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Literature review

Roflumilast: A review of chronic obstructive pulmonary disease (COPD) treatment

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ARTICLE INFO

ARTICLE INFO

Submitted : *June 2020*
Accepted : *September 2020*
Published : *January 2021*

Keywords:

COPD, Roflumilast, phosphodiesterase-4 inhibitor

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is a chronic airway inflammation with resulting progressive airflow limitation that has a high incidence, morbidity, and mortality. Roflumilast is an oral phosphodiesterase-4 inhibitor as a therapy to decrease the risk of COPD exacerbations in patients with moderate-severe COPD with a history of chronic bronchitis. Roflumilast can be given orally once daily as a single or combination drug. It can be used as COPD moderate-severe but also more beneficial as COPD mild treatment. The efficacy of Roflumilast can prevent exacerbations of repetition and can fixed lung function both in terms of FEV1 and vital capacity to force. The incidence of side effects, which are diarrhea and digestive disorders. The cost-effectiveness showed that Quality of life patient with Roflumilast is better than the group without additional. This paper aimed to review systematically Roflumilast as COPD treatment for the clinical application.

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INTRODUCTION

COPD (Chronic obstructive pulmonary disease) is a disease followed by persistent air flow obstruction symptoms because of alveolar abnormalities caused by meaningful exposure to hazardous particles or gases. COPD should be considered in patients with dyspnea, chronic coughing or sputum establishment, a history of recurrent lower respiratory tract infections, or previous exposure to disease risk factors. Chronic airflow limitations are COPD characteristics due to a combination of two types of small airway diseases (e.g., obstructive bronchiolitis) and emphysema (Global Initiative for Chronic Obstructive Lung Disease, 2019). The prevalence of COPD in Indonesia based on RISKESDAS 2013 was 3,8% (Dasar, 2013).

The most common cause of COPD is cigarette smoke, dust, air pollutants, and alpha-1 antitrypsin reduction. Chronic bronchitis can be called a long-standing mucus buildup. The mucous layer is epithelial tissue such as loose connective tissue, and it has a submucosa whose glands produce mucus naturally if pathogens enter the respiratory tract. Chronic bronchitis occurs due to an increase in mucous production so much that it causes narrowing of the respiratory tract. Usually, it occurs to be preceded by irritation by smoking dust, which is responded to by our body as an obstructive disorder narrowing the airways, by resulting in hypertrophy and hyperplasia of the mucous glands. If this goes on for a long time, there will be ciliary damage (Centers for Disease Control and Prevention (US), 2010). Smoking can cause tissue damage directly, through oxidative stress, and indirectly, by causing an inflammatory response. Toxic substances such as those in cigarettes will cause inflammation of the airways, which will then call in inflammatory mediators. COPD patients show mark inflammation that correlates to the severity of the disease; the cytokines released can induce macrophages. Production of IL-8 from alveolar macrophages together with pulmonary epithelial cells results in neutrophilic infiltrates in COPD patients. Neutrophils, macrophages, CD4 +, CD8 + are inflammatory cells that are present in COPD pathogenesis (Agustí & Hogg, 2019).

Besides, proteases are also activated by neutrophils and macrophages. Protease is the main factor that drives the development of emphysema. The effect can be resisted with anti-proteases such as α-1 antitrypsin. Antitrypsin deficiency α-1 can cause dangerous and early onset of emphysema. Arterial stiffness and neutrophils mediate inflammation activation (Berg & Wright, 2016).

There are three pathology mechanisms in COPD patients; chronic bronchiolitis obstruction, emphysema, and mucus blockage. Activation of inflammatory mediators continuously will cause a chronic inflammatory process in COPD, involving the immune system is most evident in the bronchial wall of the airways. Emphysema mainly affects the small airways caused by an inflammatory process involving the parenchyma and chronic bronchitis. Accumulation of mucus exudate in the lumen and an increase in bronchial wall tissue capacity result in small airflow obstruction (King, 2015). The pulmonary structural damage manifests inflammation in COPD induced by CD8+ T cell-mediated, neutrophil-based chronic inflammation, including interleukins, TNF-α, etc. (Zhang et al., 2018). The mediator inflammation is released by cAMP, which has been hydrolyzed by phosphodiesterase (PDE). The expression of PDE4 in the lung tissue of COPD patients shown PDE4 as a potential drug in the treatment of COPD (Zuo et al., 2019). Roflumilast is a selective phosphodiesterase-4 inhibitor (PDE4) used to treat the patient with COPD.

