol vs Placebo (95% CI) Participants (studies)	Salmeterol vs Placebo (95% CI) Participants (studies)
Total mortality	RR: 1.30 (0.91 to 1.87) 12,351 (21)	RR: 0.85 (0.72 to 1.00) 9,822 (16)
Total serious adverse events	RR: 1.02 (0.93 to 1.12) 12,631 (22)	RR: 0.97 (0.89 to 1.05) 6,666 (11)
Participants experiencing ≥1 exacerbation of any severity	RR: 0.93 (0.86 to 1.01) 10,216 (17)	RR: 0.96 (0.91 to 1.00) 8,130 (12)
Improvement in total Saint George Respiratory Questionnaire, 0-100 point score	WMD: -1.94 (-2.46 to -1.43) 10,961 (22)	WMD: -1.73 (-2.39 to -1.07) 6,456 (9)
Improvement in total Saint George Respiratory Questionnaire score by ≥ 4 points	RR: 1.34 (1.18 to 1.52) 1,266 (2)	RR: 1.20 (1.08 to 1.32) 2,112 (3)
Improvement in total TDI score	WMD: 0.73 (0.52 to 0.94) 2,938 (5)	WMD: 0.17 (-0.16 to 0.50) 1,165 (4)
Improvement in total TDI score by ≥ 1 point	RR: 1.41 (1.18 to 1.69) 664 (1)	RR: 1.38 (1.17 to 1.62) 1,219 (2)
Decreased need in the number of rescue puffs per day	RR: -0.64 (-0.74 to -0.53) 6,361 (13)	RR: -0.74 (-0.88 to -0.59) 3,941 (9)
Total adverse events	RR: 1.04 (1.01 to 1.07) 11,227 (19)	RR: 0.99 (0.97 to 1.02) 8,896 (15)
Withdrawal due to adverse effects	RR: 0.93 (0.82 to 1.05) 12,695 (22)	RR: 0.83 (0.75 to 0.93) 8,534 (15)

RR = *relative risk*; WMD = *weighted mean difference*; 95% CI = *95% confidence interval*; TDI = *Transient Dypsnea Index*

Clinical implications

Maintenance therapy with inhaled LABAs for COPD would be most useful if it improved survival or prevented hospitalization. After including indacaterol data and combining the data for the four LABAs (50 RCTs: N = 29,557), we conclude that these drugs do not prevent mortality, RR 0.89 (0.77, 1.03) based on 43 RCTs reporting mortality (N = 27,316). There was also no difference in serious adverse events, RR 0.99 (0.94, 1.06) based on 41 RCTs reporting this outcome (N = 25,144). LABAs could be justified if patients experience clinically meaningful symptomatic relief. However, we found no clinically significant mean improvement in quality of life scores, TDI scores or in a reduced need for rescue medication.

Based on our systematic review, it is possible that a small subset of patients experiences important symptomatic relief. If so, this would best be determined on a case-by-case basis after a short (e.g. 2-week) therapeutic trial. **If the patient does not experience any important symptomatic relief, long-term therapy is not justified.**

Other systematic reviews

A Cochrane review published in 2013 is outdated.[42] It includes 26 studies (N = 14,939) for both formoterol and salmeterol as compared to 40 studies (N = 23,780) included in our review. The authors judged the overall risk of bias to be minimal, in contrast with our assessment of a high risk of bias. Their assessment of the symptomatic benefit associated with inhaled LABAs was more positive. The Cochrane review agrees with our conclusions that inhaled LABAs do not reduce mortality or serious adverse events.

Conclusions

- The doses most studied in COPD clinical trials are formoterol 9 and 12 μg twice daily and salmeterol 50 μg twice daily.
- **The four inhaled long acting β2 agonists (indacaterol, formoterol, arformoterol and salmeterol) do not prolong survival or reduce the risk of hospitalization (total serious adverse events) in patients with COPD.**
- Evidence for improvement of symptom scores is of low quality and insufficient to justify long-term use.
- A subset of patients may derive clinically important symptomatic relief. Such patients can be identified on a case-by-case basis using a short therapeutic trial.

The complete list of references and additional information, including risk of bias graphs and forest plots, are available at: **www.ti.ubc.ca/letter109**

The draft of this Therapeutics Letter was submitted for review to 75 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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