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Clinical Research in Practice: The Journal of Team Hippocrates

Volume 5 | Issue 1 Article 2

2019

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Recommended Citation
SANCHEZ N. Roflumilast does not decrease COPD exacerbations in adequately treated patients, but subgroup analysis allows for shared decision making. Clin. Res. Prac. 2019 Feb 6;5(1):eP1628. doi: 10.22237/crp/1549411200

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Clinical Research in Practice
The Journal of Team Hippocrates
VOL 5 ISS 1 / eP1628 / FEBRUARY 6, 2019
doi: 10.22237/crp/1549411200

# Roflumilast does not decrease COPD exacerbations in adequately treated patients, but subgroup analysis allows for shared decision making

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**ABSTRACT** A critical appraisal and clinical application of Martinez FJ, Rabe KF, Sethi S, et al. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting beta2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. *Am J Respir Crit Care Med*. Sep 1 2016;194(5):559-567. doi: 10.1164/rccm.201607-1349OC.

***Keywords***: *Roflumilast, COPD, RE(2)SPOND, corticosteroid*

## Clinical Context

A 58-year-old female presented with shortness of breath, productive cough, and wheezing for the past two days. She has a past medical history significant for a 30 pack-year smoking history and COPD, which was confirmed with Pulmonary Function Testing at an outside institution. The patient reports frequent hospitalizations, with 7-10 visits to the emergency room and multiple hospitalizations in the past year, all for the same symptoms of shortness of breath, cough, and wheezing.

The patient was admitted for treatment of her COPD exacerbation. Her medications included a Long Acting Beta Agonist (LABA), Long Acting Muscarinic Agonist (LAMA), and inhaled corticosteroid, with an albuterol inhaler as needed. Her acute exacerbation was treated with Duonebs (Ipratropium bromide/albuterol), antibiotics, and prednisone, with resolution of acute symptoms. Her history of frequent COPD exacerbations requiring hospitalization was severely impacting her quality of life, and she wanted to know if there was some way of preventing such frequent hospitalizations. The team debated if roflumilast would decrease her frequency of hospitalizations for COPD exacerbations, as there is conflicting evidence and opinions on the topic.

## Clinical Question

Is roflumilast effective in reducing the frequency of COPD exacerbations among patients with COPD despite treatment with inhaled corticosteroid/LABA/LAMA?

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**Clinical Research in Practice**
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VOL 5 ISS 1 / eP1628 / FEBRUARY 6, 2019
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## Research Article

Martinez FJ, Rabe KF, Sethi S, et al. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting beta2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. *Am J Respir Crit Care Med*. Sep 1 2016;194(5):559-567. doi: 10.1164/rccm.201607-1349OC

## Related Literature

A search for original studies was done using the keywords “roflumilast” and “copd” in PubMed. For each relevant article found, the references were reviewed for further original research studies that addressed the clinical question. A search including both keywords in the title yielded 57 sources. Of those, 13 were clinical trials.

Of the 13 clinical trials, two pooled data from multiple studies making them not original work appropriate for appraisal in this context.[1,2] These papers found a possible benefit in decreasing the frequency of COPD exacerbations. Four of the other studies focused on the physiological and functional benefits of roflumilast in improving PFT data or decreasing inflammation, but in doing so do not address the clinical question.[3-6] Three more studies were conducted in patient populations exclusively in Asia, the results of which cannot necessarily be translated to the patient population of my patient.[7-9] One study focused on cost effectiveness of roflumilast in Germany, which is neither the patient population nor the clinical question of this appraisal.[10] One study assessed the cardiovascular safety of roflumilast, which again is not included in the clinical question.[11] There was no increase in cardiovascular risk found. Two sources remained, both of which were actually study designs.[12,13] These designs led to the discovery of their corresponding large, multi-centered studies examining the effectiveness of roflumilast in reducing the frequency of COPD exacerbations in patients with frequent COPD exacerbations: “Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial,”[14] and “Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting b2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE2SPOND): A Randomized Clinical Trial.”[15] Both trials were conducted by the same investigators with similar protocols. The REACT trial showed no benefit with an intention to treat analysis. The RE2SPOND trial was chosen because it contained a larger sample size (2,354 in RE2SPOND versus 1,934 in REACT), but patient application should include information from both these trials.