The goal of therapy in stable COPD is to overcome and prevent acute exacerbations,

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reduce disease progression, improve the patient's physical and psychological state so that the patient can carry out daily activities, reduce the number of days spent in the hospital, and reduce the number of deaths. The goal of therapy in acute exacerbations is to maintain respiratory function and prolong survival. The treatment given can be in the form of pharmacological treatment and non-pharmacological treatment. Pharmacological therapies that can be given to stable COPD include:

Table 1. The commonly drungs used in the treatment of COPD

GENERAL MEDICINE	TYPE INHALER	NEBULIZER	ORAL	INJECTION	DOA
BETA $_2$- ANTAGONIS					
SHORT-ACTING (SABA)					
Fenoterol	MDI	√	Tablet, syrup		4-6 hours
Levalbuterol	MDI	√			6-8 hours
Salbutamol (albuterol)	MDI & DPI	√	Tablet, syrup, sustain release	√	4-6 hours 12 hours sustain release
Terbutalin	DPI		Tablet	√	4-6 hours
LONG-ACTING (LABA)					
Arformoterol		√			12 hours
Formoterol	DPI				12 hours
Indaceterol	DPI				24 hours
Olodaterol	SMI				24 hours
Salmeterol	MDI & DPI				12 hours
ANTICOLINERGIK					
SHORT-ACTING (SAMA)					
Ipratropium bromide	MDI	√			6-8 hours
Oxitropium bromide	MDI				7-9 hours
LONG-ACTING (LAMA)					
Acidinium bromide	DPI, MDI				12 hours

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Glycopironium bromide	DPI		solution	√	12 -24 hours
Tiotropium	DPI, SMI				24 hours
Umeclidnium	DPI				24 hours
COMBINATION SHORT-ACTING BETA $_2$- AGONIS DAN ATIKOLINERGIK (SABA/SAMA)					
Fenoterol/Iprotropium	SMI	√			6-8 hours
Salbutamol /Iprotropium	SMI, MDI	√			6-8 hours
COMBINATION SHORT-ACTING BETA $_2$- AGONIS AND ANTICOLINERGIK (LABA/LAMA)					
Formoterol/aclidinium	DPI				12 hours
Formoterol/ Glycopironium	MDI				12 hours
Indecaterol/Glycopironium	DPI				12 -24 hours
Vilanterol/Umeclidinium	DPI				24 hours
Olodaterol/Tiotropium	SMI				24 hours
METHYLXANTIN					
Aminophilin			solution	√	Up to 24 hours
Teofilin SR			Tablet	√	Up to 24 hours

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COMBINATION SHORT-ACTING BETA $_2$- AGONIS AND KORTIKOSTEROID (LABA/ICS)	
Formoterol/Beclometasone	MDI
Formoterol/Budesonide	MDI, DPI
Formoterol/Mometasone	MDI
Salmeterol/ Fluticasone	MDI, DPI
Vilanterol/ Fluticasone furoate	DPI
TRIPEL COMBINATION LAMA/LABA/ICS	
Fluticasone/ Umeclidinium /Vilanterol	DPI
Beclometasone/Formoter/ Glycopironium	MDI
PHOSPODIESTERASE-4 INHIBITOR	
Roflumilast	Tablet
MUCOLITIC	
Erdostine	Tablet

*) MDI= Metered Dose Inhaler, DPI= Dry Powder Inhaler, SMI= Soft Mist Inhaler (GOLD, 2017)

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Roflumilast

The IUPAC name for Roflumilast is 3-(cyclopropylmethoxy) N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy) benzamide (figure 1); CAS 162401-32-3 with empirical formula C17H14Cl2F2N2O3 and molecular weight is 403,22. These compounds are achiral, a white crystalline solid, and its melting point is 158°C (Giembycz & Field, 2010). Roflumilast is a highly-selective phosphodiesterase-4 inhibitor (PDE4) part of the PDA enzyme as a therapy for severe COPD with a history of chronic bronchitis and exacerbations. The mechanism of PDE4 inhibitors is by hydrolyzing cyclic adenosine monophosphate (cAMP) in inflammatory cells. Some anti-inflammatory effects are produced by increasing intracellular cAMP, including decreased neutrophil release as an inflammatory mediator, cytokinin release, and apoptosis. Roflumilast decreases allergens that cause inflammation and stabilize the inflammatory system induced by lipopolysaccharides. Phosphodiesterase inhibition present as anti-inflammation, anti remodeling, and bronchodilator effect (Zuo et al., 2019). Other studies showed that PDE4 inhibitor reduces pulmonary fibrosis by targeted type II AEC injury, collagen accumulation, and decreased release chemokine level significantly (Sisson et al., 2018).

