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Roflumilast: Review of Phosphodiesterase-4 Inhibitor as Asthma Therapy

Rafina Syfridiana[1], *Fauna Herawati*[2]

[1]*Magister Program of Clinical Pharmacy, Faculty of Pharmacy, Surabaya University, Surabaya, Indonesia*
[2]*Department of Clinical and Community Pharmacy, Faculty of Pharmacy, Surabaya University, Surabaya, Indonesia*

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CORRESPONDENCE

E-mail: rafinasd@gmail.com
fauna@staff.ubaya.ac.id

A B S T R A C T

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways induced reversible obstruction resulting in mortality and morbidity. Roflumilast is a second-generation selective inhibitor of phosphodiesterase-4 targeting PDE type 4 isoenzymes, disturbing the breakdown of cyclic AMP (cAMP) and reducing inflammation. However, it has not been recommended for asthma patients because of insufficient evidence from trial results. The search was carried out using the PUBMED online database from 2011 to May 2021. The keywords used in this study were "Asthma" and "Roflumilast" using the Boolean Operator "AND." All articles were published until May 7, 2021. The design of the articles involved in this study was randomized. Selection of research articles was obtained to avoid duplication of articles through title and abstract screening. Next, eligible articles were extracted by reviewing the full text according to the inclusion criteria. Finally, 5 articles were used in this paper. Roflumilast can be given per-oral as a single dose or combine with ICS or montelukast. Roflumilast can increase FEV1 and reduce eosinophils, a pathological cause of asthma that induces inflammation in the airways. The side effects of roflumilast are well tolerated in asthma patients, the most common of which include headache, diarrhea, nausea, weight loss, and insomnia.

INTRODUCTION

Asthma is a heterogeneous disease characterized by chronic inflammation of the airways with symptoms of coughing, wheezing, and difficulty breathing caused by reversible airway narrowing, in response to the airways due to various stimuli – both allergens and non-allergens – such as exercise, weather changes, and viruses causing mortality and morbidity (Global Initiative for Asthma, 2019).

Asthma prevalence from WHO health survey data (World Health Organization) in 2002-2003, in young adults with the age range of 18-45 years there were 177,496 asthmatics in 70 countries. While a study was conducted by the ISAAC (International Study of Asthma and Allergies in Childhood) in the same year in 97 countries reported its prevalence in adolescents aged 13-14 years was 798,685. The result showed the highest prevalence (≥ 20%) in Australia, Europe, North America, and parts of Latin America. Meanwhile, the lowest prevalence (< 5%) was in the Indian subcontinent, Asia-Pacific, Eastern Mediterranean, Northern and Eastern Europe (Global Asthma Network 2018). Meanwhile, In Indonesia, the prevalence of asthma is unknown due to the absence of a national survey. At the same time, asthma is included in the top 10 diseases that cause death in Indonesia. In 1995, the prevalence of asthma in Indonesia was 13 out of 1000 population (Ratnawati, 2011).

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Asthma is an airway obstruction disease characterized by smooth muscle changes, immune cell infiltration, anti-inflammatory cytokines releasing, reversible airflow obstruction, and airway hyperresponsiveness. Two risk factors triggering inflammation in asthma are genetic and environmental. Environmental factors include allergens, food, certain drugs, cigarette smoke, air pollution, exercise, weather, etc. (Russell et al., 2013). Pathological factors involved in inflammation are T-cell-mediated CD4+, eosinophils, IL-4, IL-5, and lL-3 (Bodkhe et al. 2020).

The goal of asthma therapy is to control symptoms properly, maintain normal activities, minimize the risk of exacerbations, restrict airflow and minimize side effects (Global Initiative for Asthma 2019). Asthma therapy can be performed pharmacologically and non-pharmacologically. The principle of pharmacological asthma therapy is divided into 2, namely: acute asthma therapy (during an attack) and long-term asthma therapy. Reliever medication is administered when an acute attack occurs. Meanwhile, long-term asthma therapy aims to control asthma and prevent attacks, using controller drugs used in the long term and continuously (Indonesian Ministry of Health 2008). Various types of asthma drugs can be seen in Table 1.

