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The Effect of Roflumilast on Absolute Neutrophil Count, MMP-9 Serum, %FEV_1 Value, and CAT Scores in Stable COPD Patients

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Abstract

Background: *Chronic obstructive pulmonary disease is the leading cause of morbidity and mortality worldwide. Cigarette smoke and noxious agent cause oxidative stress to activate nuclear factor-κB which increases inflammatory cell releases, including neutrophil and matrix metalloproteinase-9 (MMP-9). Roflumilast possesses anti-inflammatory effect which may be used as additional therapy for stable COPD.*

Methods: *Pre-test and post-test experimental clinical trial was conducted on 40 patients with stable COPD in pulmonology outpatient clinics of Dr. Moewardi Surakarta and dr. Soehadi Prijonegoro Sragen hospital from 6 January to 6 March 2020. Forty participants were assigned into treatment group (n=20) who received standard therapy along with roflumilast 500 mg/day and placebo group (n=20) who received only standard therapy for 28 days. Decline in inflammation was measured by ANC and MMP-9 serum, improvement in obstruction was measured by %FEV_1, and clinical improvement was measured by CAT score.*

Results: *Our finding revealed a decrease in ANC and MMP-9 serum among the treatment group, although statistically insignificant (P=0.449), (P=0.195) respectively. %FEV_1 value also increased insignificantly in the treatment group (P=0.189). Chronic obstructive pulmonary disease assessment test (CAT) score decreased significantly in the treatment group (P=0.0001).*

Conclusion: *Roflumilast administration reduced inflammation as indicated by insignificant lower level of ANC, MMP-9 serum, and insignificantly increased %FEV_1, and improved clinical condition of patients with stable COPD as suggested by decrease in CAT score. (**J Respirol Indones 2022; 42 (2): 141–50)***

Keywords: *Roflumilast, stable COPD, absolute neutrophil count, MMP-9 serum, and CAT score.*

Pengaruh Pemberian Roflumilast Terhadap Jumlah Neutrofil Absolut Darah, MMP-9 Serum, Nilai %VEP_1, Dan Skor CAT pada Penderita PPOK Stabil

Abstrak

Latar belakang: *Penyakit paru obstruktif kronik merupakan penyebab utama morbiditas dan mortalitas di dunia. Asap rokok dan partikel berbahaya menyebabkan stres oksidatif yang mengaktivasi nuclear factor-Kb meningkatkan pengeluaran sel inflamasi antara lain neutrofil dan matrix metalloproteinase-9 (MMP-9). Roflumilast mempunyai efek antiinflamasi yang dapat digunakan sebagai terapi tambahan pada PPOK stabil.*

Metode: *Uji klinis eksperimental pretest dan postest design dilakukan terhadap 40 penderita PPOK stabil di poliklinik paru RSUD Dr. Moewardi Surakarta dan RSUD dr. Soehadi Prijonegoro Sragen tanggal 6 Januari sampai 6 Maret 2020. Subyek kelompok perlakuan (n=20) diberikan roflumilast 1 x 500 mg per hari selama 28 hari, kelompok kontrol (n=20) hanya mendapatkan terapi standar PPOK stabil. Penurunan derajat inflamasi diukur dengan pemeriksaan neutrofil darah dan MMP-9 serum, perbaikan derajat obstruksi diukur dengan %VEP_1, dan perbaikan klinis diukur dengan skor CAT.*

Hasil: *Hasil penelitian menunjukan adanya penurunan jumlah neutrofil absolut darah pada kelompok perlakuan tetapi tidak signifikan terlihat dari nilai P=0,449. Kadar MMP-9 serum menunjukkan adanya penurunan tetapi tidak signifikan terlihat dari nilai P=0,195. Nilai %VEP_1 pada kelompok perlakuan terdapat peningkatan tetapi tidak signifikan terlihat dari nilai p= 0,189. Skor CAT menunjukan adanya penurunan secara signifikan pada kelompok perlakuan terlihat dari P=0,0001.*

