Roflumilast Role in the Prevention of Acute Exacerbation in Chronic Obstructive Pulmonary Disease: A Narrative Review

Antonio Fabozzi and Paolo Palange

Department of Public Health and Infectious Diseases, Division of Pulmonary Medicine, Sapienza University of Rome, Rome, Italy

DOI: 10.17925/USPRD.2024.9.1.2

Acute exacerbations in chronic obstructive pulmonary disease (AECOPD) is the leading cause of mortality in patients with chronic obstructive pulmonary disease (COPD). Even today, the scientific world has not found a therapeutic strategy effective enough to drastically reduce the annual rate of exacerbations. This narrative review aims to provide an overview of the available efficacy data of roflumilast, a phosphodiesterase 4 inhibitors (PDE4) inhibitor, in preventing COPD. Seven clinical trials were analyzed and most of these reported a statistically significant increase in forced expiratory volume (FEV1) and a statistically significant reduction in the annual rate of exacerbations compared with placebo.

Keywords

Chronic obstructive pulmonary disease, COPD, acute exacerbations in chronic obstructive pulmonary disease, AECOPD, disease exacerbation, exacerbated respiratory disease, lung diseases, phosphodiesterase 4 inhibitors, pulmonary disease, respiratory function tests, roflumilast

Disclosures: Antonio Fabozzi and Paolo Palange have no financial or non- financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study or during the writing of this article.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Received: 12 September 2023

Accepted: 8 November 2023

Published online: 1 February 2024

Citation: *touchREVIEWS in Respiratory & Pulmonary Diseases.* 2024;9(1):25-28

Corresponding author: Antonio Fabozzi, Department of Public Health and Infectious Diseases, Division of Pulmonary Medicine, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy, Italy.
E: antoniofabozzi40@gmail.com

Support: No funding was received in the publication of this article.

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are the dominant cause of the worsening and high mortality of chronic obstructive pulmonary disease (COPD), and are associated with higher healthcare costs as part of COPD management. AECOPD is characterized by worsening respiratory symptoms, quality of life, respiratory function and gas exchange.[1] It represents a challenge in COPD monitoring because preventing its occurrence could avoid numerous hospital admissions to intensive care units (ICUs), use of invasive mechanical ventilation (IMV) and non-invasive mechanical ventilation (NIMV) as well as reducing inhospital mortality. Numerous factors have been highlighted that make COPD patients susceptible to frequent exacerbations; these include viral (37% of cases) and/or bacterial (31% of cases) infections of the upper and lower respiratory tract, deficits of innate and/or acquired immunity, advanced age, non cessation of cigarette smoking and exposure to environmental pollution (up to 50% of cases).[2,3] According to the latest Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023 guidelines, a patient with COPD with frequent exacerbations is defined as the occurrence of two treated exacerbations in the previous year.[4] The COPD phenotype with frequent exacerbations is at high risk of developing AECOPD, so it is crucial to be able to identify these patients early. According to the latest GOLD 2023 guidelines, AECOPD is defined as an acute respiratory event characterized by worsening dyspnoea, cough and/or sputum in the previous 2 weeks.[4] It is essential to assess the severity of AECOPD and there are three levels:

1) mild: dyspnea visual analogue scale (VAS) <5, respiratory rate (RR) <24 breaths per minute, heart rate (HR) <95 beats per minute (bpm), resting oxygen saturation (SaO_2) ≥92% on ambient air (or on patient's usual oxygen prescription), C-reactive protein (CRP) <10 mg/L

2) moderate: dyspnea VAS >5, RR ≥24 breaths per minute, HR ≥95 bpm, resting SaO_2 <92% on ambient air (or on patient's usual oxygen prescription), CRP >10 mg/L

3) severe: dyspnea, RR, HR, resting SaO_2 and CRP as per moderate levels, plus new onset or worsening hypercapnia and acidosis (partial pressure of carbon dioxide in arterial blood [$PaCO_2$] >45 mmHg and pH <7.35).