Table 1. Types of Asthma Drugs

Drug Types	Class	Generic Name	Drug Form/Packaging
Checker (Antiinflammation)	Inhaled Steroids	Fluticasone Propionate	MDI
		Budesonie	MDI, Turbohaler
	Antileukotrienes	Zafirlukast	Oral (tablet)
	Agonist β-2 Long-acting	Formoterol	DPI
		Salmeterol	MDI/DPI
	Combination of steroids and long-acting β-2 agonists	Fluticasone + Salmeterol	MDI
		Budesonie + Formoterol	Turbohaler
Relief (Bronkodilator)	β-2 agonist Short-acting	Salbutamol	Oral, MDI, rotacap solution
		Buttaline	Oral, MDI, Turbohaler, Injection
		Procaterol	Oral (tablet), MDI, Inhaling solution
		Fenoterol	MDI, Solution
	Anticholinergic	Ipratropium Bromide	MDI, Solution
	Methylxanthine	Theophylline	Oral
		Aminophylline	Oral, injection
		Slow Release Theophylline	Oral
	Systemic corticosteroids	Methylprednisolone	Oral, inhaler
		Prednisolone	Oral

MDI: Metered-dose inhalation.

DPI: Dry powder inhaler.

Solution: Solutions for nebulizing use with a nebulizer.

Oral: Can be in the form of syrup, tablets.

Injection: Can be used subcutaneously, im, and iv (Indonesian Ministry of Health 2008).

Roflumilast is administered orally, together with its active metabolite (roflumilast-N-oxide). It is a selective phosphodiesterase-4 inhibitor with anti-inflammatory effects. It consistently improves lung

function. It consistently improves lung function. In addition, it reduces the frequency of exacerbations in patients with chronic obstructive pulmonary disease (COPD) and symptoms of chronic bronchitis. Roflumilast is currently developing its potential as an effective anti-inflammatory treatment for asthma patients (Meltzer 2015). However, Phosphodiesterase-4 inhibitors, including roflumilast, have not been recommended for patients with asthma because of insufficient evidence from experimental results. The research in Indonesia discussing the effectiveness and safety of using roflumilast as a therapy in asthma patients has not been carried out. The purpose of this study is to determine the efficacy and safety of the use of roflumilast as therapy in asthmatic patients.

METHOD

The search was carried out using the PUBMED online database from 2011 to May 2021. The keywords used in this study were "Asthma" and "Roflumilast" using the Boolean Operator "AND." All articles published up to May 7, 2021, meting the research requirements included in this review study. Further, articles must meet the inclusion criteria: 1) The study design of the article was randomized, 2) The research subjects were patients with a diagnosis of asthma, 3) The treatment intervention was oral Roflumilast from the phosphodiesterase-4 inhibitor group, with or without combination with other drug classes, and control therapy was placebo with or without combination with other drug classes. The analysis in this study was carried out in a descriptive narrative. Initially, the research articles were selected to avoid duplication of articles through title and abstract screening. Next, the eligible articles were extracted by reviewing the full text according to the previously defined inclusion criteria. Data extracted from each research article included: 1) Identity of a research article (year of publication, study design, name of the researcher, year of study), 2) disease severity, 3) Population, 4) Demographic characteristics of patients (age, gender, height, and body weight), 5) Details of intervention (name of the drug, dose, frequency of administration, route of administration, duration of treatment, follow-up), 6) Measurement of outcomes, and 7) Study results.

RESULT

The number of articles identified during the search from the electronic database was 45 articles. After screening with inclusion criteria, six randomized articles were obtained. Furthermore, after reviewing the titles and abstracts of the six articles, two articles were identical, so only one of them was used. Thus, there were five articles used in this paper.

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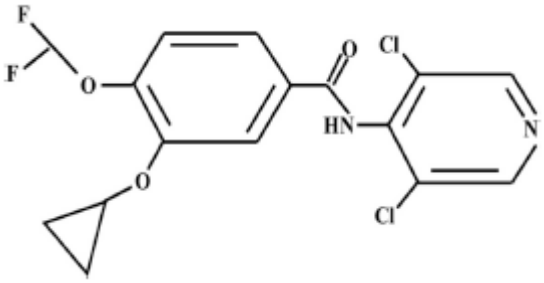
DISCUSSION

Roflumilast



Picture 1. Chemical structure of roflumilast

Roflumilast has the IUPAC (International Union of Pure and Applied Chemistry) nomenclature as 3-(cyclopropylmethoxy) N-(3,5-dihydropyridine-4-yl)-4 (difluoromethoxy) benzamide. Roflumilast has the chemical structure as in Figure 1, the molecular formula C17H14C12F2N2O3, white crystals with a molecular weight of 403.22, melts at 150°C, and has a half-life of 17 hours (Bodkhe et al. 2020).