Kesimpulan: *Pemberian roflumilast 1x500mg/hari mampu menurunkan inflamasi berdasarkan penurunan tidak signifikan jumlah neutrofil absolut darah, MMP-9 serum, meningkatkan tidak signifikan %VEP_1, dan dapat memperbaiki klinis penderita PPOK stabil yang terlihat pada penurunan skor CAT secara signifikan. (**J Respirol Indones 2022; 42 (2): 141–50)***

Kata kunci: *Roflumilast, PPOK stabil, Jumlah Neutrofil Absolute Darah, MMP-9 Serum, dan Skor CAT.*

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable lung disease characterized by persistent airflow limitation and generally progressive, associated with an exaggerated chronic inflammatory response in the airways and lung parenchyma due to toxic gases or particles.[1,2] Chronic airflow limitation in COPD is caused by a combination of small airways disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), where the contribution varies from individual to individual. In 2015, 3.17 million people died from COPD; this number is equivalent to five per cent (%) of all global deaths. The epidemiology of COPD is predicted to be the third leading cause of death and the fifth leading cause of disability in the world by 2020.[1–3]

COPD lung tissue damage is a complex interaction between oxidative stress, extracellular matrix proteolysis, inflammation, and apoptosis. Cigarette smoke and other harmful particles cause airway inflammation within minutes or hours of exposure. One of the early manifestations of COPD is the withdrawal of systemic inflammatory cells into the airway. Cigarette smoke and harmful particles cause oxidative stress that activates the nuclear factor kappa (NF-κβ), increasing the release of inflammatory genes.[4,5]

NF- dimers are inactivated in the cytoplasm of cells bound by kappa B (Iκβ) inhibitors. Phosphorylation by the Iκβ kinase complex (IKK) causes degradation of Iκβ so that the bond between NF-κβ and Iκβ is broken, causing NF- to be free and translocated into the nucleus and transcription of inflammatory genes, including tumour necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-8 cause airway inflammation in COPD. The inflammatory process that occurs continuously will cause more severe airway damage. The degree of airway inflammation correlates with the severity of existing obstruction. Therefore, the measurement of inflammatory cells count in airway can describe the degree of airway obstruction. An increase in the number of neutrophils in airway is related to the severity of COPD. Neutrophils increase during exacerbations. Neutrophils secrete serine proteases, namely matrix metalloproteinase-9 (MMP-9), which play a role in alveolar destruction, causing emphysema and activating tumour growth factor-α (TGF-α), triggering mucus hypersecretion.[4–7]

Suppressing inflammation to prevent these complications is among the objectives of COPD therapy. Long-term anti-inflammatory treatment is expected to reduce disease progression.[8–11] Roflumilast is a potent and selective phosphodiesterase 4 (PDE4) enzyme inhibitor that targets systemic inflammation. Roflumilast has various anti-inflammatory effects, including reducing inflammatory mediators, expression of cell surface markers, and inhibition of apoptosis. Phosphodiesterase 4 plays a role in the pathophysiology of COPD by increasing levels of cyclic adenosine monophosphate (cAMP). The increase in cAMP levels by roflumilast then inhibits the activity of binding deoxyribonucleic acid (DNA) sequences with NF- by preventing phosphorylation and degradation of Iκβ as an inhibitory factor of NF-.[12,13]

Based on the description above, authors are intrigued to identify and prove the role of roflumilast administration at 500 milligrams (mg) dose per day as an adjunct therapy to standard therapy for patients with COPD in reducing inflammation and improving symptoms of airway obstruction. Inflammation subsidence is indicated by the decline in absolute number of neutrophils in blood and serum MMP-9, reduced airway obstruction is marked by an improvement in the percentage of forced vital capacity in one second (%FEV_1) to the predicted value. In addition, clinical improvement is characterized by an increase in lung function and quality of life (QOL) in COPD patients, as evidenced by the decrease in COPD assessment test (CAT) score.

METHOD

This study was a quasi-experimental clinical trial with pre and post-test design for treatment and

control groups. The study was conducted at Dr Moewardi Surakarta Hospital and dr. Soehadi Prijonegoro Sragen Hospital from January 6 to March 6 2020. Study sample was patients with stable COPD who had been registered as outpatients at pulmonary clinic of RSUD dr. Moewardi Surakarta and RSUD dr. Soehadi Prijonegoro Sragen on January 6 to March 6 2020. Stable COPD in this study was described as COPD which did not undergo acute exacerbation, worsening respiratory symptoms characterized by increased tightness, sputum production, and changes in sputum colour. Consecutive selection was applied by selecting participants based on inclusion criteria to be included in the study until the required number was met.

