Peer Review File

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Reviewer A

How was the diagnosis of Bronchiectasis confirmed?

Reply: Thank you for the question. The patients with bronchiectasis was identified using the ICD-10 codes (J47 and Q33.4). This operational diagnosis of bronchiectasis has been used in the epidemiology studies for the incidence of bronchiectasis (Reference: Respir Med. 2019 May;151:121-127., BMC Pulm Med. 2020 Feb 18;20(1):45.). We added the references in the **Methods** section as below.

Methods

...

Variables

... regular inhaled treatments, and oral medications. A history of bronchiectasis was identified using the ICD-10 codes (J47 and Q33.4) (17, 18). A history of chronic bronchitis was ...

Did you exclude tuberculosis patients, and if so, how?

Reply: Thank you for the question. Patients with a history of TB were not excluded from our study. Unfortunately, we could not obtain information regarding whether tuberculosis had newly occurred during the observation period. Also, we lacked information to separately identify patients with a history of TB before the observation period.

Is the statin use reflective of cardiac disease? Do you have details?

Reply: Thank you for the insightful question. In fact, we investigated whether there could be added benefits in reducing acute exacerbation when statins and roflumilast are used simultaneously. However, as mentioned by the reviewer, the use of statins is likely to be associated with dyslipidemia or cardiac disease, and as a result, roflumilast may

have the potential to be more beneficial in patients with cardiovascular comorbidities.

In a pooled analysis of 14 clinical trials, it was observed that MACEs (Major Adverse Cardiovascular Events) were significantly lower for roflumilast when compared to placebo (Reference: Chest 2013;144:758–765). However, there was no significant difference in MACEs between the patients with baseline cardiovascular comorbid conditions and those without. Additionally, no significant association was found between the development of MACEs and the incidence of acute exacerbations. Therefore, the evidence suggesting that roflumilast can reduce acute exacerbations in patients with COPD and cardiac disease is currently lacking.

Unfortunately, we did not consider operational definitions for individual comorbid diseases other than the Charlson Comorbidity Index (CCI) during the study design phase. Consequently, specific information regarding cardiac disease is not currently available. To address the reviewer's question, it is necessary to explore the potential benefits of roflumilast in various cardiac diseases by providing detailed definitions for each condition.

Multimorbidity: there are indications that ROF worls on GLP-1. Do you have data on the efficacy in your population that also have diabetes and/or metabolic syndrome?

Reply: Thank you for the interesting comment. As the reviewer mentioned, roflumilast can elevate GLP-1 levels in patients with diabetes or metabolic syndrome. The mechanism of elevated GLP-1 levels or improved insulin sensitivity by roflumilast has been explained by weight loss, which is a well-known side effect of roflumilast (Reference: Int J Chron Obstruct Pulmon Dis. 2016; 11: 81–90). On the other hand, the efficacy of roflumilast on acute exacerbation of COPD has been understood as a result of decreased chronic systemic inflammation. Decreased chronic systemic inflammation can also improve insulin sensitivity. However, at present, there is limited evidence to suggest that there may be improvement in acute exacerbation through the GLP-1 pathway.

Unfortunately, as information regarding metabolic syndrome is not currently available

in our dataset, we were unable to analyze the effect of roflumilast in relation to diabetes mellitus and/or metabolic syndrome. Although our investigation was limited in scope, we examined whether there was a significant difference in the benefit of roflumilast based on the presence or absence of ICD-10 codes for diabetes. However, we found no significant difference in the reduction of acute exacerbations with roflumilast based on the presence of diabetes (**Table A**).

Table A. Subgroup analysis according to diabetes

Subgroup	Adjusted HR (95% CI)	P-value	P-value for interaction
Diabetes without chronic complication			0.6030
Yes	2.585 (2.380-2.807)	<0.001	
No	2.618 (2.529-2.710)	<0.001	
Diabetes with chronic complication			0.9281
Yes	2.676 (2.281-3.140)	<0.001	
No	2.606 (2.522-2.692)	<0.001	

What about weight loss on your population?

Reply: Thank you for the important question. It is known that weight loss can occur as an adverse event of roflumilast (reference: Lancet. 2012 Feb 25;379(9817):710-1). Unfortunately, our study lacks information on weight, making it difficult to confirm any weight loss associated with roflumilast.

Any datails on side effects in general?

