New Treatment Approaches and Prognostic Biomarkers for Advanced Chronic Obstructive Pulmonary Disease and Potential Associated Cardiovascular Risks

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Hastie AT, et al.; SPIROMICS Investigators. Association of Sputum and Blood Eosinophil Concentrations with Clinical Measures of COPD Severity: An Analysis of the SPIROMICS cohort. *Lancet Respir Med* (1)

Reviewed by Omar Khorfan

Chronic obstructive pulmonary disease (COPD) has been traditionally characterized by increased concentrations of neutrophils, macrophages, proteases, IL-6 and -8, and T-helper cell type 1 cytokines, whereas asthma has been characterized by increased concentrations of eosinophils and T-helper cell type 2 cytokines (1). This paradigm has shifted in recent years, and COPD and asthma are now viewed as heterogeneous with respect to symptoms, physiology, and response to treatments. This has driven investigators to identify subpopulations of patients with specific phenotypes for which treatment can be tailored.

The ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) study reported that in COPD, sputum neutrophil concentrations were weakly associated with lung function and health status but not associated with exacerbations, emphysema, or systemic inflammation (2). Other COPD studies have reported that increased eosinophils in both blood and sputum are associated with respiratory exacerbations and greater hyperinflation (3, 4). Trials aimed at targeting eosinophils in patients with COPD have shown that they play an important yet not completely understood the role in the pathogenesis of COPD (5, 6).

This multicenter observational cohort study conducted by Hastie and colleagues sought to assess whether high eosinophil

concentrations in either sputum or blood were associated with a severe COPD phenotype, including greater exacerbation frequency, and whether blood eosinophils were predictive of sputum eosinophils (1). Data were obtained from 2,737 patients from the SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) cohort who had COPD and were between 40 and 80 years of age with a history of smoking at least 20 pack-years. Blood eosinophil counts from 2,499 patients (1,262 patients with low counts [<200 cells/ μ L] and 1,237 with high counts [≥ 200 cells/ μ L]) and sputum eosinophils from 827 patients (656 patients with low counts [$<1.25\%$] and 171 patients with high counts [$\geq 1.25\%$]) were available for analysis.

Study results showed a significantly lower median FEV₁ percent predicted in patients with a high sputum eosinophil count than in patients with a low sputum eosinophil count both before and after bronchodilation (65.7% vs. 75.7%, $P < 0.0001$, and 77.3% vs. 82.9%, $P = 0.001$, respectively). Patients in the high sputum eosinophil group experienced more exacerbations that required corticosteroid treatments than patients in the low sputum eosinophil group (32 [19%] of 171 vs. 66 [10%] of 656; $P = 0.002$) as well as a higher proportion of patients with severe exacerbations requiring an emergency department visit (22 [13%] vs. 52 [8%] of 656; $P = 0.044$). In addition, patients in the high eosinophil group also exhibited an increase in airway wall thickness (0.02-mm difference; $P = 0.032$) and increased wheezing ($P = 0.018$) but no increase in COPD exacerbations ($P = 0.35$). The researchers found a significant association between blood eosinophil counts and sputum eosinophil counts (correlation coefficient $r = 0.178$; $P < 0.0001$) with a weak receiver operating characteristic and area under the curve of 0.64. The high blood eosinophil group had

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slightly increased airway wall thickness (0.02-mm difference; $P = 0.032$), higher St. George's Respiratory Questionnaire symptom scores ($P = 0.037$), and increased wheezing ($P = 0.018$), but no evidence of an association with COPD exacerbations ($P = 0.35$) or other indices of COPD severity.

To our knowledge, this is the largest prospective study to have investigated sputum and blood eosinophils and associations with clinical outcomes in patients with a range of COPD disease severities. The SPIROMICS cohort that was studied included former and current smokers (at least 20 pack-years) who were stratified by mean blood and sputum eosinophil counts. The population had a relatively low exacerbation rate, and of those studied with an available blood or sputum sample, only 20% to 25% had one or more exacerbations in the previous year. The study concluded that a high sputum eosinophil count ($\geq 1.25\%$) was a superior biomarker for identifying patients at a higher risk for more severe COPD, more frequent exacerbations, and increased emphysema by quantitative computed tomography than a blood eosinophil count. A higher blood eosinophil count alone, however, was not found to be a significant predictor of COPD exacerbations unless combined with a high sputum eosinophil count or a history of exacerbations.