Roflumilast overview

Roflumilast is an oral selective phosphodiesterase 4 (PDE4) inhibitor, first identified by Amschler et al. in 1995.[5] PDE4 is an enzyme that hydrolyzes cyclic adenosine monophosphate (cAMP) into its inactive form, adenosine-5-monophosphate (5-AMP), at the level of immune and inflammatory cells.[6] PDE4 is present in the airways within epithelial cells, lung fibroblasts, smooth muscle cells and endothelial cells.[7] Through the production of protein kinase A (PKA) and exchange protein activated by cAMP (Epac), cAMP has an anti-inflammatory and smooth muscle cell-releasing effect.[8] By inhibiting PDE4 and preventing the hydrolysis of cAMP into 5-AMP, it stimulates the intracellular accumulation of cAMP at the airways wall, thus increasing the anti-inflammatory effect. Roflumilast, by inhibiting PDE4, plays a role in reducing the release of inflammatory mediators and

the production of cytokines such as interleukin 1- β and interleukin- 10 by neutrophils, T-lymphocytes and macrophages.[9,10] Current guidelines recommend the use of roflumilast in patients with severe COPD with frequent flare-ups and post-bronchodilator forced expiratory volume in the first second (FEV1) <50% of predicted, with the aim of reducing the rate of exacerbations. The current recommended dosage is 250 mcg daily for the first month and 500 mcg daily thereafter, for 1 year.[11] Despite current scientific guidlines, real-world use of roflumilast is still low compared with the percentage of patients eligible for it; with uptake reported to be 22.6%.[12] This controversy could be explained by the specificity of action of roflumilast against PDE4 and its ineffectiveness in inhibiting chronic inflammation of the bronchial mucosa.[13] Consequently, as there is a lack of biomarkers that can be used in daily clinical practice that assess PDE4 levels in individual patients, roflumilast is not yet sufficiently used by physicians managing patients with COPD. Therefore, the aim of this narrative review is to evaluate the benefits of roflumilast in patients with COPD with frequent exacerbations and its efficacy at reducing the risk of moderate-severe exacerbations.

Selection process

One database was utilized to cover the literature: PubMed. Search terms used in the PubMed were: "roflumilast" and "COPD", with the filter "clinical trial" applied. Clinical trials were searched from 2005 to 2023. This narrative review considered seven randomized clinical trials that studied the efficacy of roflumilast 500 mcg daily compared with placebo in the prevention of AECOPD in patients with COPD with frequent flare-ups.

The inclusion criteria included patients aged ≥40 years with: a history of COPD lasting more than 1 year; ≥2 moderate or severe exacerbations in the previous 12 months; a history of being a former or current smoker (with a history of at least 10 pack-years); eligiblity for enrollment; and a stable clinical disease status with no change in COPD treatment during the last month. A post-bronchodilator FEV1 of ≤50% of predicted and an FEV1/forced vital capacity (FVC) ratio of <70% were required. In some trials (REACT and RE^{2}SPOND), all the patients were on concomitant bronchodilator therapy (long-acting muscarinic antagonists [LAMA], inhaled corticosteroids [ICS]/long-acting β2-agonists [LABA] or a combination of the two); while in the other trials the percentage of patients who were on concomitant bronchodilator therapy was variable.[14,15]

The exclusion criteria included the following conditions: COPD exacerbation in the last month; diagnosis of asthma and/or other relevant lung disease (e.g. history of primary bronchiectases, cystic fibrosis, bronchiolitis, lung resection, lung cancer, interstitial lung disease [e.g. fibrosis, silicosis, sarcoidosis], or active tuberculosis); alpha-1 antitrypsin deficiency; treatment with systemic glucocorticosteroids; lower respiratory tract infection not resolved before the last month.

In this review the following data were collected: post-bronchodilator FEV1 and FVC (present in seven and five trials, respectively) at 24 or 52 weeks of roflumilast treatment depending on the study design, the annual rate of moderate-severe COPD exacerbations (present in six trials) and the annual percentage reduction of this rate (present in five trials). The primary objective of this review was to assess the efficacy of roflumilast on respiratory function and possible reduction of AECOPD versus placebo. Analysis of the other data contained in the trials considered, such as those relating to adverse effects, GOLD stage and COPD Assessment Test (CAT) score, was therefore considered inappropriate.

Randomized controlled trials

The main findings of the randomized controlled trials (RCTs) are shown in *Table 1*. The M2-107 trial by Rabe et al.[16] was a phase III, multicentre, double-blind, randomized, placebo- controlled clinical trial conducted in 2005 in which 1,141 patients from 159 European, Australian and American centres were included. Post-bronchodilator FEV1 and post-bronchodilator FVC at 24 weeks of treatment was significantly increased with Roflumilast 500 mcg compared with placebo. Roflumilast was shown to have greater effect on moderate or severe COPD (increase in post-bronchodilator FEV1 was +103 mL and +85 mL, in moderate and

Table 1: Comparison of lung function parameters and annual rate of moderate or severe COPD exacerbations between roflumilast versus placebo in 7 randomized controlled trials

