JAMA Clinical Evidence Synopsis

Long-Acting β-Agonists (LABA) Combined With Long-Acting Muscarinic Antagonists or LABA Combined With Inhaled Corticosteroids for Patients With Stable COPD

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CLINICAL QUESTION Are inhaled long-acting muscarinic antagonists (LAMA) combined with long-acting β-agonists (LABA) associated with differences in the incidence of chronic obstructive pulmonary disease (COPD) exacerbation and serious adverse events and with differences in quality of life and forced expiratory volume in the first second of expiration (FEV_1) vs inhaled LABA plus inhaled corticosteroids therapy for the treatment of stable COPD?

BOTTOM LINE Compared with inhaled LABA combined with corticosteroids, inhaled LAMA combined with LABA may be associated with a lower risk of COPD exacerbation and with greater improvement in FEV_1 without differences in the incidence of serious severe adverse events or quality of life.

Introduction

This JAMA Clinical Evidence Synopsis summarizes a Cochrane review[1] that assessed inhaled long-acting muscarinic antagonists (LAMA), long-acting β-agonists (LABA), and inhaled corticosteroids (ICS). These are important medications to treat stable chronic obstructive pulmonary disease (COPD). These medication combinations (LAMA + LABA or LABA + ICS) can be administered via 1 inhaler. The LABA + ICS therapies (eg, salmeterol + fluticasone) are the preferred option for patients who are at high risk of COPD exacerbation events.[2] However, it is unclear which of the 2 combined inhaler treatments is associated with better outcomes.[3-5]

Evidence Profile

No. of randomized clinical trials: 11

Study years: Conducted, 2004-2015; published, 2008-2016; date of last literature search: June 4, 2016

No. of patients: 9839

Men: 74% **Women:** 26%

Race/ethnicity: Not reported

Age range: 61-71 years

Setting: Outpatients

Countries: 44 countries in Asia, Europe, Latin America, North America, Oceania, and South Africa

Comparisons: Long-acting β-agonists combined with long-acting muscarinic antagonists vs long-acting β-agonists with inhaled corticosteroids

Primary outcomes: Chronic obstructive pulmonary disease exacerbation, serious adverse event, St George Respiratory Questionnaire total score (range: 0-100; 0 is the best score) change from baseline (mean difference), predose forced expiratory volume in the first second of expiration change from baseline. Predose means the measurement was performed in the morning prior to any inhaled medication.

Secondary outcomes: Pneumonia, all-cause death, St George Respiratory Questionnaire total score change from baseline (≥4 points)

Summary of Findings

Follow-up ranged from 6 to 52 weeks.[1] In the analysis of the included studies, LAMA + LABA was associated with fewer patients with at least 1 COPD exacerbation event vs LABA + ICS (1562/4461 [35.0%] vs 1682/4461 [37.7%], respectively; odds ratio [OR], 0.82 [95% CI, 0.70-0.96]; **Figure**), a larger improvement in forced expiratory volume in the first second of expiration (FEV_1) measured in the morning before the first dose of inhaled medication (mean difference, 0.08 L [95% CI, 0.06-0.09 L]; absolute data not available), and a lower incidence of pneumonia (61/4271 [1.4%] vs 109/4269 [2.6%], respectively; OR, 0.57 [95% CI, 0.42-0.79]).

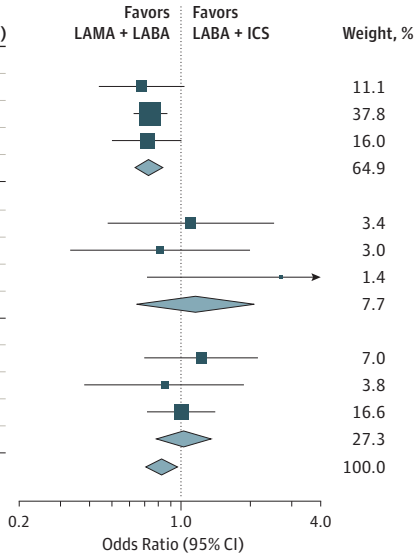
There was no difference between LAMA + LABA and LABA + ICS in rates of serious adverse event rates (431/4900 [8.8%] vs 468/4839 [9.7%], respectively; OR, 0.91 [95% CI, 0.79 to 1.05]) or all-cause death (31/4101 [0.8%] vs 30/4839 [0.6%]; OR, 1.01 [95% CI, 0.61 to 1.67]). The between-group difference for change in St George Respiratory Questionnaire total score from baseline was not significant (−4.48 [95% CI, −4.92 to −4.04] for LAMA + LABA vs −3.71 [95% CI, −4.15 to −3.27] for LABA + ICS; mean difference, −1.22 [95% CI, −2.52 to 0.07]). More patients in LAMA + LABA group vs the LABA + ICS group experienced improvement by 4 or more points on the St George Respiratory Questionnaire, which represents the minimal clinically important difference (808/1615 [50.0%] vs 701/1577 [44.4%], respectively; OR, 1.25 [95% CI, 1.09 to 1.44]).