Reply: Thank you for the question. The primary objective of this study was to identify potentially better-responsive subgroups to roflumilast, and as such, we did not separately investigate general side effects. Roflumilast's most common side effects include respiratory infections and gastrointestinal issues. However, many of these cases are not severe enough to warrant hospital visits, which poses limitations when analyzing the data from claim records.

How do you view the fact that less than 1 % of the population in on ROF?

Reply: Roflumilast is primarily used as an adjunct therapy in COPD patients who do not respond adequately to standard treatments like ICS/LABA/LAMA or LABA/LAMA, particularly in cases of severe COPD with chronic bronchitis and FEV1<50%. In addition to this indication, roflumilast has been prescribed in real-world clinical situations when bronchodilators could not be used sufficiently. It is worth noting that the indication for roflumilast is limited to a small proportion of COPD patients.

However, our study suggests that the clinical indication for roflumilast could potentially be expanded. Our findings indicate that roflumilast may offer benefits in various clinical phenotypes. A recent randomized controlled trial of ensifentrine, a PDE3/PDE4 inhibitor, demonstrated efficacy in a broader range of COPD patients, suggesting a wider clinical indication (reference: Am J Respir Crit Care Med. 2023 Aug 15;208(4):406-416). Particularly, in COPD patients with bronchiectasis where it's challenging to use ICS, roflumilast could be a favorable option for reducing exacerbations.

Would your data lead to the recommendation to use the drug earlier in the cours of COPD?

Reply: Thank you for this important question. According to our findings, roflumilast appears to be more effective in elderly COPD patients compared to young COPD patients. It also seems to be more beneficial in patients with a higher comorbidity burden and pulmonary comorbidities such as bronchiectasis or chronic bronchitis. Additionally, it showed greater effectiveness in patients with a history of acute exacerbations and when used in combination with treatments that include ICS. This suggests that roflumilast may offer more clinical benefits in COPD patients characterized by more severe airway inflammation.

Considering the regular inhaled treatment profiles of the included patients, it becomes apparent that our study included a higher proportion of patients with COPD in the early stages of the disease compared to previous clinical trials for roflumilast. In subgroup

analysis, our study suggests that roflumilast may be helpful even in COPD patients who use only mono-bronchodilator therapy. Therefore, even in early-stage COPD with pronounced airway inflammation, there may be potential benefits to using roflumilast.

We revised the **Discussion** section as follows.

Discussion

…

… *These findings suggest that roflumilast provides greater clinical benefits to COPD patients with more severe airway inflammation. Notably, our study included more patients with COPD in the early stages of the disease, while previous clinical trials for roflumilast included patients with more severe or advanced stages of COPD. Therefore, even in patients with milder severity or at earlier stages of COPD with pronounced airway inflammation, roflumilast can be considered to reduce acute exacerbations in COPD patients with specific clinical phenotypes.*

…

You advocate to use in subgroups which seems logic but would you you recommend in practical terms of how such a stratification should be performed? Any ideas of a panel of criteria? Biomarkers!?

Reply: Thank you for the interesting suggestion. In our study, we calculated the ratio of HR within each subgroup using adjusted HRs with different covariables. Consequently, we can suggest that roflumilast independently reduces moderate-to-severe exacerbations in patients with various phenotypes, such as older patients (age ≥50), patients with more comorbidities, patients with a history of moderate-to-severe exacerbations in the previous year, patients with bronchiectasis or chronic bronchitis, and patients who use inhaled therapy, methylxanthine, or statins. Stratifying patients expected to benefit from roflumilast is indeed feasible through the development of a predictive model and validation in an external cohort database. However, due to the nature of our database, it lacks clinical variables necessary for the development of a refined predictive model for moderate-to-severe exacerbations. Furthermore, our study

does not include a separately prepared validation cohort, making it challenging to provide a definitive response to the reviewer's question. Therefore, addressing the reviewer's inquiry may be achievable through further research.

Reviewer B

This very large retrospective study essentially confirms data derived from RCT studies and is therefore confirmatory in nature. Using sophisticated analytic methods, the authors are able to conclude that roflumilast reduced the incidence of AECOPD in those settings in which exacerbations are most common, as expected, and especially when bronchiectasis is present. There are other useful tidbits such as the documentation that prescribers frequently used the drug contrary to the recommendation of use of full bronchodilator and anti-inflammatory therapy prior to its use. When the latter is done roflumilast's additional therapeutic effect is substantially less. Clinicians still must be encouraged to rely on findings from RCTs to balance therapeutic effects and limiting side effects, which are not trivial with this drug. The presentation of the findings is dense and, in my opinion, difficult to follow for clinicians without statistical expertise. Better explanations of some key finding would make the Ms more readable.

