CHEST

A Systematic Review With Meta-Analysis of Dual Bronchodilation With LAMA/LABA for the Treatment of Stable COPD

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BACKGROUND: The wide availability of long-acting muscarinic antagonist (LAMA)/long-acting β2-agonist (LABA) fixed-dose combinations (FDCs) in the absence of head-to-head comparative pragmatic trials makes it difficult to choose which combination should be used. Therefore, we carried out a systematic review with meta-analysis that incorporated the data from trials lasting at least 3 months to evaluate the effectiveness of LAMA/LABA FDCs for COPD treatment.

METHODS: Randomized controlled trials were identified by searching different databases of published and unpublished trials. We aimed to assess the influence of LAMA/LABA combinations on trough FEV_1, transitional dyspnea index, St. George's Respiratory Questionnaire, and cardiac safety vs monocomponents.

RESULTS: Fourteen papers and one congress abstract with 23,168 patients with COPD (combinations, n = 10,328; monocomponents, n = 12,840) were included in this study. Our results showed that all LAMA/LABA combinations were always more effective than the LAMA or LABA alone in terms of the improvement in trough FEV_1. Although there was not significant difference among LAMA/LABA combinations, we identified a gradient of effectiveness among the currently available LAMA/LABA FDCs. LAMA/LABA combinations also improved both transitional dyspnea index and St. George's Respiratory Questionnaire scores, but did not increase the cardiovascular risk when compared with monocomponents.

CONCLUSIONS: The gradient of effectiveness emerging from this meta-analysis is merely a weak indicator of possible differences between the various LAMA/LABA FDCs. Only direct comparisons will document if a specific LAMA/LABA FDC is better than the other. In the meanwhile, we believe it is only proper to consider that dual bronchodilation is better than a LAMA or a LABA alone, regardless of the drugs used. CHEST 2016; 149(5):1181-1196

KEY WORDS: combination therapy; COPD; long-acting β2-agonist (LABA); long-acting muscarinic antagonist (LAMA)

ABBREVIATIONS: DPI = dry powder inhaler; FDA = US Food and Drug Administration; FDC = fixed-dose combination; LABA = long-acting β2-agonist; LAMA = long-acting muscarinic antagonist; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized clinical trial; SAE = serious adverse events; SGRQ = St. George's Respiratory Questionnaire; SMI = soft mist inhaler; TDI = transitional dyspnea index

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In all current guidelines and recommendations of the management of COPD, inhaled bronchodilators are the pillar of therapy at each stage of the disease.[1-3] In particular, results of randomized clinical trials (RCTs) conducted using different combinations of long-acting muscarinic antagonists (LAMAs) and long-acting β2-agonists (LABAs) show that coadministering different classes of bronchodilators induces a significantly greater improvement in lung function and other meaningful outcomes such as inspiratory capacity, dyspnea, symptom scores, rescue medication use, and health status in comparison with an individual drug.[4]

This finding is not surprising considering that recent preclinical and translational studies demonstrated that combining a LAMA with a LABA causes synergistic benefit on airway smooth muscle relaxation,[5-7] which may have major implications for the use of LAMA/LABA combinations in the treatment of COPD.[8] This is the likely reason why there has been, and there still is, a strong interest in developing new once- or twice-daily LAMA/LABA fixed-dose combinations (FDCs).

Currently, the European Medicines Agency and/or the US Food and Drug Administration (FDA) have approved four different LAMA/LABA FDCs. Two (umeclidinium/vilanterol and tiotropium/olodaterol) have been developed as a once-daily FDC, the third (aclidinium/formoterol) as a twice-daily FDC, and the fourth (glycopyrronium/indacaterol) as once-daily FDC (except in the United States, where it will be marketed as a twice-daily FDC). Another FDC (glycopyrronium/formoterol) is still under clinical development.

Regrettably, despite the wide availability of LAMA/LABA FDCs, there is an absence of head-to-head comparative pragmatic trials that makes difficult and empiric regarding the choice of the combination to be used. Moreover, it is likely that these trials will not be carried out because of their cost and a lack of interest that pharmaceutical companies may produce potential data that might be unfavorable to them.

In view of the lack of this important information, we have carried out a treatment comparison by systematic review and synthesis on the available clinical evidence to evaluate the effectiveness and cardiac safety of these LAMA/LABA FDCs for COPD treatment, with analyses that incorporate the data from all LAMA/LABA FDC trials lasting at least 3 months.

Materials and Methods

Searching Strategy

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Fig 1).[9]

We performed a comprehensive literature search for RCTs lasting at least 3 months and concerning the influence of treatment with LABAs and LAMAs administered in combination in patients suffering from COPD diagnosed by pulmonary function testing.[1,10]

The terms "chronic obstructive pulmonary disease" and "COPD" were included for the disease; the terms "LABAs" and "LAMAs" for the class of drugs; the terms "aclidinium," "formoterol," "glycopyrronium," "indacaterol," "olodaterol," "tiotropium," "umeclidinium," and "vilanterol" for specific compounds; and the term "combination" to identify RCTs investigating combination therapy. The search was performed on PubMed and Google Scholar for relevant studies published up to October 1, 2015.[11] Further search was carried out on clinicaltrials.gov, the European Union Clinical Trials Register, and the European Respiratory Society Congress Abstract Book (updated August 2015) to find potential RCTs not yet published. Citations of previously published meta-analyses and relevant reviews were examined to identify further pertinent studies, if any.[12-15]

All RCTs involving patients with COPD who have received inhalant administration of LAMA/LABA combinations vs at least one monocomponent were included in the analysis. Two reviewers independently checked the relevant RCTs found from literature and databases. RCTs were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

Quality Score and Risk of Bias Assessment

The Jadad score, with a scale of 1 to 5 (with 5 being highest), was used to assess the quality of the papers concerning the likelihood of bias related with randomization, double blinding, withdrawals, and dropouts.[16] Two reviewers independently assessed the quality of individual studies, and any difference in opinion about the quality score was resolved by consensus. RCTs with Jadad scores ≥ 3 were included in the meta-analysis.

The risk of publication bias was assessed by applying the funnel plot and Egger test through the following regression equation: $SND = a + b \times precision$, where SND represents the standard normal deviation (treatment effect divided by its SE), and precision represents the reciprocal of the standard error.[17-19] Evidence of asymmetry from Egger test was considered to be significant at $P < .1$, and the graphical representation of 90% confidence bands have been presented.[19]

Data Extraction

Data from included studies were extracted and checked for study characteristics and duration, doses of medications, inhaler devices, disease characteristics, age, sex, smoking habits, smoking history, FEV_1, trough FEV_1, transition dyspnea index (TDI), St. George's Respiratory Questionnaire (SGRQ), cardiac adverse events, and Jadad score.

End Points

The primary end point of this meta-analysis was to assess the effectiveness of LAMA/LABA combinations in modulating the change from baseline in trough FEV_1 vs monocomponents. Table 1 shows the definition of trough FEV_1 according to the studies included in the meta-analysis.