RCT	Post-bronchodilator FEV1 with roflumilast compared with placebo (mL)	p value	Post-bronchodilator FVC with roflumilast compared with placebo (mL)	p value	Annual rate of COPD exacerbations in the roflumilast group (n per year)	Annual rate of COPD exacerbations in the placebo group (n per year)	p value	Percentage reduction of COPD exacerbations with roflumilast comparedwith placebo (%)
M2-107 Rabe et et al.[16]	+97	<0.03	+114	0.03	0.75	1.03	<0.01	-34.0%
M2-124 M A Calverley et al.[17]	+57	<0.01	+68	<0.01	1.08	1.27	0.03	-6.0%
M2-111/112 Rennard et collab.[18]	+53	<0.01	NE	NE	0.52	0.61	0.03	-14.0%
REACT Martinez et et.[14]	+56	<0.01	+92	<0.01	0.82	0.96	0.04	-14.0%
RE2SPOND Martinez et al.[15]	+53	<0.01	+83	<0.01	1.17	1.27	NS	-8.5%
TREAT Mackay et al.[19]	+94	NS	NE	NE	0.45	0.33	NS	+12%
Liu et al.[20]	+32	<0.01	+38	<0.01	0.08	0.11	NS	-3.4%

Value are means.
In all of the 7 RCTs, the following parameters were compared between roflumilast versus placebo: post-bronchodilator FEV1 and FVC, annual rate of COPD exacerbations and percentage reduction of COPD exacerbations. For each of these parameters, the p value is shown.
COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in the first second; FVC = forced vital capacity; NE = not evaluated; NS = not stated; RCT = randomized controlled trial.

severe COPD, respectively). The number of annual exacerbations per patient was significantly lower with roflumilast 500 mcg (0.75 per year) than with placebo (1.13 per year) and this resulted in a 34% lower rate of exacerbations with roflumilast 500 mcg compared with the placebo group.

The M2-124 trial by Calverley et al. was a placebo-controlled, double-blind, multicentre trial conducted in 2009 in which 1,525 patients from 246 centres were included.[17] Post-bronchodilator FEV1 and post-bronchodilator FVC at 52 weeks of treatment were significantly increased with roflumilast 500 mcg compared with placebo. The number of moderate-severe annual exacerbations per patient was lower with roflumilast 500 mcg (1.08 per year) compared with placebo (1.27 per year) (p=0.03). M2-111 and M2-112 by Rennard et al. were two previous replicate, randomized, double-blind, placebo-controlled, parallel-group studies conducted in 2003 that included 2690 patients from 188 and 159 centres, respectively.[18] Roflumilast 500 mcg showed a significant improvement in post-bronchodilator FEV1 compared with placebo at 52 weeks of treatment. The number of annual exacerbations per patient was significantly lower with roflumilast 500 mcg (0.52 per year) than with placebo (0.61 per year). This resulted in a 14.3% lower rate of exacerbations in the roflumilast 500 mcg group compared with the placebo group.

Roflumilast seemed to have a greater effect in the subgroup of patients with chronic bronchitis with or without emphysema (-26% annual exacerbation rate compared to placebo group).

The Receiving Appropriate Combination Therapy (REACT) study by Martinez et al was a 1-year double-blind, placebo-controlled, parallel group, multicentre, phase III/IV trial performed in 2014, in which 1,945 patients from 203 centres in 21 countries were included.[14] Post-bronchodilator FEV1 and post-bronchodilator FVC at 52 weeks of treatment was significantly increased with roflumilast 500 mcg versus placebo. The annual rate of exacerbations was 0.82 per year in the roflumilast 500 mcg group and 0.96 per year in the placebo group, resulting in a 14.2% annual reduction in the rate of exacerbations with roflumilast compared with placebo (p=0.042). In this RCT, in which all patients were being treated with bronchodilator therapy, there were no significant differences in FEV1 and annual rate of exacerbations compared with patients not given bronchodilator therapy in other RCTs included in this review.

