

# The Dosing Strategy to Improve Adherence to Roflumilast in Treatment for Chronic Obstructive Lung Disease: A Systemic Review and Meta-Analysis

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**Background:** The clinical efficacy of roflumilast, an oral phosphodiesterase-4 inhibitor, has been demonstrated in patients with severe chronic obstructive pulmonary disease (COPD). However, roflumilast has shown frequent adverse drug reactions (ADRs). This study was performed to investigate the dosing strategy that will improve adherence to roflumilast in COPD.

**Methods:** We conducted a systematic review and meta-analysis using PubMed, Embase, and Cochrane Central Register. The dosing strategy for roflumilast was classified into a dose-escalation group and a low-dose group. We investigated clinical outcomes according to dosing strategy.

**Results:** Five clinical trials involving 2424 patients were included. Both the dose-escalation and the low-dose groups showed a decrease in discontinuation rate compared to the standard dosing group for roflumilast (risk ratio [RR], 0.81; 95% confidence interval [CI], 0.67–0.97;  $P = 0.02$  and RR, 0.62; 95% CI, 0.48–0.80;  $P < 0.01$ , respectively). In the two strategies, the pooled proportions of discontinuation were 27.9% and 11.7%, respectively. Although the pooled proportion of any ADR was not statistically decreased in the two strategies, diarrhea was significantly reduced in the low-dose group compared to the standard group (RR, 0.58; 95% CI, 0.42–0.82;  $P < 0.01$ ). The pooled incidence of acute exacerbations was similar between the low-dose and the standard groups (22.9% and 20.1%, respectively;  $P = 0.27$ ).

**Conclusion:** Our findings show that the two alternative dosing strategies might have the benefit of improving adherence to roflumilast in COPD. Further large-scale trials are required to support our findings.

**Keywords:** drug tolerance, meta-analysis, phosphodiesterase 4 inhibitor, pulmonary disease, chronic obstructive, roflumilast

## Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible and is one of the leading causes of morbidity and mortality worldwide.<sup>1</sup> Patients with COPD can experience periodic exacerbations by worsening of respiratory symptoms.<sup>2</sup> Hospitalizations for COPD exacerbations are associated with worsening lung function and increased mortality.<sup>2</sup> Although patients with severe COPD receive adequate maintenance inhalation therapy including long-acting  $\beta_2$  agonists, long-acting anticholinergics, and inhaled corticosteroids, they frequently continue to experience exacerbations.<sup>2</sup> This indicates the demand for novel or additional effective agents for reducing the risk of COPD exacerbations.

Phosphodiesterase 4 (PDE4) is the subtype of PDE that is expressed in airway smooth muscle cells and inflammatory cells.<sup>3</sup> Roflumilast is an orally administered selective PDE4 inhibitor that interferes with the breakdown of cyclic

adenosine monophosphate, which may contribute to the reduction of airway inflammation.<sup>4</sup> A meta-analysis of 13 randomized controlled trials demonstrated that oral roflumilast at 500 µg once per day reduced the risk of acute exacerbations (AEs) in patients with severe COPD related to chronic bronchitis and a history of frequent AEs.<sup>5</sup> Current guidelines recommend the use of roflumilast for reducing moderate and severe AEs treated with systemic corticosteroids in these patients.<sup>6</sup>

Adverse drug reactions (ADRs) associated with roflumilast, including diarrhea, nausea, and weight loss, have been commonly reported in clinical studies, and the frequency and severity of ADRs are dose-dependent.<sup>7</sup> ADRs can cause treatment discontinuation, and rates of early discontinuation were higher for patients receiving roflumilast compared with placebo.<sup>8</sup>

Therefore, the purpose of this study is to explore whether the rate of treatment discontinuation can be reduced by alternative dosing strategies. Based on a systematic review and meta-analysis of clinical trial data, we investigated the discontinuation rate and the incidence of ADRs by the dose-escalation or low-dose strategy of roflumilast compared to the standard dose.