## Critical Appraisal

The RE2SPOND study is a 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 4 trial, which examined the efficacy and safety of roflumilast added to inhaled corticosteroid (ICS)/LABA FDC therapy with or without LAMA. The primary outcome was the rate of moderate or severe COPD exacerbations per participant per year. The authors report that the analysis was done with stratification by LAMA use, but this was not a pre-defined outcome in the ClinicalTrials.gov registry (NCT01443845), making this highly suspicious for data dredging. In addition, this paper was sponsored by a pharmaceutical company and involved the active participation of pharmaceutical personnel, which also occurred in the REACT trial. This is cause for doubting the veracity of these research reports. Patients eligible to participate had to be at least 40 years old, with severe to very severe COPD, chronic bronchitis, had two or more exacerbations and/or hospitalizations in the past year, and were receiving ICS and LABA, with or without LAMA use for the past 3 months or longer. They could not have any changes in their medications throughout the randomization process. Randomization 1:1 ultimately assigned 1,178 participants to the treatment group who received roflumilast in addition to their other controller medications, and 1,176 participants to the group who received a placebo in addition to their other controller medications. The treatment was carried out for 52 weeks, in which time data was collected from all 380 sites across 17 countries, including number of hospitalizations and adverse events. All analyses included the intention to treat population.

Regarding the level of evidence, the RE2SPOND study can be classified as a level 2 study according to the Strength of Recommendation Taxonomy (SORT) guidelines.[16] This is due to the reservation related to the author’s bias described above. Additional strengths of this study include that it is a double-blind study, including concealed allocation, analyzed with the intention-to-treat population, with an adequate size (n=2,354) and follow-up.

In analyzing the effect size, there are a few numbers that are important. First is the relative risk (RR) of moderate to severe COPD exacerbation in the study as a whole, which is 0.92 (95% CI: 0.81-1.04). This means that roflumilast failed to show benefit. Figure 3 in the manuscript is unintelligible.

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One strength of this study is that the study design, including primary outcomes, number of patients, and statistical analysis, was published prospectively in August 2016.[13] This ensures transparency throughout the process, and eliminates the idea of a publication bias, as the methods, analysis, and primary outcomes were put forth before data collection.

Another strength is the foresight evident in the exclusion criteria. Patients were excluded from the study if they had other lung diseases, moderate to severe liver impairment, HIV or hepatitis, asthma, cancer within 5 years, alpha1 antitrypsin deficiency, cardiovascular conditions, elevated QTc, elevated BMI, had used theophylline within 2 weeks, or had pulmonary rehabilitation within 3 months. Any one of these conditions could be a confounding variable, and excluding these patients from consideration in the study was an important step in limiting bias. It does however limit the generalizability of the findings.

Table 1 in the study laid out the results of randomization, including age, sex, race, and BMI. It also included pertinent information like smoking status, cigarette pack-years, COPD grading, functional measures, number of hospitalizations, and LAMA use. All of these measures were very similar between the two groups.

With the level of evidence and strengths of the study in mind, there are still some limitations to the study. The process of patient recruitment was not laid out in detail. Also, a significant difference in drop-out rate was observed in the roflumilast group versus the control group (337 in treatment versus 254 in control). However, the intention-to-treat analysis is an attempt to eliminate this bias. Also, itemization of adverse events, including diarrhea, weight loss, and headache, organized by treatment group in Table 2 further shows transparency as a strength of this study.[15] There is a clinically increased risk of diarrhea in the treatment group.

Another potential bias to consider relates to how this study was funded. Daliresp® is the brand name of Roflumilast, and is owned by the pharmaceutical company AstraZeneca. In the disclosures section of this study design, many of the authors disclose that they have received funds from AstraZeneca.

## Clinical Application

The RE2SPOND trial failed to show a decrease in COPD exacerbations within the first year." [15]

The patient described above would have fit in with this trial. She met the requirements of the inclusion criteria and did not meet any exclusion criteria. In fact, she would have fit in the subgroup of patients with more than 3 exacerbations in the year before starting roflumilast, since she had 7-10 in the year prior. Subgroup analysis showed benefit from roflumilast therapy by reducing frequency of hospitalizations. The patient specifically wanted something to decrease her number of hospitalizations; however, we cannot justify a strong recommendation. The patient could trial the drug and see if she experiences any adverse events with the medication, including diarrhea, weight loss, and headache, as these were noted to be significantly higher in patients receiving treatment with roflumilast. This is a good case for shared decision making, given the poor quality evidence available.

Learning points:

1. Roflumilast is an effective pharmacologic option to decrease frequency of hospitalizations for patients with COPD who are already treated with ICS and LABA, with or without LAMA, and who still experience more than 3 hospitalizations in a year.
2. Roflumilast may cause adverse events, including nausea, diarrhea, weight loss, insomnia, and headache.
3. Considering its efficacy and adverse events, joint decision-making and patient education are vital parts of prescribing roflumilast.

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VOL 5 ISS 1 / eP1628 / FEBRUARY 6, 2019
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