Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Letter to the Editor

Waiting for Actionable Evidence: Roflumilast or Azithromycin?

Jerry A. Krishnan, MD, PhD[1] Richard K. Albert, MD[2] Stephen I. Rennard, MD[3] on behalf of the RELIANCE study

Abbreviations: chronic obstructive pulmonary disease, **COPD**; long-acting muscarinic antagonist, **LAMA**; long-acting beta2-agonist, **LABA**; inhaled corticosteroid, **ICS**; American College of Chest Physicians, **ACCP**; Canadian Thoracic Society, **CTS**; randomized clinical trial, **RCT**; U.S. Food and Drug Administration, **FDA**; U.S. Veterans Health Administration Corporate Data Warehouse, **VHA CDW**; hazard ratio, **HR**; confidence interval, **CI**; Patient-Centered Outcomes Research Institute, **PCORI**

Funding Support: Not applicable
Date of Acceptance: November 11, 2021 | **Published Online Date:** November 15, 2021
Citation: Krishnan JA, Albert RK, Rennard SI, on behalf of the RELIANCE study. Waiting for actionable evidence: roflumilast or azithromycin? *Chronic Obstr Pulm Dis.* 2022;9(1):1-3. doi: https://doi.org/10.15326/jcopdf.2021.0272

1. University of Illinois Chicago, Chicago, Illinois, United States
2. Anschutz Medical Campus, University of Colorado, Denver, Colorado, United States
3. University of Nebraska Medical Center, Omaha, Nebraska, United States

Keywords:
roflumilast; azithromycin; RELIANCE; chronic obstructive pulmonary disease

Address correspondence to:
Jerry A. Krishnan, MD, PhD
Breathe Chicago Center
Division of Pulmonary, Critical Care, Sleep, and Allergy
University of Illinois Chicago
1220 S. Wood Street, 3rd floor
Chicago, IL 60608
Phone: (312) 413-0637
Email: jakris@uic.edu

Dear Editor

Chronic obstructive pulmonary disease (COPD) exacerbations are triggered by complex responses of the host to viruses, bacteria, and/or inhaled irritants that contribute to airway inflammation. Some patients with COPD, particularly individuals who continue to smoke or have ongoing exposure to inhaled irritants, also have associated chronic bronchitis. Patients with more frequent or severe COPD exacerbations lose lung function more quickly, do not recover to the pre-exacerbation levels, have a greater decline in health status and higher likelihood of becoming housebound.[1] Chronic bronchitis, defined as chronic cough and sputum, identifies a subgroup of people with COPD who have an elevated risk of exacerbations and death.[2]

Even with inhaled maintenance therapy (e.g., inhaled long-acting muscarinic antagonist [LAMA], inhaled long-acting beta2 agonists [LABA] combined with inhaled corticosteroids [ICS], or inhaled ICS/LABA/LAMA), many patients continue to have COPD exacerbations. In recognition of the growing burden attributable to COPD exacerbations, the American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS) published the first evidence-based guidelines[3] devoted to preventing exacerbations in 2015. In patients with COPD who continue to have exacerbations despite inhaled maintenance therapy, the 2015 ACCP/CTS guidelines suggest treatment escalation with long-term oral azithromycin therapy, a macrolide with immunomodulatory, anti-inflammatory, and anti-bacterial effects that reduced the risk of COPD exacerbations in randomized clinical trials (RCTs) when compared to placebo. Post-hoc analyses of data from a RCT suggests that the salutatory benefits of azithromycin on COPD exacerbations may be largely driven by benefits among those who formerly smoked.[4] However, RCTs of azithromycin in COPD to confirm or exclude the potential for effect modification by smoking status have not yet been conducted. Azithromycin was approved in 1991 by the U.S. Food and Drug Administration (FDA) to treat mild to moderate infections caused by susceptible bacteria; long-term use of oral macrolides to prevent COPD exacerbation is an example of an "off-label" use of an FDA-approved medication.

Roflumilast, a long-acting oral selective phosphodiesterase-4 inhibitor with anti-inflammatory

effects,[5] was approved by the FDA in 2011 as a treatment to reduce the risk of COPD exacerbations in patients with COPD associated with chronic bronchitis. The FDA-approved indication is limited to patients with COPD associated with chronic bronchitis, because the protective effects of roflumilast compared to placebo on exacerbations appear to be specific to this subgroup of patients with COPD.[6] The 2015 ACCP/CTS guidelines recommend roflumilast as an option for treatment escalation in the subgroup of patients with COPD who have associated chronic bronchitis. The 2017 European Respiratory Society/American Thoracic Society guidelines[7] and the 2021 Global Initiative for Chronic Obstructive Lung Disease report[8] offer recommendations for treatment escalation with long-term azithromycin and roflumilast in COPD similar to the 2015 ACCP/CTS guidelines.