## Methods

### Data Sources and Search Strategy

We performed a systematic search of three electronic databases (PubMed, Embase, and Cochrane Central Register) to identify potentially relevant studies on dosing strategies for roflumilast published prior to May 2023. A systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The present study was registered in PROSPERO with registration number CRD42023428270. The following key search terms were used: (“chronic obstructive pulmonary disease or COPD or emphysema or chronic bronchitis or chronic airway disease”) and [“phosphodiesterase 4 inhibitor or PDE4 inhibitor or PDE-4 inhibitor or roflumilast”] and [“250 µg or dosing strategy or dose escalating or low dose or dosing regimen”]). The search was limited to articles published in a peer-reviewed English journal and studies conducted on human beings. We included full-length articles or letters, while reviews, case reports and series, and commentaries were excluded. Because this study was a meta-analysis of published articles, neither informed consent nor ethics approval was required.

### Study Selection, Outcomes, and Data Extraction

We included trials that met the following criteria in our study: (1) randomized controlled or observational trials for treatment in patients diagnosed with COPD according to the Global Initiative for Chronic Obstructive Lung Disease guidelines;<sup>6</sup> (2) patients who received roflumilast using dosing strategies; (3) available clinical outcomes for discontinuation and ADRs; and (4) available risk estimates and 95% confidence intervals (CIs) or the data from which these could be calculated.

A dose of 500 µg roflumilast once daily is the only approved treatment for severe COPD patients.<sup>9</sup> We examined two dosing strategies to improve adherence to roflumilast. First, the dose-escalation strategy was defined as the regimen that increased from a starting dose of 250 µg roflumilast to the full dose of 500 µg. Second, the low-dose strategy was defined as maintenance of a dose of 250 µg once daily.

The clinical measurements were the discontinuation rate and the incidence of any ADRs. As detected by the investigators, ADRs were defined as adverse effects in which there was a possible causal relationship to roflumilast therapy. We also investigated the incidence of diarrhea, which is a known frequent ADR of roflumilast therapy. For the low-dose strategy, we additionally compared the effectiveness of roflumilast through the rate of AEs compared to that of the conventional group. AE was defined as a worsening of any respiratory symptoms requiring treatment with systemic corticosteroid.

The two authors independently screened potentially relevant studies and reviewed each study according to the predetermined criteria. Data from the selected studies were extracted onto a predefined form. The following information was retrieved after a review of the full text: authors, year of publication, study design, sample size, patient age and sex, current smoker, body mass index, triple inhaled therapy, pre-bronchodilator forced expiratory volume in one second, population, and primary outcome.

## Quality Assessment

Randomized controlled trials (RCTs) were categorized as “low”, “high”, or “unclear” risk of bias based on the Cochrane Handbook for Systemic Reviews of Interventions.<sup>10</sup> The risk of bias in non-randomized studies was categorized as low, moderate, serious, critical, or no information using the Risk of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool.<sup>11</sup> Any disagreements during the study search, data extraction, or quality assessment were discussed and resolved.