The inclusion criteria were group C and D stable COPD patients aged 40 years or older, willing to participate in the survey and to sign the consent form. The exclusion criteria were patients with stable COPD who had pulmonary or extrapulmonary malignancies, pneumonia, severe hepatic dysfunction, severe renal function impairment, and gastroenteritis. The termination criteria were patients resigning, passing away, or experiencing severe side effects of roflumilast.

Patients with stable COPD who met the inclusion criteria were explained about the aims and objectives of the study. Patients who agreed were asked to sign an informed consent. Forty patients with stable COPD were included and assigned into control and treatment group (20 patients each). The treatment group received standard therapy for stable COPD and roflumilast 1 x 500 mg for 28 days, while the control group only received standard treatment for 28 days. The control and treatment groups were examined for absolute neutrophil counts, serum MMP-9, and asked to fill out CAT questionnaire and spirometry at the beginning and end of the study. The homogeneity test of research characteristics in the form of qualitative variables with a categorical scale (nominal/ordinal) was carried out by using chi-square test. The homogeneity test for quantitative variables with a numerical scale was carried out by using a 2-mean difference test whose type of test was based on the data distribution of sample characteristic variables. Data on all variables were analyzed using SPSS 21 for windows. Analysis of normally distributed data was carried out by using the paired t-test and independent-sample t-test. In contrast, the data with abnormal distribution was carried out by using Wilcoxon signed-rank test for the paired group or the Mann-Whitney test for the unpaired group.

RESULTS

Forty participants who met the inclusion and exclusion criteria were assigned into two groups, 20 people in the treatment and control group respectively. The treatment group received standard therapy for stable COPD and roflumilast 1 x 500 mg/day for 28 days. The control group only received standard treatment for stable COPD.

Characteristics of research subjects, including age, sex, education, occupation, degree of smoking with Brinkman Index (BI), body mass index (BMI), degree of obstruction (GOLD), group score, frequency of exacerbations in one year, and comorbid diseases were measured and compared between the treatment and control group. Qualitative characteristic variables with categorical scale include gender, education, occupation, degree of smoking (IB), BMI, degree of obstruction, frequency of exacerbations in one-year, comorbid diseases, and group scores, while quantitative characteristic variable with numerical scale is age. The characteristics of research subjects are demonstrated in table one.

The homogeneity test results between the control and treatment group for quantitative characteristic variables, namely the age variable, obtained P=0.537, it's indicated that the control and treatment group have the same mean or average. The homogeneity test result of qualitative characteristic variables, including gender, education, occupation, IB, BMI, degree of obstruction, group scores, and comorbidities, showed that these variables had a homogeneous distribution between the control and treatment group.