To date, there are no published RCTs directly comparing the relative benefits and harms of treatment escalation with long-term oral azithromycin versus roflumilast in patients with COPD with associated chronic bronchitis; so, patients, clinicians, and others do not have sufficient evidence to guide decision-making about which medication to try first. The authors of this letter are conducting a comparative effectiveness study using a randomized trial design (RELIANCE study) that is funded by the Patient-Centered Outcomes Research Institute to fill this evidence gap (ClinicalTrials.gov Identifier: NCT04069312).[9]

It is in this context that the study by Lam J et al provides interesting new information.[10] The authors used an observational comparative effectiveness design to study patients in the U.S. Veterans' Health Administration Corporate Data Warehouse (VHA CDW) who had at least 1 inpatient or 2 outpatient visits for a COPD exacerbation between 2011 to 2017, received concurrent inhaled LABA/LAMA treatment for at least 30 days, and a subsequent, new prescription for 30 or more days of roflumilast or azithromycin. The primary analyses focused on 1302 patients who were prescribed long-term roflumilast and 2573 patients prescribed long-term azithromycin. The mean treatment duration was about 1 month longer in the azithromycin group (243 days versus 273 days) and cross-over rates between roflumilast and azithromycin were approximately 12% in both directions. In multi-variable regression models that account for baseline characteristics available in the VHA CDW, roflumilast was associated with a higher risk of death (hazard ratio [HR] 1.16, 95% confidence interval [CI] 1.04 to 1.29). In analyses that included data about hospitalization within and outside of the VHA (data available in about half of the total study population), the risks of COPD-related and all-cause hospitalization were higher with roflumilast treatment (versus azithromycin; HR 1.21, 95% CI 1.05 to 1.41, and HR 1.23, 95% 1.09 to 1.38, respectively).

Importantly, the authors note that the VHA CDW did not contain information about chronic bronchitis, lung function, or tobacco use – factors that are associated with the baseline risk of COPD exacerbations, treatment response to roflumilast or azithromycin, or both. Since prescribing long-term roflumilast in the VHA is restricted to patients with COPD associated with chronic bronchitis (but such restrictions do not exist when prescribing long-term azithromycin in the VHA), it is very likely that comparisons of individuals with COPD treated with azithromycin versus roflumilast through the VHA using observational designs is subject to selection bias due to a higher proportion with chronic bronchitis in the roflumilast group. There may also be confounding due to differences in the proportion of patients with lower lung function or with current tobacco use in the azithromycin and roflumilast groups.

So where do we go from here? We could advocate for translating the findings by Lam et al into clinical practice now by sharing the results with patients, clinicians, and other decision-makers when considering options for treatment escalation in patients with COPD with associated chronic bronchitis. However, Lam and colleagues acknowledge the inherent limitations of their observational study design, and we agree with their conclusion that we should instead wait for the results of the ongoing RCT (i.e., RELIANCE).

Acknowledgements

The authors thank the Patient-Centered Outcomes Research Institute (contract # PCS-1504-30430). The statements in this report are solely the responsibility of the authors and do not necessarily represent the views of PCORI, the PCORI Board of Governors, or the PCORI Methodology Committee. We also thank the RELIANCE Executive Committee who reviewed an earlier version of this Letter to the Editor (Nina E. Bracken, MSN, ACNP-BC, Janet T. Holbrook, PhD, Elisha Malanga, BS, David M. Mannino, MD, FCCP, FERS, Richard A. Mularski, MD, MSHS, MCR, ATSF, FCCP, FACP, Jean Rommes, PhD, Gem Roy, MD, Elizabeth A. Sugar, PhD, and Robert A. Wise, MD).

References

1. Sapey E, Stockley RA. COPD exacerbations · 2: aetiology. *Thorax*. 2006;61(3):250-258. doi: https://doi.org/10.1136/thx.2005.041822

2. Kim V, Criner GJ. Chronic bronchitis and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2013;187(3):228-237. doi: https://doi.org/10.1164/rccm.201210-1843CI

3. Criner GJ, Bourbeau J, Diekemper RL, et al. Prevention of acute exacerbations of COPD: American College of Chest Physicians and Canadian Thoracic Society guideline. *Chest*. 2015;147(4):894-942. doi: https://doi.org/10.1378/chest.14-1676

4. Han MK, Tayob N, Murray S, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med*. 2014;189(12):1503-1508. doi: https://doi.org/10.1164/rccm.201402-0207OC

5. Beghè B, Rabe KF, Fabbri LM. Phosphodiesterase-4 inhibitor therapy for lung diseases. *Am J Respir Crit Care Med*. 2013;188(3):271-278. doi: https://doi.org/10.1164/rccm.201301-0021PP

6. Rennard SI, Calverley PM, Goehring UM, Bredenbröker D, Martinez FJ. Reduction of exacerbations by the PDE4 inhibitor roflumilast - the importance of defining different subsets of patients with COPD. *Respir Res*. 2011;12:18. doi: https://doi.org/10.1186/1465-9921-12-18

7. Wedzicha JA, Calverley PMA, Albert RK, et al. Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2017;50(3):1602265. doi: https://doi.org/10.1183/13993003.02265-2016

8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease, 2021 report. GOLD website. Published 2021. Accessed November 2021. https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf

9. Clinical Trials.gov. Roflumilast or azithromycin to prevent COPD exacerbations (RELIANCE). ClinicalTrials.gov website. Published August 2019. Updated November 2021. Accessed November 2021. https://clinicaltrials.gov/ct2/show/NCT04069312

10. Lam J, Tonnu-Mihara I, Kenyon NJ, Kuhn BT. Comparative effectiveness of roflumilast and azithromycin for the treatment of chronic obstructive pulmonary disease. *Chronic Obstr Pulm Dis*. 2021;8(4):450-463. doi: https://doi.org/10.15326/jcopdf.2021.0224