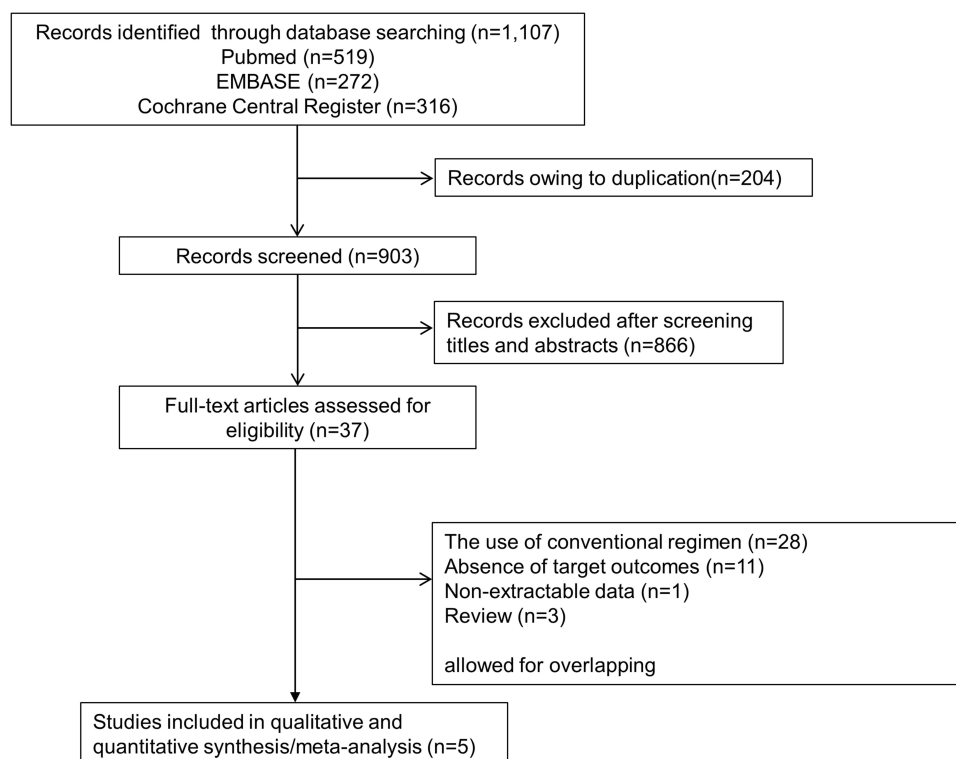
## Statistical Analysis

To assess the safety and tolerability of dosing strategies for roflumilast, we analyzed frequencies for categorical variables, with the weight corresponding to the sample size from the eligible studies. The risk ratios (RRs) and mean differences with associated 95% CIs were extracted for clinical outcomes, and the pooled RRs were calculated using the Mantel-Haenszel method. Between-study heterogeneity was assessed using the  $I^2$  statistic on a scale of 0–100%.  $I^2 > 50\%$  was indicated as a substantial level of between-study heterogeneity.<sup>12</sup> If notable heterogeneity did not exist, a fixed effects model was performed for analysis; otherwise, a random effects model was used. A  $P$  value  $< 0.05$  was considered statistically significant. All statistical analyses were conducted using Review Manager Software, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

## Results

### Study Search, Characteristics of Included Studies, and Study Quality

A total of 1107 titles was initially obtained through database searches. After removing duplicate articles, we identified published articles of 903 studies that were potentially eligible for inclusion. Of these articles, 866 were excluded based on the screening by title and abstract. The remaining 37 papers underwent full-text review, of which 5 were included in the final analysis (Figure 1).<sup>13–17</sup> The baseline characteristics of the included studies are shown in Table 1. The included articles were published between 2005 and 2019 and consisted of RCTs ( $n=3$ ) and studies with a retrospective



**Figure 1** Flow chart of study selection.

**Table 1** Characteristics of the Studies Included in the Meta-Analysis

Study, year	Design	Patients (Number)		Age (Mean)		Male (%)		Current Smoker (%)		Body mass Index (kg/m <sup>2</sup> )		Triple Inhaled Therapy (%)		Pre-Bronchodilator FEV1, % Predicted (Mean)		Population	Primary Outcome	
		DE	CV	DE	CV	DE	CV	DE	CV	DE	CV	DE	CV	DE	CV			
<b>Dose escalation strategy</b>																		
Hwang, 2015 <sup>13</sup>	Single-center, retrospective observational trial	59	26	69.3	71.9	100	80.8	32.2	11.5	20.9	20.1	49.2	11.5	NA	NA	Severe and very severe COPD and chronic bronchitis symptoms	The discontinuation rate and the incidence of any AEs	
Park, 2019 <sup>14</sup>	Single-center, randomized, prospective, open-label, single-blind study	27	28	70.5	69.8	96.3	96.4	3.7	17.9	21.2	22.2	63.0	92.9	34.6	34.9	Severe and very severe COPD, smoking history, exacerbation history in previous year, and chronic bronchitis symptoms	The discontinuation rate	
Watz, 2019 <sup>15</sup>	Multicenter, double-blind, Phase III randomized trial	441	443	64.2	64.6	72.6	76.3	48.3	44.2	26.4	26.4	NA	NA	NA	NA	Severe and very severe COPD, smoking history, exacerbation history in previous year, and chronic bronchitis symptoms	The discontinuation rate	
<b>Low-dose strategy</b>																		
Joo, 2018 <sup>16</sup>	Single-center, retrospective review of medical records	91	178	74.5	71.6	93.4	93.8	17.2	11.4	22.9	21.9	NA	NA	45.7	42.5	COPD	The discontinuation rate and the incidence of any AEs	
Rabe, 2005 <sup>17</sup>	Multicenter, double-blind, Phase III randomized trial	576	555	65	64	73	74	46	46	26	26	NA	NA	50	51	Moderate and severe COPD and smoking history	Postbronchodilator FEV1 and St. George's respiratory questionnaire total score	