The Roflumilast Effect on Exacerbations in Patients on Dual [LABA/ICS] Therapy (RE^{2}SPOND) trial by Martinez et al. was a 52 week, phase IV, double-blind, placebo-controlled trial performed in 2016 in which 2,354 patients from 380 centres in 17 countries were included and followed-up with treatment for 52 weeks (roflumilast 500 mcg versus placebo).[15] The rate of moderate-severe COPD exacerbations was reduced by 8.5% with roflumilast (1.17 per year) compared with placebo (1.27 per year); however, this was not statistically significant. However, when stratifying patients according to the number of exacerbations in the previous year, it was seen that patients with COPD with two or three exacerbations in the previous year had a significantly lower rate of exacerbations with roflumilast compared with placebo (-25% and -39%, respectively). Functionally, all patients with COPD receiving roflumilast 500 mcg showed a strong and significant improvement in post-bronchodilator FEV1 and post-bronchodilator FVC compared with placebo. Also in this RCT, the combination of roflumilast with LABA/ICS did not lead to significant increases in FEV1 compared with patients not on bronchodilator therapy in the other RCTs included in this review; however, it seems that roflumilast + LABA/ICS leads to very significant reductions in the annual rate of exacerbations in patients with COPD with frequent exacerbations.

The Treatment with Roflumilast at Exacerbation (TREAT) study by Mackay et al. was a randomized, double-blind, placebo-controlled, parallel-group, single-center, phase II trial conducted in 2017 in which 81 patients with AECOPD were included.[19] At day 28 of exacerbation, the roflumilast group showed a non-statistically significant increase in FEV1 compared with the placebo group. In addition, roflumilast showed anti-inflammatory effect by significantly reducing the percentage of neutrophils in sputum compared with placebo (-13.9%; p=0.049) and by significantly reducing the concentration of myeloperoxidase in sputum (-7.800 ng/mL; p=0.018). The peculiarity of this trial was the timing of the use of roflumilast, in fact it was administered right from the time of acute exacerbation and demonstrated its maximum effect from 14 to 28 days post-exacerbation, although this was not statistically significant in terms of FEV1.

In the two-arm, randomized, double blinded, placebo-controlled trial by Liu et al. performed in 2018, 121 patients were included and the comparison of roflumilast versus placebo at 12 months of treatment was studied.[20] Respiratory function tests performed at 12 months of treatment with roflumilast 500 mcg showed a statistically significant increase compared with placebo in post-bronchodilator FEV1 and post-bronchodilator FVC. The annual rate of COPD exacerbations was lower with roflumilast 500 mcg (0.083 per year) than with placebo (0.117 per year), with -3.4% annual reduction rate with roflumilast; however, it did not reach statistical significance. This RCT shows a reduction in the annual rate of COPD exacerbations with roflumilast that may not justify using the PDE4 inhibitor for 1 consecutive year in patients with COPD.

Discussion

Post-bronchodilator FEV1 following roflumilast therapy increased statistically significantly compared with placebo in all seven RCTs included in this review, with a minimum of +32.4 mL to a maximum of +103 mL.[17,20] Furthermore, when stratifying patients according to the severity of COPD, FEV1 was found to improve more in patients with more frequent exacerbations or moderate-to-severe on respiratory function tests.[15,17,18] The other major finding highlighted by this review is the effect of roflumilast on the AECOPD rate compared with placebo, with a minimum of -14% to a maximum of -39%.[15,19] Again, the AECOPD rate was reduced the most in patients with severe COPD and/or frequent exacerbations.[15,18] In the TREAT trial by Mackay et al., roflumilast showed functional benefit when used during AECOPD, with its maximum effect occurring 14 to 28 days post-exacerbation.[19] The RE2SPOND trial also showed increased FEV1 and reduced annual AECOPD rates in patients with COPD patients already on dual bronchodilator therapy (ICS+LABA).[15]

There are some uncertainties surrounding roflumilast therapy and its chronic use for more than 1 year, including its effect on patients with COPD on triple bronchodilator therapy (ICS+ LAMA+LABA), the lack of biomarkers that would allow the effect of roflumilast to be monitored over time and the insufficient data on the use of roflumilast during AECOPD itself. Despite evidence supporting pulmonary function tests and their association with reducing the annual rate of exacerbations, more studies and trials, as well as new systematic reviews and meta-analyses will be needed to resolve these latter controversies on the use of roflumilast to treat patients with severe and/or frequent COPD. ❑