One limitation of the study was that, in patients who had sputum samples, a large majority had mild to moderate COPD (patients with post-bronchodilator FEV₁ percent predicted $< 35\%$ did not have sputum induction for safety reasons). Another limitation was the difficulty of accurate sputum analysis, which requires training for induction and processing and is not as readily available as blood eosinophil levels. Finally, it is important to delineate the difference between the increased risk of exacerbations in relation to blood and sputum eosinophils and response to therapy. Target eosinophil concentrations might need to be different depending on the outcome that is to be modified, whether aiming to decrease exacerbation risk or relieve symptoms once an exacerbation has started. Nevertheless, the findings from this study should be considered in the design of therapeutic trials that target eosinophilic inflammation in COPD. ■

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Reviewed by Samer Alsamman

There are an increasing number of long-acting β -agonist–long-acting muscarinic antagonist (LABA–LAMA) combination inhalers available on the market for COPD; however, their role and effectiveness in the management of COPD and the prevention of exacerbations has not been clearly established. The FLAME (Indacaterol–Glycopyrronium versus Fluticasone–Salmeterol for COPD Exacerbations) trial published in 2016 by Wedzicha and colleagues aimed to explore the precise role of a combination of LABA–LAMA as first-line therapy in reducing COPD exacerbations of all severities for patients with COPD who were at risk of exacerbation as compared with an LABA–inhaled corticosteroid (LABA–ICS) combination (7).

The FLAME trial was a multicenter, randomized, double-blind, double-dummy, parallel-group, noninferiority trial comparing the efficacy of a LABA–LAMA (indacaterol–glycopyrronium) with a LABA–ICS (salmeterol–fluticasone) regimen in decreasing the annual rate of COPD exacerbations (7). A total of 3,362 patients were enrolled from July 2013 through September 2015 across 356 centers in 43 countries. Patients 40 years of age or older who had symptomatic moderate to severe COPD, grade 2 or higher on the modified Medical Research Council scale, and at least one exacerbation during the previous year for which they received treatment were enrolled. The annual rate of all COPD exacerbations was 11% lower in the LABA–LAMA group than the LABA–ICS group (3.59 vs. 4.03; rate ratio, 0.89 per 100 patient-days; 95% confidence interval [CI], 0.83–0.96; $P = 0.003$). Those treated with LABA–LAMA also had a longer time to first exacerbation than did the LABA–ICS group (71 d; 95% CI, 60–82 d vs. 51 d; 95% CI, 46–57 d; hazard ratio, 0.84; 95% CI, 0.78–0.91; $P < 0.001$) and lower annual rate of moderate to severe COPD exacerbations requiring the use of healthcare services (0.98; 95% CI, 0.88–1.10 vs. 1.19; 95% CI, 1.07–1.32; $P < 0.001$). Exacerbation rates remained lower in the LABA–LAMA group regardless of the eosinophil count at baseline. Compared with baseline, there was a greater change in FEV₁ in the LABA–LAMA group at Week 52 (62 ml; $P < 0.001$). In addition, at Week 52, the percentage of patients who had a clinically important decrease of at least 4 points in the total score on the St. George's Respiratory Questionnaire for COPD was significantly higher in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (49.2% vs. 43.7%; odds ratio, 1.30; 95% CI, 0.4–2.1; $P < 0.001$). The incidence of pneumonia was also lower in the indacaterol–glycopyrronium group than the salmeterol–fluticasone group (3.2% vs. 4.8%; $P = 0.02$).

This study is in harmony with the ILLUMINATE (NCT01315249) (8) and LANTERN (NCT01709903) (9) trials, which helped to inform the updated Global Initiative for Chronic Obstructive Lung Disease statement in 2017 recommending LABA–LAMA as first choice therapy for patients with symptomatic COPD (10). The FLAME trial is the first clinical trial to prove the effectiveness of a LABA–LAMA over LABA–ICS combination in reducing the annual risk of COPD exacerbation

and improving quality of life. The study was well designed, multicenter, and involved a large sample of patients. It targeted patients who had moderate to severe symptoms, with a modified Medical Research Council scale score of grade 2 or higher. Exacerbations were carefully monitored, with daily symptom recording allowing the detailed capture of exacerbations during the study and their grouping on the basis of severity. The FLAME trial prospectively studied the relationship between blood eosinophil counts and exacerbation outcomes. The exacerbation rate remained lower in the indacaterol-glycopyrronium arm regardless of the baseline blood eosinophil count. These data, however, should be interpreted in the context of the WISDOM (Withdrawal of Inhaled Steroid during Optimized Bronchodilators Management) study (11), which showed that withdrawal of ICS increased the rate of moderate and severe exacerbations among individuals with blood eosinophil count of 4% or more or absolute eosinophil count of at least 300 cells/ μ L. The mechanisms responsible for the increased benefit of LABA-LAMA combinations over LABA-ICS in decreasing exacerbations are likely related to its effect in alleviating lung hyperinflation and reducing inflammation and excessive mucus production, leading to decreased symptom severity (8).

One potential limitation of this study is that patients who were treated with an LABA-ICS combination before enrollment and then assigned to the LABA-LAMA group may have had withdrawal effects from the cessation of their ICS-containing regimen that could have resulted in an increase in exacerbations. The authors state, however, that there was no evidence that patients who had been receiving ICS before the trial withdrew from the trial during the run-in period at higher rates than did patients who did not and that overall exacerbation rates during the run-in period were low. An additional limitation is that only 19.3% of the study population had two or more exacerbations in the previous year, and in this subgroup, the annual rate of exacerbations was not significantly lower with LABA-LAMA than with LABA-ICS. Patients with frequent exacerbations and high eosinophil counts are more likely to benefit from ICS-containing therapy than from therapies without ICS (12).