**Abbreviations:** AE, acute exacerbation; COPD, chronic obstructive pulmonary disease; CV, conventional; DE, dose-escalation; FEV1, forced expiratory volume in one second; LD, low dose; NR, not available.

observational design (n=2). The number of patients within each study ranged from 55 to 1131, and the total number of patients in our meta-analysis was 2424, of whom 1194 received an alternative dosing strategy, and 1230 received the standard dosing regimen. A quality assessment of the included studies is presented in Table 2. Based on this assessment, the quality for each included study was likely to be mostly satisfactory. One trial was considered to be at high risk of bias because it did not blind participants, researchers, or outcome assessment.<sup>14</sup>

## Dose-Escalation Strategy

Three trials with a total of 1024 patients compared the safety and tolerability of roflumilast between the dose-escalation group and the standard dosing group for treatment in patients with COPD.<sup>13–15</sup> Figure 2A shows the forest plot of the discontinuation rate for the two strategies of roflumilast. The pooled estimates showed a statistical reduction in the discontinuation rate in the dose-escalation group compared with the standard dosing group (RR, 0.81; 95% CI, 0.67–0.97;  $P = 0.02$ ). Because there was low statistical heterogeneity ( $I^2 = 41\%$ ), the fixed effects model was used for the current meta-analysis. The discontinuation rates of roflumilast were 27.9% and 35.2% in the dose-escalation group and the standard dosing group, respectively.

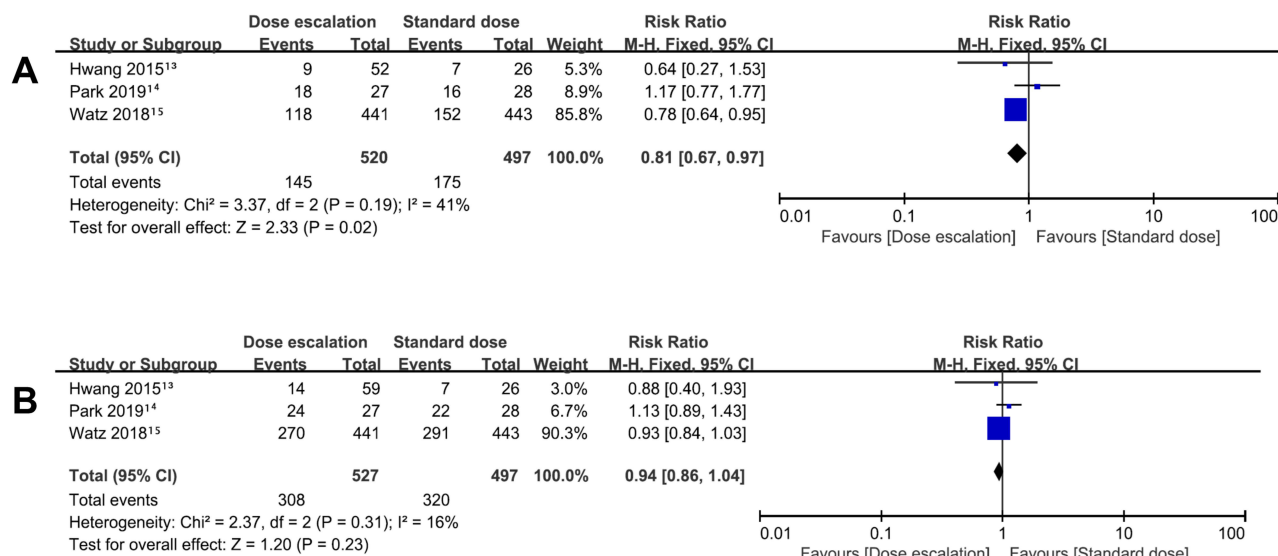
The pooled proportion of any ADRs at the end point of the study did not differ significantly between the two groups (58.4% in the dose-escalation and 64.4% in the standard dosing group; RR, 0.94; 95% CI, 0.86–1.04;  $P = 0.23$ ;  $I^2 = 16\%$ ; Figure 2B). The pooled estimates using a fixed effects model demonstrated that diarrhea was also not statistically different between the two groups (23.9% in the dose-escalation and 30.0% in the standard dosing group; RR, 0.83; 95% CI, 0.68–1.01;  $P = 0.06$ ;  $I^2 = 0\%$ ).