1. Pépin JL, Degano B, Tamisier R, Viglino D. Remote monitoring for prediction and management of acute exacerbations in chronic obstructive pulmonary disease (AECOPD). *Life*. 2022;12:499. DOI: 10.3390/life12040499.
2. Jafarinejad H, Moghoofei M, Mostafaei S, et al. Worldwide prevalence of viral infection in AECOPD patients: A meta-analysis. *Microb Pathog*. 2017;113:190–6. DOI: 10.1016/j.micpath.2017.10.021.
3. Sin DD, Doiron D, Agusti A, et al. GOLD scientific committee. Air pollution and COPD: GOLD 2023 committee report. *EurRespir J*. 2023;61:2202469. DOI: 10.1183/13993003.02469-2022.
4. Agustí A, Celli BR, Criner GJ, et al. Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. *Eur Respir J*. 2023;61:2202469. DOI: 10.1183/13993003.E6104-2023.
5. Amschler H. Fluoroalkoxy-substituted benzamides and their use as cyclic nucleotide phosphodiesterase inhibitors. *PCT Patent*. 1995;WO95:01338. DOI: 10.1183/13993003.00239-2023.
6. Zuo H, Cattani-Cavalieri I, Musheshe N, et al. Phosphodiesterases as therapeutic targets for respiratory diseases. *Pharmacol Ther*. 2019;197:225–42. DOI: 10.1016/j.pharmthera.2019.02.002.
7. Al-Sajee D, Yin X, Gauvreau GM. An evaluation of roflumilast and Pde4 inhibitors with a focus on the treatment of asthma. *Expert Opin Pharmacother*. 2019;20:609–20. DOI: 10.1080/14656566.2019.1570132.
8. Grandoch M, Roscioni SS, Schmidt M. The role of EPAC proteins, novel cAMP mediators, in the regulation of immune, lung and neuronal function. *Br J Pharmacol*. 2010;159:265–84. DOI: 10.1111/j.1476-5381.2009.00458.x.
9. Dong H, Zitt C, Auriga C, et al. Inhibition of PDE3, PDE4 and PDE7 potentiates glucocorticoid-induced apoptosis and overcomes glucocorticoid resistance in CEM T leukemic cells. *Biochem Pharmacol*. 2010;79:321–9. DOI: 10.1016/j.bcp.2009.09.001.
10. Sanz MJ, Cortijo J, Morcillo EJ. PDE4 inhibitors as new anti-inflammatory drugs: Effects on cell trafficking and cell adhesion molecules expression. *Pharmacol Ther*. 2005;106:269–97. DOI: 10.1016/j.pharmthera.2004.12.001.
11. Baye J. Roflumilast (Daliresp): A novel phosphodiesterase-4 inhibitor for the treatment of severe chronic obstructive pulmonary disease. *P T*. 2012;37:149–61.
12. Holm CP, Holm J, Nørgaard A, Godtfredsen N. COPD, stage and treatment in a large outpatient clinic. *Eur Clin Respir J*. 2017;4:1267470. DOI: 10.1080/20018525.2017.1267470.
13. Blasco LM. Avoiding backward steps in COPD: Looking again at roflumilast. *Eur Respir J*. 2012;39:224–5; . DOI: 10.1183/09031936.00140311.
14. Martinez FJ, Calverley PMA, Goehring U-M, et al. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): A multicentre randomised controlled trial. *Lancet*. 2015;385:857–66. DOI: 10.1016/S0140-6736(14)62410-7.
15. Martinez FJ, Rabe KF, Sethi S, et al. Effect of roflumilast and inhaled corticosteroid/long-acting β2-agonist on chronic obstructive pulmonary disease exacerbations (RE(2)SPOND). A randomized clinical trial . *Am J Respir Crit Care Med*. 2016;194:559–67. DOI: 10.1164/rccm.201607-1349OC.
16. Rabe KF, Bateman ED, O'Donnell D, et al. Roflumilast--an oral anti- inflammatory treatment for chronic obstructive pulmonary disease: A randomised controlled trial. *Lancet*. 2005;366:563–71. DOI: 10.1016/S0140-6736(05)67100-0.
17. Calverley PMA, Rabe KF, Goehring U-M, et al. M2-124 and M2-125 study groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: Two randomised clinical trials. *Lancet*. 2009;374:685–94. DOI: 10.1016/S0140-6736(09)61255-1.
18. Rennard SI, Calverley PMA, Goehring UM, et al. Reduction of exacerbations by the Pde4 inhibitor roflumilast--the importance of defining different subsets of patients with COPD. *Respir Res*. 2011;12:18. DOI: 10.1186/1465-9921-12-18.
19. Mackay AJ, Patel ARC, Singh R, et al. Randomized double-blind controlled trial of roflumilast at acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;196:656–9. DOI: 10.1164/rccm.201612-2518LE.
20. Liu D-Y, Wang Z-G, Gao Y, et al. Effect and safety of roflumilast for chronic obstructive pulmonary disease in Chinese patients. *Medicine (Baltimore)*. 2018;97:e9864. DOI: 10.1097/MD.0000000000009864.