In conclusion, indacaterol-glycopyrronium showed not only noninferiority but also superiority to salmeterol-fluticasone in reducing the annual rate of COPD exacerbations. Recent studies have compared different combinations of inhaled therapy, including daily triple inhaled therapy LABA/LAMA/ICS, LAMA alone, LABA-ICS, and LABA-LAMA, and it has been shown that fixed triple therapy is more effective in exacerbation reduction than LAMA alone or LABA-ICS dual therapy (9, 11–13). Future trials, conducted over a longer duration and including more patients with severe disease, are needed comparing different inhaled therapy combinations to help guide clinicians in tailoring therapy on the basis of patient phenotypes. ■

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Wang MT, *et al.* Association of Cardiovascular Risk with Inhaled Long-Acting Bronchodilators in Patients with Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study. *JAMA Intern Med* (14)

Reviewed by Hawazin Abbas

The associations between cardiovascular disease (CVD) and inhaled long-acting bronchodilators in COPD are greatly debated (14). Current COPD guidelines recommend dual long-acting bronchodilator therapy for patients who are both symptomatic and at risk for exacerbation (10). Several recent studies have assessed the therapeutic benefits of LABAs and LAMAs; however, few studies have examined the risk of CVD associated with these inhaled therapies.

The TORCH (Toward a Revolution in COPD Health) (15) trial evaluated salmeterol-fluticasone therapy in 6,112 randomized subjects with COPD with a planned follow-up of 3 years. The primary causes of death in this study were cardiac and pulmonary. More than 50% of the enrolled patients with COPD were already on long-acting bronchodilators to start with, which limits the assessment of the causal relationship between these inhalers and adverse events. On the other hand, more recent trials, such as the FLAME trial by Wedzicha and colleagues, showed that using LABA-LAMA combinations decreased the rate of COPD exacerbation; however, they excluded patients with CVD and did not report adverse cardiovascular events during the 52-week enrollment period (7).

This study by Wang and colleagues investigated the relationship between LAMA and LABA combination use and the risk of CVD using a large database from the Taiwan National Health Insurance Repository (14). The study used a nested case-control research design and screened records from January 2007 to December 2011 using diagnostic codes and medication used. Patients aged 40 years or more with COPD without prior use of inhaled LAMA or LABA were included in the study. A total of 280,000 patients with COPD were enrolled and followed for 2 years after background checking for symptoms of CVD, cerebrovascular accident, arrhythmia, and congestive heart failure

1 year before enrollment. The remaining patients were divided into two groups: the case group of 37,719 patients with CVD (mean age, 75.6 yr; 71.6% men) and the control group of 146,139 patients (mean age, 75.2 yr; 70.1% men). The cardiovascular event was defined by emergency room visits with a primary diagnosis of a CVD, arrhythmia, or ischemic stroke. The trial excluded patients who started treatment for CVD or had coronary artery disease or congestive heart failure before the study. The researchers followed the patients' compliance by tracking the number of prescription refills of LAMA and/or LABA and emergency room visits for COPD exacerbation. The primary finding of this study was that new initiation of LABA and LAMA therapy was associated with an increased cardiovascular risk within 30 days of initiation. The incidence of CVD with new use of LABA was 1.4% versus 0.8% in control subjects and with new use of LAMA was 0.5% versus 0.3% in control subjects. After adjusting for all covariates, new initiation of LABA and LAMA therapy was associated with a 1.50-fold (95% CI, 1.35–1.67; $P < 0.001$) and a 1.52-fold (95% CI, 1.28–1.80; $P < 0.001$) increased cardiovascular risk within 30 days of initiation, respectively.

One of the theories behind the cardiovascular risk associated with using combined LABA and LAMA inhaled therapy in patients with COPD is that the treatment activates sympathetic β_2 adrenergic receptors and suppresses parasympathetic muscarinic-3 receptors, which could contribute to the CVD risk (11). Also, LABA and LAMA use in COPD has been observed to increase inflammatory cytokine levels, which might also play a role in the observed surge in CVD events (16).

This is the first study to identify new use of and duration since initiation of LABA and LAMA in COPD as important determinants of therapy-related CVD risk. The take-home message is that

in patients with COPD, the new administration of inhaled LABA and LABA needs close monitoring of cardiovascular symptoms, especially in the first 30 days of use. There are several limitations to note: first and foremost is the possibility of confounding by the indication for prescription of a new inhaler for which the indication may have been shortness of breath related to cardiovascular disease as opposed to COPD. Additional limitations include the lack of clear adjustment to potential confounders, such as smoking, alcohol use, underlying diseases or other comorbidities, which may affect both COPD and CVD; the use of older-generation inhaled LABAs and LAMAs, such as salmeterol, formoterol, and tiotropium, without including the new LABA and LABA generations; and, finally, that the assessment of compliance to treatment depended only on the rates of the prescription refills, which does not confirm the actual or effective use of these medications. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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