## Low-Dose Strategy

Two trials involving 1400 patients were available for the current analysis, with 667 patients in the low-dose group and 733 in the standard dosing group.<sup>16,17</sup> In pooled estimates using the fixed effects model, the low-dose regimen of roflumilast reduced the discontinuation rate in comparison to the standard dose (11.7% in the low dose group and 21.4% in the standard dosing group; RR, 0.62; 95% CI, 0.48–0.80;  $P < 0.01$ ;  $I^2 = 0\%$ ; Figure 3A). The incidence of any ADRs was similar in the two groups (60.7% in the low-dose group and 59.8% in the conventional group; RR, 0.85; 95% CI, 0.57–1.27;  $P = 0.43$ ; Figure 3B). The pooled analysis showed that the use of low-dose roflumilast significantly reduced the incidence of diarrhea compared to the standard dosing group (6.6% in the low-dose group and 12.7% in the conventional group; RR, 0.58; 95% CI, 0.42–0.82;  $P < 0.01$ ;  $I^2 = 0\%$ ).

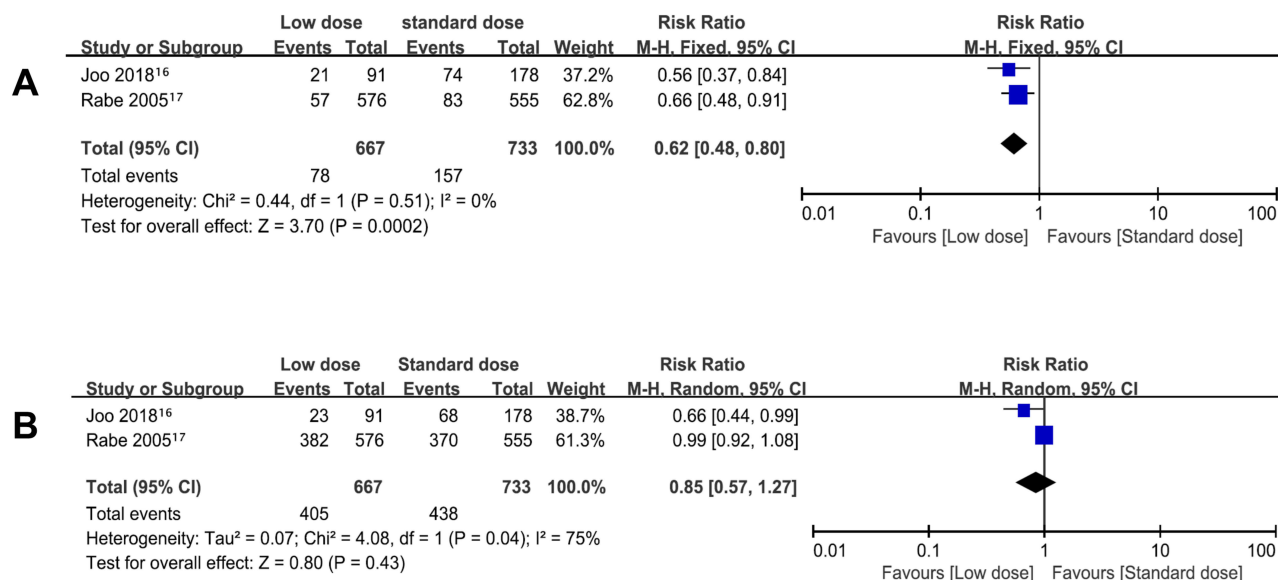
**Table 2** Quality Assessment for the Studies Included in the Meta-Analysis