Tabel 1. Characterisics of Study's Subjects

Variable	Groups		*P*
	Control (n=20)	Treatment(n=20)	
Age (mean±SD)	63.15±1.73	64.80±2.00	0.537
Gender			
Male	15 (75.0%)	17 (85.0%)	0.435
Female	5 (25.0%)	3 (15.0%)	
Education			
Elementary School	15 (75.0%)	17 (85.0%)	0.404
Junior High School	0 (0%)	1 (5.0%)	
Senior High School	1 (5.0%)	0 (0%)	
Bachelor's degree	4 (20.0%)	2 (10.0%)	
Job			
Farmer	10 (30.0%)	11 (55.0%)	0.079
Laborer	2 (10.0%)	4 (20.0%)	
Retired Civil Servants	1 (5.0%)	0 (0%)	
Trader	1 (5.0%)	0 (0%)	
Housewife	1 (5.0%)	2 (10.0%)	
Driver	1 (5.0%)	0 (0%)	
Seamstress	1 (5.0%)	0 (0%)	
Teacher	2 (10.0%)	2 (10.0%)	
Fisherman	0 (0%)	1 (5.0%)	
Carpenter	0 (0%)	1 (5.0%)	
Indonesian National Armed Forces	1 (5.0%)	0 (0%)	
Smoking Degree (IB)			
Nonsmokers	7 (35.0%)	5 (25.0%)	0.407
Light	7 (35.0%)	6 (30.0%)	
Moderate	5 (25.0%)	9 (45.0%)	
Heavy	1 (5.0%)	0 (0.0%)	
Body Mass Index (BMI)			
Underweight	6 (30.0%)	9 (45.0%)	0.232
Normal	12 (60.0%)	8 (40.0%)	
Overweight	2 (10.0%)	3 (15.0%)	
Frequency of Exacerbations			
1 time	15 (75.0%)	18 (90.0%)	0.218
2 times	5 (25.0%)	2 (10.0%)	
Degree of Obstruction			
Light	2 (10.0%)	0 (0.0%)	0.873
Moderate	0 (0%)	4 (20.0%)	
Severe	15 (75.0%)	11 (55.0%)	
Very Severe	3 (15.0%)	5 (25.0%)	
Group Score			
C	6 (30.0%)	1 (5.0%)	0.091
D	14 (70.0%)	19 (95.0%)	
Comorbid			
No Comorbidity	12 (60.0%)	7 (35.0%)	0.179
Hypertension	7 (35.0%)	13 (65.0%)	
Hypertensive heart disease (HHD)	1 (5.0%)	0 (0%)	
Neutrophil pretest (mean±SD)	612.2±1658.3 µL	981.2±2315.0 µL	0.797
MMP-9 pretest (mean±SD)	364.85±274.07 ng/mL	346.30±179.62 ng/mL	0.665
%FEV_1 pretest (mean±SD)	45.80±15.5341	39.15±11.85	0.136
CAT pretest (mean±SD)	16.20±3.750	17.10±2.936	0.540

Table 2. Absolute neutrophil count blood pretest, posttest, and changes in the control and the treatment group

Group	Absolute neutrophil count of blood			
	Pretest	Posttest	*P*	Δ (Postest-Pretest)
Treatment	5981.15±2315.08	5740.10±2090.84	0.303	114.50
Control	5612.20±1658.37	5998.45±2221.51	0.618	80.0
P	0.646	0.707	-	0.449

Table 3. The value of MMP-9 serum pretest, posttest, and changes in the control group and treatment group

Group	MMP-9 serum			
	Pretest	Posttest	*P*	Δ (Posttest-Pretest)
Treatment	346.30±179.62	293.00±126.89	0.167	-53.30±181.82
Control	364.85±274.07	402.15±225.47	0.520	-37.30±247.18
P	0.665	0.123	-	0.195

Table 4. Percentage of FEV_1 pretest, posttest, and changes in the control group and treatment group

Group	%FEV_1			
	Pretest	Postest	*P*	Δ (Postest-Pretest)
Treatment	39.5±11.85	41.60±12.72	0.122	4.45±11.13
Control	45.80±15.53	46.25±15.50	0.472	0.45±7.037
P	0.136	0.306	-	0.189

Table 5. CAT scores pretest, posttest, and changes in the control group and the treatment group

Group	CAT Score			
	Pretest	Postest	*P*	Δ (Postest-Pretest)
Treatment	17.10±2.93	16.65	0.0001	-1.950±1.23
Control	16.20±3.75	24.35	0.112	0.40±1.046
P	0.778[a]	0.069[a]	-	0.0001

The *P*>0.05. The result revealed that all qualitative characteristic variables, namely gender, education, occupation, IB, BMI, GOLD, and group scores had similar proportions between control and treatment group.

The result of calculating the absolute number of blood neutrophils before and after treatment in the control and treatment groups was described in Table 2. T-test was applied to examine two different means of absolute neutrophil count between pretest and posttest in the control group. The result obtained *P*=0.618, it's suggested an insignificant increase in absolute neutrophil count in the blood after standard therapy.

Wilcoxon test was applied to examine two different means of absolute neutrophil count between pretest and posttest in the treatment group. The result obtained *P*=0.303, it's indicated no significant decrease in absolute neutrophil count in blood post-treatment.