Reply: Thank you for the positive assessment of the study's value in confirming the effectiveness of roflumilast in reducing AE-COPD, especially in specific patient subgroups.

We fully understand the difficulty in comprehending certain aspects of the statistical methods used in our study. However, there were reasons for employing the complex statistical methods in our research. Given the indication of roflumilast, a considerable bias was expected because it was likely that more patients at high risk of AE-COPD were included in the roflumilast group. Unfortunately, our claim data lacked sufficient clinical information to perform propensity-score matching or adjust for clinical variables. Therefore, we resorted to estimating the ratio of the hazard ratio (RHR) for roflumilast in moderate-to-severe AE-COPD.

We acknowledge the reviewer's feedback that our study may be challenging to read. Therefore, we have made the following revisions to the **Results** section as below.

Result

…

Variables associated with moderate-to-severe exacerbation

In multivariable time-dependent Cox regression analyses, the HR for moderate-to-severe exacerbation was lower in patients with a longer duration of roflumilast use (≥3 months, HR=2.131 [95% CI=2.044–2.221]) compared to those with shorter duration of roflumilast use (<3 months, HR=3.842 [95% CI=3.657–4.036]). The HR of roflumilast for moderate-to-severe exacerbation was significantly reduced when roflumilast was treated for ≥3 months compared to <3 months (RHR=0.555 [95% CI=0.520–0.592]).

…

Demographic and comorbidity factors

Differential efficacy of roflumilast in reducing moderate-to-severe exacerbation according to demographic and comorbidity factors was summarized in ***Figure 2****. The adjusted HR of roflumilast in reducing moderate-to-severe exacerbation exhibited a notable decrease in patients aged ≥50 & <65 (RHR=0.838 [95% CI=0.706–0.996]) and those aged ≥65 (RHR=0.818 [95% CI=0.692–0.966]) compared to their younger counterparts aged <50. The adjusted HR of roflumilast for moderate-to-severe exacerbation was statistically reduced in patients with a CCI score of 1 (RHR=0.843 [95% CI=0.716–0.992]), 2 (RHR=0.814 [95% CI=0.685–0.966]), or ≥3 (RHR=0.803 [95% CI=0.677–0.952]) in comparison to those with a CCI score of 0. The effectiveness of roflumilast in reducing moderate-to-severe exacerbations was more pronounced in patients with a documented history of moderate-to-severe exacerbations in the previous year (RHR=0.913 [95% CI=0.855–0.974]). Additionally, patients with bronchiectasis*

or chronic bronchitis experienced significant benefits from roflumilast therapy, as their adjusted HR for moderate-to-severe exacerbations was markedly reduced (bronchiectasis, RHR=0.791 [95% CI=0.740–0.846]; chronic bronchitis, RHR=0.793 [95% CI=0.737–0.854]).

Treatment factors

Differential efficacy of roflumilast on reducing moderate-to-severe exacerbation according to treatment factors was summarized in ***Figure 2****. The adjusted HR of roflumilast for moderate-to-severe exacerbation was significantly reduced in the patients who were prescribed with mono-bronchodilator (LABA or LAMA, RHR=0.794 [95% CI=0.689–0.914]), ICS/LABA (RHR=0.586 [95% CI=0.509–0.673]), LABA/LAMA (RHR=0.802 [95% CI=0.696–0.924]), and ICS/LABA/LAMA (RHR=0.570 [95% CI=0.400–0.812]) compared to those without regular inhaled treatment. Notably, the effectiveness of roflumilast for moderate-to-severe exacerbations was even more pronounced among patients receiving ICS/LABA therapy compared to those with mono-bronchodilator (RHR=0.717 [95% CI=0.662–0.777]) or LABA/LAMA (RHR=0.719 [95% CI=0.663–0.779]). The patients treated with methylxanthine (RHR=0.888 [95% CI=0.807–0.977]) and statins (RHR=0.897 [95% CI=0.818–0.984]) experienced a significantly reduced risk of moderate-to-severe exacerbations when administered with roflumilast.*