Randomized controlled trials							
Author, year	Sequence generation	Allocation concealment	Blinding of participants and researchers	Blinding of outcome assessment	Incomplete outcome data addressed	Free of selective reporting	
Park, 2019 <sup>14</sup>	Unclear	Unclear	High risk	High risk	Unclear	Unclear	
Watz, 2019 <sup>15</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Rabe, 2005 <sup>17</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	
Non-randomized observational studies							
Author, year	Confounding	Selection bias	Classification of interventions	Deviation from interventions	Missing data	Measurement of outcome	Selection of reported result
Hwang, 2015 <sup>13</sup>	Low risk	Low risk	Low risk	Low risk	No information	Low risk	Low risk
Joo, 2018 <sup>16</sup>	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk



**Figure 2** Forest plots for the rates of (A) discontinuation and (B) any adverse drug reactions after treatment with the dose-escalation strategy of roflumilast in patients with chronic obstructive lung disease.

**Abbreviations:** CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.



**Figure 3** Forest plots for the rates of (A) discontinuation and (B) any adverse drug reactions after treatment with the low-dose strategy of roflumilast in patients with chronic obstructive lung disease.

**Abbreviations:** CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

The pooled incidence of AEs to assess the effectiveness of roflumilast was 22.9% in the low-dose group and 20.1% in the standard dosing group. There was no significant difference between the two groups (RR, 1.13; 95% CI, 0.91–1.40;  $P = 0.27$ ;  $I^2 = 0\%$ ).

## Discussion

Roflumilast has commonly been used as an adjunctive pharmacotherapy to combination therapies of inhaled corticosteroids and long-acting bronchodilators to further improve treatment efficacy in patients with severe to very severe COPD. Although roflumilast does not have direct bronchodilator activity, it has anti-inflammatory effects through inhibiting the

release of inflammatory mediators.<sup>5</sup> Recent meta-analyses have demonstrated that roflumilast was substantially effective for patients with severe and very severe COPD in reducing lung function decline and the incidence of AEs.<sup>5,18</sup>

In terms of safety, previous studies have reported that roflumilast for COPD is associated with more frequent ADRs than is inhaled therapy.<sup>5,18</sup> The most frequent ADRs are diarrhea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. These ADRs have led to increased discontinuation of roflumilast. A meta-analysis for drug safety of roflumilast 500 µg once-daily in patients with COPD revealed that the rates of discontinuation and ADRs for roflumilast were approximately 6% and 9% higher than for those who received placebo.<sup>7</sup> However, a real-life study reported much higher AEs rates of 69.1%, which lead to discontinuation of treatment in 49.1% patients.<sup>19</sup> Therefore, improved adherence to roflumilast treatment can have an important influence on the management of COPD.

This systematic review and meta-analysis evaluated clinical trials that assessed the effectiveness of dosing strategies to improve adherence to roflumilast pharmacotherapy in patients with COPD. Through detailed searching, we identified three dosing strategies to promote adherence: dose-escalation, low-dose regimens, and standard dosing every other day (EOD). The clinical efficacy of the dose-escalation strategy was investigated in three studies.<sup>13–15</sup> From a pooled result of these studies, the discontinuation rate was reduced in the dose-escalation strategy compared to a standard dosage of roflumilast, but the discontinuation rate of roflumilast was high at 27.9% even in the dose-escalation group. Three trials reporting adherence showed little difference in any ADRs between the intervention and conventional groups.<sup>13–15</sup> In addition, the lower-dose strategy of roflumilast improved the drug adherence rate in two studies.<sup>16,17</sup> The pooled estimates revealed that treatment with roflumilast 250 µg led to a lower incidence of discontinuation by approximately 38% than treatment with roflumilast 500 µg. There was no significant difference in the number of patients who experienced any ADRs between the two groups. We also identified one study investigating the tolerability of the standard dosing of roflumilast EOD.<sup>15</sup> Patients receiving roflumilast at 500 µg EOD did not experience a significantly reduced rate of treatment discontinuation and ADRs compared to those on the 500 µg once-daily regimen.<sup>15</sup>