Roflumilast is available in a once-daily oral dosage form (tablets of 500 µg) with a bioavailability of 80%. The maximum concentration (Cmax) is reached 1 hour (range 0.5 – 2 hours) after a single dose, while the active metabolite reaches Cmax within 8 hours (range 4 – 13 hours). Both are firmly bound to plasma proteins (≥97%), metabolized in the liver by CYP450 enzymes in stage I and conjugation reactions in stage II. Elimination may be impaired in patients with hepatic and renal impairment, but no dose adjustment is required. Roflumilast is not recommended to be given concurrently with potent CYP3A4, CYP3A4 and CYP1A2 enzyme inhibitors. Those inhibitors include erythromycin, ketoconazole, fluvoxamine, enoxacin, cimetidine, and rifampin (Wedzicha, Calverley, and Rabe 2016).

Roflumilast is administered orally with or without food. Its active metabolite (roflumilast-N-oxide) is a selective phosphodiesterase-4 inhibitor with an anti-inflammatory effect. It consistently improves lung function and reduces the frequency of exacerbations in patients with Chronic obstructive pulmonary disease (COPD) and chronic bronchitis, also individuals with a history of exacerbations. Roflumilast is currently developing its potential as an effective anti-inflammatory treatment for asthma patients (Meltzer 2015).

Phosphodiesterase-4 (PDE4) is expressed in smooth muscle cells and inflammatory cells (eosinophils, neutrophils, monocytes, macrophages, T-lymphocytes). Therefore, it can be a potential target for asthma therapy. Selective phosphodiesterase-4 inhibitors are new, second-generation drugs that target the PDE type 4 isoenzyme. Those interfere with the breakdown of cyclic AMP (cAMP) and reduce inflammation (Luo et al. 2018). The improvement of cAMP concentrations also increases smooth muscle relaxation. Finally, roflumilast produces anti-inflammatory effects by inhibiting the production of kappa B (NF-kB),

interleukins (IL-4 and IL-5), and TNF-, and eosinophils. It prevents airway hyperresponsiveness (Bodkhe et al. 2020).

Efficacy And Safety

Meltzer *et al.* (2015) conducted a study to assess the efficacy of roflumilast in nine randomized research. The nine research was placebo-controlled, monotherapy, and combination clinical studies in phases II and III. The study collected research data (1997-2005) in Europe, North and South America, Africa, Australia, and Asia. The efficacy of roflumilast was measured by changes in FEV1 (Forced Expiratory Volume in 1). In detail, 500 µg Roflumilast each day has been approved as a treatment for COPD. The study evaluated the efficacy of roflumilast for asthma between 125 µg and 250 µg monotherapy doses. In addition, roflumilast administration was compared with combination with ICS (inhaled corticosteroid) or placebo monotherapy. ICS consisted of 250 µg fluticasone propionate (FP) and 400 µg and 500 µg beclomethasone dipropionate (BDP).

Roflumilast consistently increased FEV1 compared to placebo in 9 studies. However, in some studies did not show statistically significant differences between roflumilast and placebo. Insignificant differences showed in comparison between phase II monotherapy and placebo. In addition, it also indicated through comparison between BDP combination and placebo combined ICS (study duration 4-6 weeks) conducted when it was unknown whether roflumilast had efficacy for asthma. Further studies in phase III monotherapy versus placebo (study duration 12-24 weeks) showed that doses of 250 µg and 500 µg consistently increased FEV1 over time and showed statistically significant differences. Two follow-up studies in phase III that compared the BDP combination roflumilast with the BDP combination placebo showed a statistically significant increase in FEV1. In addition, FP combination roflumilast and placebo combination FP for 24 weeks showed a statistically significant increase in FEV1(Meltzer et al. 2015).

Roflumilast has shown potential as an anti-inflammatory therapy for asthma. When given in combination with ICS, roflumilast showed improvement in lung function. However, the studies conducted did not have sufficient duration to observe the effects of roflumilast further.

Research by Bateman *et al.*, (2015) was conducted 6-12 weeks in Europe, North America, South Africa, and Australia in 3,802 patients aged 12-70 years. It reviewed seven randomized clinical studies (double-blind) from 1998 to 2005, non-placebo-control, phase II, and III. It evaluated the efficacy of roflumilast at a dose of 100 µg, 250 µg, or 500 µg once a day, compared with BDP 400 µg or 500 µg twice a day, and with montelukast 10 mg once a day on FEV1 changed.