The result concurs this study hypothesis which stated that roflumilast decreases absolute neutrophil counts in stable COPD patients. The total number of blood neutrophils in pre and post-treatment group decreased but was not statistically significant (*P*=0.449).

The calculation result of serum MMP-9 values between pretest and posttest in the control and treatment group is described in Table 3. Wilcoxon test was used to examined two different tests mean of MMP-9 serum between pretest and posttest in the control group and obtained *P*=0.520, it's indicated no significant increase in serum MMP-9 following standard therapy. T-test was applied to examine two different means of MMP-9 serum between pretest and posttest in the treatment group and obtained *P*=0.167, it's implied no significant decrease in serum MMP-9 following the treatment.

The result also concurs this study hypothesis which stated that roflumilast decreases serum MMP-9 in stable COPD patients. The mean of serum MMP-9 between pre and post-treatment groups decreased but was not statistically significant (*P*=0.195).

The results of value of %FEV_1 value between pretest and posttest in the control and treatment group is demonstrated in Table 4. Different tests of 2 means of %FEV_1 between pretest and posttest in the control group using the Wilcoxon test obtained *P*=0.472, it's implied insignificant increase in %FEV_1

value after receiving standard therapy. The difference test of 2 mean of %FEV_1 between pretest and posttest in the treatment group using the t-test obtained *P*=0.122, it's signified that there was an increase in %FEV_1 value following the treatment though statistically insignificant.

This result also agrees the research hypothesis which stated that roflumilast leads to an increase in %FEV_1 in patients with stable COPD. The number of %FEV_1 in pre and post-treatment group increased but was not statistically significant (*P*=0.189).

The results of CAT score before and after receiving treatment in control and treatment group is detailed in Table 5. The CAT score of control group using paired t-test between pretest and posttest treatment obtained *P*=0.112, it's mean that the control group's CAT score after receiving standard therapy did not increase significantly. The treatment group used 2 different test mean t-test for paired samples and obtained *P*=0.0001, it's indicated that there was a significant decrease in CAT score in the group following the treatment. The result also agrees the study hypothesis stating that roflumilast lowers CAT score in patients with stable COPD.

DISCUSSION

The result reveals that majority of participants were male, 17 people (85.0%) in the treatment group and 15 people (75.0%) in the control group. The Indonesian Society of Respirology (ISR) in 2016 explained that the prevalence of COPD patients mainly affected men. It is associated with smoking habits and because most men work outside which increases risk of exposure to outdoor air pollution. WHO in 2017 explained that increased risk of exposure to outdoor and indoor air pollution increases the risk of COPD in men and women.[1-3] The average age (years) of subjects in the treatment group was (64.80±2.00) years old, while in the control group was (63.150±1.73) years old. Chronic Obstructive Pulmonary Disease treatment guideline by ISR in 2016 and GOLD 2019 revealed that COPD prevalence increases with age and is highest at >60 years of age. The increased risk of COPD is 2–3 times in old age. Two hypotheses are believed about the increased risk of COPD in old age: age is associated with lung structure and function changes. In old age, lung structure and function decrease, increasing susceptibility to COPD. Another factor that plays a role is the accumulation of exposure to harmful gases and particles during life, causing damage to the lungs and making it easier to develop COPD.[14,15]

The smoking status based on Brinkman index (IB) among participants was mostly moderate in the treatment group (9 people or 45.0%) and light smoker in the control group (7 people or 35.0%). Smoking is the leading cause of COPD; 85% of COPD cases are smokers. Cigarette smoke is a risk factor that plays an essential role in COPD and causes more than 90% of COPD in Western countries. Cigarette smoke is one of the leading causes of respiratory symptoms and impaired lung function. The 2016 Indonesian Lung Doctors Association explained that smoking and COPD is a dose-response relationship; the more cigarettes smoked and the longer the smoking habit, the higher the risk of suffering from COPD. Secondhand smoke with repeated exposure, exposure to environmental pollutants and exposure to particulate matter in the workplace also affects COPD. The results showed that the majority of COPD patients had moderate IB; according to Barnes in 2004 that cigarette smoke is a vital risk factor for the occurrence of COPD.[1,15–17]

Participant's nutritional status in the treatment group mostly had average values (40.0%) and 60.0%in the control group. The highest education level among participants in treatment and control groups was elementary school (SD), at 85.0% and 75.0% respectively. Most participants in the treatment group worked as farmers (5.0%) and as labourer (30.0%) in the control group. Educational and occupational status affect the development of COPD. Lower level of education causes common knowledge of the dangers of cigarette smoke or particle exposure to health. Lower education also causes lack of control and learning about the disease and its treatment. Employment history may determine an individual's socioeconomic status.

