Pulmonary Pharmacology & Therapeutics 25 (2012) 40–47

Contents lists available at SciVerse ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: A systematic review

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ARTICLE INFO

Article history:
Received 10 May 2011
Received in revised form
17 October 2011
Accepted 27 October 2011

Keywords:
Long-acting beta2-agonists
Long-acting muscarinic antagonists
COPD
Therapy
Inhaled corticosteroids

ABSTRACT

Background: Guidelines recommend the use of inhaled long-acting bronchodilators, inhaled corticosteroids (ICS) and their combinations for maintenance treatment of moderate to severe COPD. However, there are limited data supporting combination therapy.
Methods: This systematic review assessed the efficacy of three therapeutic approaches: tiotropium plus long-acting beta2-agonist (LABA) ("dual" therapy), LABA/ICS ("combined" therapy), and tiotropium plus LABA/ICS ("triple" therapy), all compared with tiotropium monotherapy. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.
Results: Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in forced volume in the first second (FEV_1), health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV_1, HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to treat for harm [NNTH] = 20; 95% CI: 11–119). Finally, "triple therapy" increased FEV_1, improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, $p = 0.21$).
Conclusions: "Dual" and "triple" therapy seem like the most promising for patients with moderate to very severe COPD. However, data are still scarce and studies too short to generate a strong recommendation. Future studies should examine long-term efficacy and safety.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a prominent cause of disability and death worldwide [1]. As COPD is a progressive disease, guidelines recommended a stepwise approach to treatment [1,2]. Pharmacotherapy has improved substantially in the last decade. The availability of long-acting beta2-agonists (LABA), fixed combinations of inhaled corticosteroids (ICS) add to LABA, and long-acting muscarinic antagonists (LAMA), have allowed improved different outcomes of the disease. While short-acting beta2-agonists (SABA) are used for the relief of symptoms, inhaled LABA, LAMA, ICS and their combinations are reserved for maintenance treatment of patients with moderate to severe COPD [1,2] Although the relative benefits of which agent to use first have not been systematically studied, initial treatment of these patients with a LAMA (tiotropium) appears to be a rational approach than twice daily LABA [3,4]. However, when symptoms are not adequately controlled with monotherapy, guidelines recommended the addition of a LABA to a LAMA ("dual" long-acting bronchodilator therapy), the addition of an ICS to a LABA ("combined" therapy), or even a LABA plus an ICS to a LAMA ("triple" therapy), although data supporting these different therapeutic approaches are limited to date. The objective of this

Abbreviations: COPD, Chronic obstructive pulmonary disease; FEV_1, forced volume in the first second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; LAMA, long-acting muscarinic antagonists; MID, minimal important difference; NNTB, number need to treat for benefit; NNTH, number need to treat for harm; OR, odds ratio; SABA, short-acting beta2-agonists; SAE, severe adverse effects; SGRQ, St. George Respiratory Questionnaire; TDI, transitional dyspnea index; WMD, weighted mean difference.

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doi:10.1016/j.pupt.2011.10.006

systematic review is to assess the efficacy of these therapeutic combinations compared with tiotropium monotherapy in COPD patients.

2. Methods

2.1. Search and selection criteria

We identified studies from MEDLINE, EMBASE (January 1980 to May 2011) and the Cochrane Controlled Trials Register (CENTRAL) (first quarter 2011) databases using the following Medical Subject Headings, full text, and keywords (long-acting beta-2-agonists OR salmeterol OR formoterol OR indacaterol ORQAB-149 OR long-acting antimuscarinics agents OR tiotropium OR inhaled corticosteroids OR fluticasone OR budesonide OR ciclesonide OR mometasone OR beclomethasone AND chronic obstructive pulmonary disease. Also, we performed a search of relevant files from the drugs manufacturer's databases. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed. The specific inclusion criteria were as follows: 1) adult patients aged greater than 40 years with stable COPD satisfying American Thoracic Society/European Respiratory Society [2], or Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria [1]; 2) tiotropium plus LABA ("dual" long-acting bronchodilator therapy), LABA plus ICS ("combined" therapy) and tiotropium plus LABA plus ICS ("triple" therapy), all compared with tiotropium monotherapy; 3) studies with more than 2 weeks of duration; 4) randomized (parallel group or cross sectional) controlled trials without language restriction; 5) primary outcomes: forced volume in the first second (FEV_1) (pre and post bronchodilator test), use of rescue medications, health-related quality of life (HRQoL) (St. George Respiratory Questionnaire [SGRQ]) [5], dyspnea, and COPD exacerbations. Secondary outcomes measures: all-cause mortality, withdrawals during treatment period, and severe adverse effects (SAE). A serious adverse event was defined as any untoward medical occurrence that results in sometimes death, is life-threatening, requires inpatient hospitalization, or results in persistent or significant disability/incapacity [6].

