EDITORIAL

Another Choice for Prevention of COPD Exacerbations

James F. Donohue, M.D.

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines[1] recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as first-line therapy for patients with chronic obstructive pulmonary disease (COPD) who have a risk of exacerbation. The precise role of a combination of a LABA plus a LAMA in fixed doses in the prevention of COPD exacerbations is unclear. Previous studies have shown a LABA–LAMA regimen to be a preferred approach for symptomatic nonexacerbating COPD, especially among patients in GOLD group B (i.e., those who have low risk and a high symptom burden), but the role of a LABA–LAMA regimen in patients with a history of COPD exacerbations has not been studied until now.

The FLAME trial, now reported in the *Journal* by Wedzicha et al.,[2] compares a LABA–inhaled glucocorticoid regimen with a LABA–LAMA regimen for the prevention of COPD exacerbations of all severities. The exacerbations, which were defined according to the criteria of Anthonisen et al.,[3] were categorized as mild (involving symptoms lasting for >2 days but not leading to treatment with systemic glucocorticoids or antibiotic agents), moderate (leading to treatment with systemic glucocorticoids, antibiotics, or both), and severe (leading to hospitalization, as well as treatment with systemic glucocorticoids, antibiotics, or both). The LABA–LAMA regimen of indacaterol–glycopyrronium showed not only noninferiority but also superiority to the LABA–inhaled glucocorticoid regimen of salmeterol–fluticasone in reducing the rate of exacerbations; the rate was 11% lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group. Furthermore, a blood eosinophil count of 2% or higher[4] was not a useful clinical biomarker in identifying patients who are likely to have a response to a LABA–inhaled glucocorticoid regimen. Finally, the use of inhaled glucocorticoids has been associated with an increased risk of pneumonia, and in the FLAME trial, there was a significant between-group difference in the rate of pneumonia episodes (3.2% in the indacaterol–glycopyrronium group vs. 4.8% in the salmeterol–fluticasone group).

The combination of two bronchodilators, such as a LABA and a LAMA, would be expected to produce more robust effects on lung function than would a LABA–inhaled glucocorticoid regimen among patients with symptomatic nonexacerbating COPD. In one trial,[5] indacaterol–glycopyrronium was superior to salmeterol–fluticasone in improving the pretreatment trough forced expiratory volume in 1 second (FEV_1), and the area under the curve for FEV_1 from 0 to 4 hours at 26 weeks. In another trial,[6] a LABA–LAMA regimen of inhaled vilanterol–umeclidinium had a greater effect than did salmeterol–fluticasone in improving the trough FEV_1 and the weighted mean area under the curve for FEV_1 from 0 to 24 hours. However, in these trials, despite the improvement in lung function, there was less convincing evidence for the superiority of a dual-bronchodilator regimen with respect to patient-reported outcomes, such as the total score on the St. George's Respiratory Questionnaire, the use of rescue medication, and the transitional dyspnea index score.

Does it make sense to switch patients from a LABA–inhaled glucocorticoid regimen to a LABA–

LAMA regimen on the basis of the improvement in lung function and the lower exacerbation rates? Are there identifiable subgroups of patients for whom a regimen including an inhaled glucocorticoid would be a better treatment? Previous observational data have shown that therapy including an inhaled glucocorticoid was associated with a greater reduction in exacerbation rates than was LAMA therapy or placebo among patients with a blood eosinophil count of 2% or higher (found in 57 to 73% of the population).[4] In the FLAME trial, there was no between-group difference in the exacerbation rate among patients with a blood eosinophil count of 2% or higher or among those with a count lower than 2%. The authors mentioned that the results were the same in subgroups defined according to multiple eosinophil counts but did not provide the data. In the WISDOM (Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management) trial,[7] inhaled glucocorticoids were withdrawn in half the patients who were receiving triple therapy with a LABA, a LAMA, and an inhaled glucocorticoid; a post hoc analysis that was performed after withdrawal of the inhaled glucocorticoids was complete[8] showed that rates of moderate and severe exacerbations had increased among patients who had a blood eosinophil count of 4% or higher or an absolute eosinophil count of at least 300 cells per microliter. I think the final word on the use of blood eosinophil count as a predictor of response to inhaled glucocorticoids is not yet established.

Is increased mortality a concern when switching from a LABA–inhaled glucocorticoid regimen to a LABA–LAMA regimen, especially among patients with severe COPD? In the INSPIRE (Investigating New Standards for Prophylaxis in Reduction of Exacerbations) trial,[9] the mortality associated with a LAMA alone (6%) was higher than the mortality associated with a LABA plus an inhaled glucocorticoid (3%). In a population-based longitudinal cohort study, new use of a LABA–inhaled glucocorticoid regimen was associated with a moderately lower risk of death or hospitalization than was new use of a LABA alone.[10] We do not know the relevance of that finding to a LABA–LAMA regimen, such as the regimen used in the FLAME trial, in which no between-group difference in mortality was seen. Some have raised concerns about the removal of inhaled glucocorticoids from triple therapy for patients with very severe COPD, especially because such patients had a loss of lung function (decrease in trough FEV_1 of 40 ml) during the first 3 months after glucocorticoids were removed from the regimen in the WISDOM trial.[8] One advantage of the FLAME trial is that it includes patients with severe disease (2514 patients in GOLD group D [i.e., those who have high risk and a high symptom burden] and 256 patients with very severe disease according to the 2011 GOLD staging system [i.e., those with an FEV_1 of <30% of the normal value]).

Physicians who treat patients with COPD should continue to use guidelines to determine the appropriate regimen for the various phenotypes of COPD. The FLAME trial shows that use of a LABA–LAMA regimen appears to be safe and efficacious with respect to a wide variety of outcomes, including exacerbation rate, lung function, and health status. However, does the FLAME trial provide sufficient data to support the use of a LABA–LAMA regimen over the use of a LABA–inhaled glucocorticoid regimen in patients in GOLD group C or D (i.e., high-risk patients) who have a history of exacerbations? The FLAME trial seems to indicate that the answer is yes. More trials — especially trials that have a longer duration, include more patients with severe disease and coexisting conditions, and examine additional biomarkers — are needed before we can be sure that the FLAME trial has cast a new light on the prevention of COPD exacerbations.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Division of Pulmonary Diseases and Critical Care Medicine, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill.

This article was published on May 15, 2016, at NEJM.org.

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease. 2015 (http://www.goldcopd.org).
2. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol–glycopyrronium versus salmeterol–fluticasone for COPD. N Engl J Med. DOI: 10.1056/NEJMoa1516385.
3. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.
4. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD. Thorax 2016;71:118-25.
5. Zhong N, Wang C, Zhou X, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in

patients with COPD. Int J Chron Obstruct Pulmon Dis 2015;10:1015-26.
6. Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. Respir Med 2015;109:870-81.
7. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med 2014;371:1285-94.
8. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med 2016 April 7 (Epub ahead of print).
9. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19-26.
10. Gershon AS, Campitelli MA, Croxford R, et al. Combination long-acting β-agonists and inhaled corticosteroids compared with long-acting β-agonists alone in older adults with chronic obstructive pulmonary disease. JAMA 2014;312:1114-21.
DOI: 10.1056/NEJMe1604444