According to GOLD 2019, low socioeconomic status is a risk factor for COPD. Low socioeconomic status is associated with an increased risk of COPD, but the causative component is unclear. There is a strong relationship between the risk of developing COPD inversely related to socioeconomic status.[2,16]

The most common type of obstruction was severe, affecting 11 patients (55.0%) in the treatment group and 15 patients (75.0%) in the control group. According to GOLD 2019, Roflumilast combined with LABA either with or without inhaled corticosteroids or long-acting muscarinic antagonists is an excellent alternative management option for patients with COPD with severe to very severe obstruction associated with chronic bronchitis and a history of repeated exacerbations.[2]

The most common comorbidities was hypertension, affecting 13 people (65%) in the treatment group and 7 people (35.0%) in the control group. Airflow limitation in COPD has effects on cardiac function and air exchange, leading to systemic consequences. COPD inflammation causes the spill-over of inflammatory mediators into the systemic circulation leading to systemic manifestations. Systemic inflammation also worsens comorbid diseases, including ischemic heart disease, heart failure, osteoporosis, and depression. Comorbid conditions in COPD lead to increased hospitalization, mortality, and costs.[16,17]

The results showed no significant effect of giving roflumilast 500 mg on reducing the absolute number of neutrophils in stable COPD patients (P=0.449). However, the administration of roflumilast 500 mg descriptively was better in reducing the absolute neutrophil count in the blood compared to the control.

Neutrophils are found in the bronchial epithelium, bronchial glands, and bronchial smooth muscle, which have increased production during a stimulus. They are found in the sputum and BAL of COPD patients. The mechanism of systemic neutrophilia is the spill-over of airway neutrophils into the systemic circulation; besides, the inflammatory stimulus directly triggers an increase in the production of neutrophils by the bone marrow. COPD patients have an increased migration of neutrophils into the airways triggered by strong chemoattractants, including IL-8 and LTB4.[18,19]

Neutrophilic inflammation is the key to pathogenesis of asthma and corticosteroid-resistant COPD. In vitro studies of Hatzelmann et al., quoted from 20 in 2010, showed that roflumilast and roflumilast N-oxide could inhibit neutrophil release from interleukin 8 (CXCL8), LTB4, MMP-9, and neutrophil elastase (NE). In addition, these PDE4 inhibitors inhibit neutrophil degranulation with a PDE4-selective effect that PDE3 inhibitors or theophylline do not have.[20,21]

The study result indicates that the administration of roflumilast 500 mg reduced the absolute blood neutrophil count lower than standard therapy alone, albeit not statistically significant. The causes were not substantial; first, the included patients were stable COPD who had average absolute blood neutrophil counts resulting in an overall mean difference between treatment and control, which was not significant for various cellular inflammatory markers. Second, according to several studies that the window period for evaluating the anti-inflammatory effect of roflumilast treatment on COPD is at least 6 months; a decrease in sputum neutrophils can occur within four weeks, while the neutrophils studied are whole blood, neutrophil counts. Third, the effect of possible confounders such as smoking status and previous use of inhaled steroids on roflumilast treatment could not be assessed.[22]

The results showed no significant effect of giving roflumilast 500 mg on the decrease in serum MMP-9 of stable COPD patients (P=0.195). However, descriptively giving roflumilast 500 mg was better in lowering serum MMP-9 compared to controls. Matrix metalloproteinase-9 is a major elastolytic MMP, responsive to tissue remodelling and repair through basement membrane degradation of type IV collagen and other matrix proteins. Macrophages and neutrophils are the primary cells that secrete MMP-9, but other cells can also secrete MMP-9, including epithelial cells and lymphocytes. In COPD, MMP-9

can be used as a biomarker measured from peripheral blood to describe disease progression.[20,23]