2.2. Data abstraction and assessment of risk of bias

This systematic review was performed according to the PRISMA guidelines (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [7]. Titles, abstracts, and citations were independently analyzed by all reviewers. From full text, they independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, they assessed eligibility. The authors were independently involved in all stages of study selection, data extraction, and risk of bias assessment. The later was assessed according to recommendations outlined in Cochrane Handbook [8] for the following items: 1) allocation sequence generation; 2) concealment of allocation; 3) blinding of participants and investigators; and 4) handling of missing data. Each potential source of bias was graded as yes, no or unclear, relating to whether the potential for bias was low, high or unknown respectively. Disagreements were resolved by group consensus.

2.3. Data analysis

Outcomes were pooled using weighted mean differences (WMD) (continuous outcomes) or Mantel–Haenszel odds ratios (ORs) (binary outcomes). The precision of the mean estimates was quantified by the 95% confidence intervals (CIs). When effect estimates were significantly different between groups, the number needed to treat for benefit (NNTB) or for harm (NNTH) was obtained. Heterogeneity was measured by the I^2 test [9] (<40% might be unimportant, 40%–60% might be moderate, and 60%–100% may be substantial) [8]. Because selected studies differed in the mixes of participants and interventions, a random-effects meta-analysis was performed to address this variation across studies in all outcomes [10]. In those outcomes that showed statistically significant differences but with moderate to substantial heterogeneity, 95% predictive intervals were calculated to address the distribution of true effects sizes [11]. Publication bias of primary outcomes was evaluated by visual inspection of funnel plots [12]. As a priori subgroup analysis, we explore the influence of type LABA (formoterol vs. salmeterol vs. indacaterol), and length of treatment (<24 weeks vs. ≥24 weeks). Subgroups were compared using the interaction test [13] $P \leq 0.05$ (2-tailed test) was considered significant. Meta-analysis was performed with the Review Manager 5.1.4 software (Cochrane IMS, 2011).

3. Results

Twenty RCTs [14–33] (including 6803 subjects) fulfilled the inclusion criteria (Fig. 1). Five trials were unpublished [19–21,23,24].

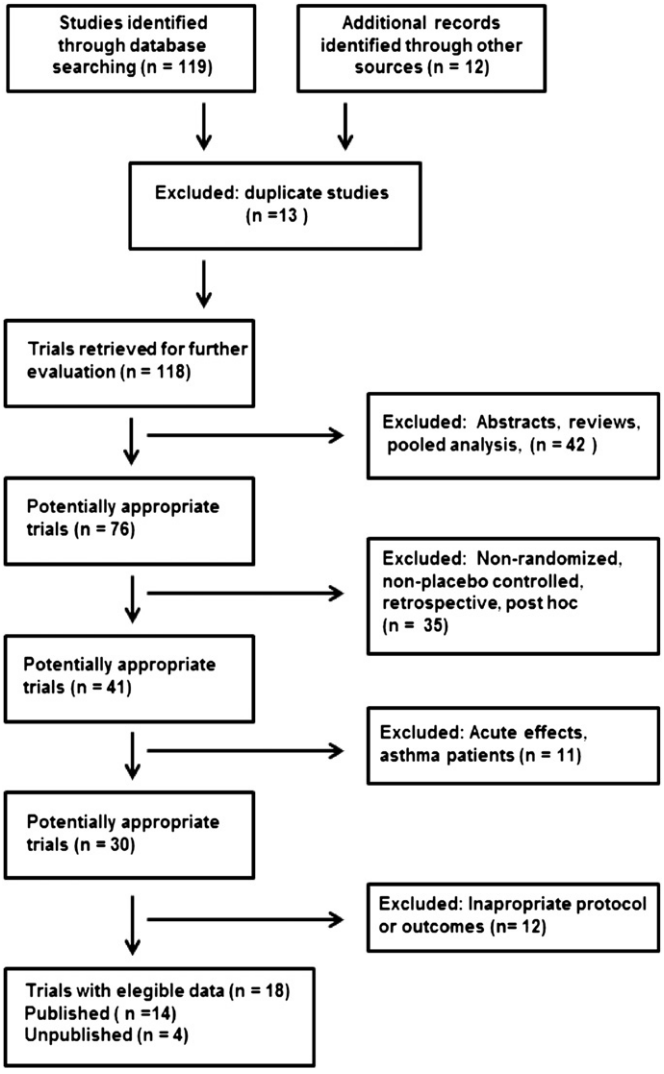

Fig. 1. Flowchart for identification of usable studies.