Based on our findings, two dosing strategies, dose-escalation and low-dose regimens, may help patients maintain their treatment. However, a population-based pharmacokinetic/ pharmacodynamics modeling study found that a low dose of roflumilast was associated with lower plasma concentrations of roflumilast and lower total PDE4 inhibition, although it reduced the risk of related ADRs.<sup>20</sup> The results of an *in vitro* study raise concerns that a lower dose of roflumilast can impact clinical efficacy. To date, there are few studies examining the efficacy of the low-dose regimen of roflumilast. In clinical practice, because AEs of COPD are related to a poor prognosis, the expected reduction rate of AE is one of the main factors used to assess drug efficacy in the treatment of COPD. We found two studies reporting the incidence of the AEs of COPD in subjects receiving a dose of 250 µg once daily of roflumilast.<sup>16,17</sup> Our pooled estimates revealed that 250 µg roflumilast once daily did not increase the incidence of AEs compared to the standard dose. These findings suggest that a low dose of roflumilast may reduce the incidence of AEs as effectively as the standard dose. And a Phase III, multicenter, double-blind, randomized, placebo-controlled study demonstrated that 250 µg roflumilast significantly increased postbronchodilator forced expiratory volume in the first second by mean 74 mL and health-related quality of life compared with placebo during the 24-week treatment period.<sup>17</sup> In view of the scarcity of studies on the efficacy of low dose strategy, further studies are required.

In line with previous results, diarrhea was the most common ADR, and diarrhea has been regarded as one of the major reasons for discontinuation of roflumilast.<sup>21</sup> A recent meta-analysis of six RCTs involving 9715 subjects reported that the incidence of diarrhea was 9.4% in the standard dose of roflumilast.<sup>16</sup> In the present study, the pooled incidence of the dose-escalation and the low-dose groups was 23.9% and 6.6%, respectively, and a low dose of roflumilast was associated with significant reduction of diarrhea. Despite little difference in any ADRs between the dosing strategies and conventional groups in our study, the discontinuation rate of roflumilast was lower in the intervention groups. Diarrhea may be considered the main factor for terminating treatment early compared to other ADRs such as nausea, fatigue, decreased appetite, and weight loss.

The current study provides pooled results regarding the usefulness of dosing strategies of roflumilast. However, the present study has some limitations. First, despite a rigorous search, we identified a small number of trials, which might be insufficient to support our results. However, because there was low statistical heterogeneity across the included studies, our findings could have reliable aspects. Second, low body mass index (BMI) has previously been reported as a significant predictive factor leading to discontinuation of roflumilast.<sup>21</sup> Because of the scarcity of materials to evaluate the risk factors associated with roflumilast discontinuation in the selected studies, we could not extract data to compare

BMI among the dosing strategies. Third, cytochrome (CYP)3A4 and CYP3A5 enzymes are associated with a divergence of drug reactions.<sup>22</sup> Since frequency differences exist among ethnicities, they are likely to affect total PDE4 inhibitory activity level.<sup>22</sup> Trials analyzed in the pooled estimates were only conducted in South Korea and Europe, limiting generalization of the results.

## Conclusion

In conclusion, our systemic review and meta-analysis found that dose-escalation and low-dose strategies might be useful tools to improve roflumilast adherence. Between-study heterogeneities were low, but, in the dose-escalation strategy, the discontinuation rate of roflumilast was relatively high at 27.9%, and the rate of any ADRs did not decrease. In the low-dose strategy, the discontinuation rate was 11.7%, and the pooled incidence of diarrhea was lower than in the conventional regimen. The low-dose strategy did not increase the incidence of COPD with AEs. However, we could not draw robust conclusions because of the methodological limitations and the scarcity of trials for analysis. Additional large-scale RCTs are warranted to evaluate the efficacy of individual strategies in patients with severe COPD.

## Abbreviations

ADR, adverse drug reaction; AE, acute exacerbation; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; EOD, every other day; RCT, randomized controlled trial; RR, risk ratio.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by a 2024 scientific promotion program funded by Jeju National University. The sponsor had no role in the design of the study, collection and analysis of the data, or preparation of the manuscript.

## Disclosure

The authors report no conflicts of interest in this work.

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