Roflumilast can reduce ROS formation after exposure to cigarette smoke and consequently inhibit PI3Kδ activation and increase HDAC2 activity. In addition, Roflumilast inhibits NF- translocation (p65). The effect shown by roflumilast allows the reduction of inflammatory proteins, such as MMP-9.[24]

This study indicates that administration of roflumilast 500 mg can reduce serum MMP-9 lower than standard therapy alone, and the serum MMP-9 value in control patients is still higher than usual but not statistically significant. Insignificant causes include roflumilast being able to inhibit critical cells such as neutrophils and macrophages but unable to stop MMP-9 synthesis by lymphocytes, smooth muscle cells, and airway endothelial cells triggered by inflammation. Most of the population in this study had comorbid diseases, which can be a confounding factor for serum MMP-9 levels since comorbid disorders can also induce inflammation.[20]

The results showed no significant effect of giving roflumilast 500 mg on the increase in %FEV_1 in stable COPD patients (*P*=0.189). However, roflumilast 500 mg descriptively on standard therapy is better than standard therapy alone (control). Administration of roflumilast 500 mg as an anti-inflammatory led to a decrease in airway proinflammatory cytokines in stable COPD patients. Reduction of inflammation will reduce airway obstruction through the improvement of %FEV_1 from spirometry results. Mucus hypersecretion, emphysema, and small airway fibrosis lead to a decrease in the %FEV_1 value. In addition, roflumilast can increase intracellular cAMP levels, thereby inhibiting the release of ROS from neutrophils and eosinophils. This pathway leads to decreased myofibroblast levels and enhanced fibrosis repair through inhibition of epithelial-to-mesenchymal transition.[12,25,26]

This study indicates that the administration of roflumilast 500 mg increased the value of %FEV_1 better than standard therapy alone, though statistically insignificant. The reason is that the administration of roflumilast has not been able to ultimately reduce the degree of inflammation because phosphodiesterase 4 acts on macrophages (NF-), epithelial cells, and fibroblasts, while the inflammatory process of lymphocytes, endothelial cells, smooth muscle cells continue.[20]

This study showed a significant effect of giving roflumilast 500 mg on the decrease in CAT score of patients with stable COPD (*P*=0.0001). The CAT score is a score for detecting and measuring COPD symptoms on the patient's clinical health status.[2] One of the roles of phosphodiesterase 4 in COPD is as an anti-inflammatory. The anti-inflammatory effect of phosphodiesterase 4 is to suppress NF- activation by inhibiting IKK activity, thereby suppressing the production of proinflammatory cytokines. Decreased cytokine production causes a decrease in airway inflammation and mucus hypersecretion. Therefore, it will reduce airflow resistance and lessen symptoms, which can assess a reduction in the CAT score. (*P*=0.0001). The decline in CAT score in the treatment group was more significant than in the control group.

This study results and some previous research evidence that many factors influence the effect of roflumilast on the respiratory tract. The limited-time of giving roflumilast due to the limited availability of roflumilast in Indonesia as well as side effects leading to gastroinstestinal disorders can be considered for further research. In addition, it is necessary to examine sputum neutrophils to determine the decrease in the degree of airway inflammation, but sputum neutrophil examination is currently not available in Indonesia. Laboratory and radiology examinations for screening patients with impaired liver, kidney function, pneumonia, and lung cancer may support further study.

CONCLUSION

Additional therapy of roflumilast 1 x 500 mg/day for 28 days in stable COPD patients could significantly reduce the CAT score of stable COPD patients. Reducing blood absolute neutrophil levels, serum MMP-9, increased %FEV_1 although statistically insignificant, descriptively giving

roflumilast 500 mg caused a decrease in total neutrophil count, serum MMP-9, CAT score, and an increase in %FEV_1. At the same time, in the control group, there was an increase in the absolute number of blood neutrophils and serum MMP-9, so it can be concluded that the administration of roflumilast is recommended for patients in group C and D of stable COPD with high score CAT.

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