Roflumilast is available in a 500 mg single dose daily tablet. Bioavailability is around 80%. Maximum plasma Roflumilast concentration is achieved approximately 1 hour (range 0.5-2 hours) after a single dose administration. At the same time, the high concentration in the form of active N-oxide metabolites is accomplished within 8 hours (range 4-13 hours). Roflumilast has an active metabolite form both have strong plasma protein bonds of around 97%. In phase I, cytochrome P450 (CYP) isoenzymes 1A2 and 3A4 and in phase II, conjugation reactions metabolic processes takes place. Roflumilast has a half-life of 17 hours. In patients with hepatic disorders, Roflumilast elimination disorder is likely to occur, however dosage adjustments are not required. Dose adjustment is also not necessary in patients with kidney disorders. Roflumilast is not supposed to be given along with CYP3A4 strong inhibitors or dual CYP3A4 and CYP1A2 inhibitors such as erythromycin, ketoconazole, cimetidine or rifampicin. Azithromycin is a macrolide group that is generally given to patients with COPD who is only a weak inhibitor of CYP3A4 and interactions with Roflumilast lighter than erythromycin (Wedzicha et al., 2016).

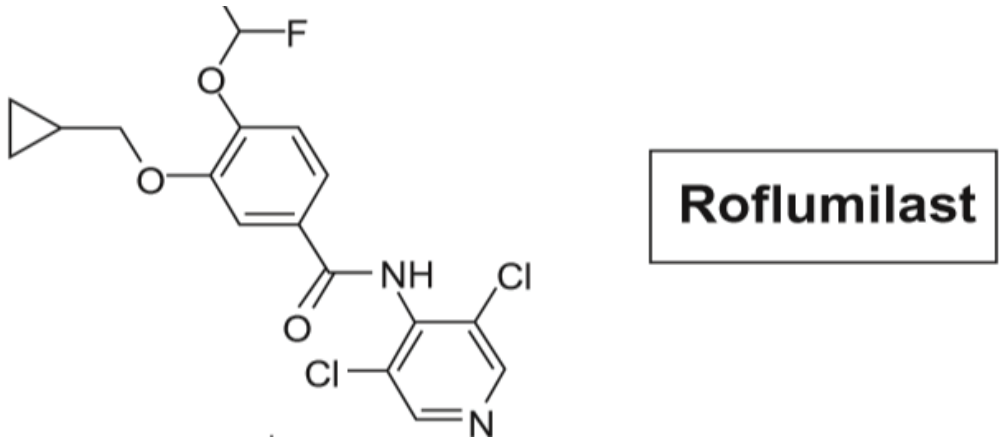

Figure 1. The Structure of Roflumilast (Giembycz & Field, 2010)

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An adverse drug reaction of Roflumilast is digestive disorders such as diarrhea, nausea, and weight loss. Other side effects that arise are sleep disturbance, decreased appetite, and back pain when compared with placebo. The general side effect of severe COPD is weight loss. This can be attributed to increased cAMP on lipolysis regulation. Research conducted in China states that the most common adverse effects related to the use of Roflumilast are upper respiratory tract infections, anorexia, weight loss, and diarrhea. Physical check and laboratory tests, such as complete blood tests, blood chemistry, urine analysis, and electrocardiogram, did not explain clinically relevant side effects (Lee et al., 2016).

Seven randomized controlled trials on the participants' safety tend to have more side effects of Roflumilast than placebo, gastrointestinal side effects (diarrhea, nausea, vomiting), headaches, and weight loss. There was no meaningful difference in the risk of heart complications or flu-like symptoms or upper respiratory infections. Roflumilast reduces moderate to severe attacks and leads to significant improvements in pulmonary function regardless of the severity of the disease and concomitant use of standard COPD therapies (Andarian et al., 2016).

Table 2. Side Effects of Roflumilast

	Roflumilast (n=102)		**Placebo (n=105)**		**value *p***
	n (%)	**case**	**n (%)**	**case**	
All bad events	71 (69,6)	176	48 (45,7)	78	<0,01
Upper respiratory tract infection	21 (20,6)	24	10 (9,5)	10	0,03
Diarrhea	14 (13,7)	14	0	0	<0,01
Weight loss	9 (8,8)	9	1 (1,0)	1	0,01
Anorexia	9 (8,8)	9	0	0	<0,01
COPD exerbation	9 (8,8)	9	12 (11,4)	14	0,64
Decreased appetite	6 (5,9)	6	1 (1,0)	1	0,06
Gastritis	5 (4,9)	5	0	0	0,03
Constipation	4 (3,9)	4	1 (1,0)	1	0,20
Dizzy	4 (3,9)	4	0	0	0,06
Rhinorrhea	4 (3,9)	4	1 (1,0)	1	0,21

Source: Lee et al., 2016

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Efficacy and safety

The effectiveness and safety of Roflumilast for the administration of COPD were assessed in 9 phase II / IV randomized double-blind clinical trials. Past phase III studies, treatment with 500 mg Roflumilast tablets, have an increased pulmonary function association compared with placebo. Other studies also explained Roflumilast could fixed lung function in severe COPD. It could reduce exacerbations in moderate to severe COPD compared to placebo. The study showed that Roflumilast therapy significantly reduced the average incidence of repeated exacerbations and the length of stay in the hospital (Cilli et al., 2019).