In the phase II study, the group given a single dose of roflumilast 500 µg once daily for six weeks showed a significant increase in FEV1 (measured in the morning), but no significant difference when taken in the morning or evening. In addition, roflumilast administration at a dose of 500 µg had a more significant

increase in FEV1 than 100 µg. Meanwhile, there was no statistical difference between roflumilast administration at a dose of 500µg and 250µg. (E. D. Bateman et al. 2015).

Studies compared roflumilast 500 µg with BDP 400 µg (phase II, for six weeks), and roflumilast 500 µg with BDP 500 µg (phase III, for 12 weeks). Roflumilast showed a significant increase in FEV1 during the treatment period. However, there was no significant difference between roflumilast and BDP. Similarly, the efficacy of roflumilast versus montelukast in phase III. All treatment groups showed the same increase in FEV1 over 12 or 24 weeks (E. D. Bateman et al. 2015).

The above studies provide a basis for considering roflumilast as asthma (controller). Roflumilast at a dose of 500 µg once a day can be taken in the morning or evening (E. D. Bateman et al. 2015).

In 2015 Bardin, P. et al. conducted a study to evaluate roflumilast's therapeutic efficacy and mechanism of action in asthmatic patients, using eight randomized clinical studies (double-blind), placebo-control, cross-over study, and parallel-group, phase I and III. The study was conducted in Europe, North America, and South Africa (1997-2005). Effects of roflumilast 250 µg, 500 µg, 1000 µg, compared with placebo in 197 patients with asthma, ages 18-70 years. The study variables were the change in the number of sputum eosinophils, exhaled nitric oxide, and FEV1. The study reported increased FEV1 and decreased allergens that induce airway inflammation by observing the number of eosinophils and neutrophils in the sputum samples. Eosinophils are a pathological cause of asthma. Therefore, the use of roflumilast had additional advantages for asthmatic patients by significantly reducing inflammation in the airways (Bardin et al. 2015).

In addition, a study reported the effect of combination roflumilast and montelukast. The results showed improved lung function, symptoms, and more controlled asthma in individuals with moderate to severe asthma who required combination therapy. The combination of the two resulted in an increase in FEV1 compared to the placebo combination of montelukast for four weeks (Eric D. Bateman et al. 2016).

The most common side effects of roflumilast based on clinical trials are shown in Table 2. Weight loss is associated with increased cAMP in the lipolysis pathway (Wedzicha, Calverley, and Rabe 2016).

Table 2. Side effects associated with roflumilast from four placebo-controlled trials during 1-year and four trials for 6-month (Wedzicha *et al*., 2016).

Side effect (%) (n)	Roflumilast (n= 4438)	Placebo (n= 4192)
Diarrhea	9.5 (420)	2.7 (113)
Weight loss	7.5 (331)	2.1 (89)
Nauseous	4.7 (209)	1.4 (60)
Back pain	3.2 (142)	2.2 (92)
Influenza	2.8 (124)	2.7 (112)
Insomnia	2.4 (105)	1.0 (41)
Decreased appetite	2.1 (91)	0.4 (15)

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The safety and tolerability of roflumilast for asthma were investigated by Chervinsky *et al.,* (2015). The overall incidence of 10 randomized controlled trials in Phase II and III reported adverse events of roflumilast were headache, diarrhea, nausea, weight loss, and insomnia. It was concluded from the safety analysis that the adverse events were well tolerated by asthma patients with mild to moderate severity. It may be due to the systemic effect of roflumilast and will decrease with continued use of roflumilast. In patients with COPD, diarrhea, nausea, and headache would disappear within three weeks of roflumilast continued use. The side effects are considered proportional to the potential given.

CONCLUSIONS

Roflumilast is a second-generation selective phosphodiesterase-4 inhibitor that targets the PDE type 4 isoenzyme. It interferes with the breakdown of cyclic AMP (cAMP) and reduces inflammation. It can be given as a single dose or combined with ICS or montelukast. Furthermore, roflumilast can increase FEV1 and reduce eosinophils, a pathological cause of asthma that induces inflammation in the airways. The side effects are well tolerated in patients with asthma, the most common being headache, diarrhea, nausea, weight loss, and insomnia.

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