Discussion

Compared with LABA + ICS, treatment with LAMA + LABA is associated with fewer patients with COPD exacerbation events and greater improvement in predose FEV_1. There were no between-group differences in the incidence of severe adverse events or all-cause death.

Figure. Association of Combined Inhaler Therapy With Incidence of Chronic Obstructive Pulmonary Disease (COPD) Exacerbation

Source	LAMA + LABA: No. of Patients With ≥1 COPD Exacerbation	LAMA + LABA: Total No. of Patients	LABA + ICS: No. of Patients With ≥1 COPD Exacerbation	LABA + ICS: Total No. of Patients	Odds Ratio (95% CI)
Indacaterol + glycopyrronium vs salmeterol + fluticasone					
Vogelmeier, 2013	44	258	62	264	0.67 (0.44-1.03)
Wedzicha, 2016	1290	1675	1377	1679	0.73 (0.62-0.87)
Zhong, 2015	75	372	97	369	0.71 (0.50-1.00)
Subtotal	1409	2305	1536	2312	0.72 (0.63-0.83)
Umeclidinium + vilanterol vs salmeterol + fluticasone					
Donohue, 2015	12	353	11	353	1.09 (0.48-2.51)
Donohue, 2015	9	349	11	348	0.81 (0.33-1.98)
Singh, 2015	8	358	3	358	2.70 (0.71-10.30)
Subtotal	29	1060	25	1059	1.15 (0.64-2.06)
Other LAMA + LABA vs salmeterol + fluticasone					
Magnussen, 2012	29	332	24	329	1.22 (0.69-2.14)
Rabe, 2008	12	297	14	295	0.85 (0.38-1.86)
Vogelmeier, 2016	83	467	83	466	1.00 (0.71-1.40)
Subtotal	124	1096	121	1090	1.02 (0.78-1.34)
Total	1562	4461	1682	4461	0.82 (0.70-0.96)



The other long-acting muscarinic antagonists (LAMA) + long-acting β-agonists (LABA) indicates tiotropium plus olodaterol, umeclidinium plus vilanterol, tiotropium plus indacaterol, tiotropium plus salmeterol, tiotropium plus formoterol, glycopyrronium plus indacaterol, or aclidinium plus formoterol. In all studies, LABA plus inhaled corticosteroids (ICS) was salmeterol plus fluticasone. A Mantel-Haenszel random-effects model was used. The size of the squares indicates the weight of each study.

Limitations

First, the statistical power was insufficient for some of the outcomes. Second, some of the studies did not include data on long-term follow-up. Third, there was significant heterogeneity among the included studies. Fourth, the results may not be generalizable to patients who did not qualify for the included studies. Fifth, the risk of exacerbation was reduced only in participants who received glycopyrronium + indacaterol.

Comparison of Findings With Current Practice Guidelines

Our findings are compatible with the GOLD 2017 guidelines[6] that recommended LAMA + LABA as the second choice after single bronchodilator therapies for more symptomatic patients with low risk of COPD exacerbation events (group B of the GOLD guidelines) and less symptomatic patients with frequent exacerbation events (group C of the GOLD guidelines). The GOLD guidelines recommend LAMA + LABA as the first choice for more symptomatic patients at high risk of exacerbation (group D of the GOLD guidelines).[6]

Areas in Need of Future Study

Identifying the best combination of therapies among the LAMA + LABA class is needed. Longer-term follow-up data would be beneficial, especially to identify the effects of specific therapies on serious adverse events and mortality. Whether blood eosinophil level can be used to identify the best therapy for individual patients should be further investigated.[7]

ARTICLE INFORMATION

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