The safety dan clinical effect of Roflumilast in the COPD patient was evaluated by a Chinese study group using RCT. They identified nine articles and 13 RCT studies showing that patients given with Roflumilast benefited from improved lung function and quality of life only with some side effects. Roflumilast can prevent exacerbation, increase lung function in terms of FEV 1, and forced vital capacity. As for safety, the overall cumulative incidence of ADR for the Roflumilast group was more significant than the placebo group (Liu et al., 2018).

Table 3. Cost-Effectiveness of Roflumilast Addition

	LAMA+ Roflumilast	LAMA	Incremental	LABA/ICS+ Roflumilast	LABA/ICS	Incremental	LAMA+ LABA/ICS+ Roflumilast	LAMA +LABA/ICS	Incremental
Total cost of CHF	86.754	83.364	3390	91.470	88.161	3308	99.364	95.564	3799
Maintenance costs, CHF	35.857	25.481	10.376	40.917	30.279	10.638	43.533	37.682	10.851
Exerbation treatment costs, CHF	2039	2.331	-292	20248.5285	2331	-306	2036	2331	-295
Ex-hospital maintenance fees	48.858	55.552	-6694	9.642	55.552	-7024	48.795	55.552	-6757
Life year (LY)	9.625	9.278	0,347	6.479	9.278	0,364	9.628	9.278	0.351
QALY	6.466	6.191	0,275	11.456	6191	0,289	6.468	6.191	0,278
ICER,CHF per QALY	12.313			9078			13.671		
ICER,CHF per LY	9.757						10.833		

*) note: maintenance costs including medical services and COPD fees, reimbursement of costs (deduction of Roflumilast fees) (Samyshkin et al., 2014)

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Combination Roflumilast with salmeterol and tiotropium also gives significant results when compared with single drug administration. Patients with COPD exacerbations of more than 2 years receiving treatment with Roflumilast showed a very large reduction in the duration of exacerbations compared to placebo. The same results were also shown with the use of Roflumilast combined LABA (long-acting beta-2 agonist) or ICS (inhalation corticosteroid). In DAKOTA (Daxas for COPD therapy) research on the impact of Roflumilast on the quality of life of patients with COPD, it shows that Roflumilast can provide a substantial improvement in the quality of life than placebo. However, the statistics did not show a difference significant in terms of cost; the use of Roflumilast can save costs if used in treatment standards. Roflumilast can also save costs when combined with tiotropium and salmeterol/fluticasone or LABA or ICS. Glucagon-like-peptide-1 levels are increased by PDE4 inhibitor. Where glucagon receptors like peptide agonists are one treatment for diabetes. In a 12-week study, compared with placebo patients newly diagnosed with type II diabetes, Roflumilast can increase insulin sensitivity and reduce the HbA1c value (Wedzicha et al., 2016).

Cost-effectiveness

The cost-effectiveness of adding therapy with Roflumilast can be seen from the magnitude of treatment costs and the effectiveness of the therapy as in (Table 3). From observations, show that the addition of Roflumilast can increase the total cost. The addition of Roflumilast for maintenance can lead to increased medical costs. Costs needed in patients with increased exacerbations, in outpatients and inpatients can reduce treatment costs. In terms of age, a little longer in patients using additional Roflumilast. While in terms of quality of age in patients with Roflumilast slightly higher than those not using additional Roflumilast. (van der Schans et al., 2017).

Table 4. Cost Effectiveness of Roflumilast

First author (year) country	Type of research	Horizon	Punding	Drug therapy	Differential total cost (year)	Differential	ICER	Author's conclusions	QHES scores
(Samyshkin et al., 2014) (UK)	Marcov model (CUA)	lifetime	takeda	1. LABA +Roflumilast 2. LABA	1 vs 2 + £3197 (+£3656) several years research	+0.164QALYs +0,175 LY	£19,505 (€22.305)per QALY	Roflumilast combination with PROFIT becomes cost effective in COPD	91

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(Samyshkin et al., 2013) (Switzerland)	Marcov model (CUA)	lifetime	takeda	1. The addition of Roflumilast on: a. LAMA b. LABA/ICS c. LAMA +LABA /ICS 2. LABA a. LAMA b. LABA/ICS c. LAMA +LABA /ICS	1 vs 2ac + £3390 CHF (+£2815) 1b vs 2bc + 3308 CHF (£2747) 1c vs 2c +3799 CHF (£3155) (2011)	1a vs 2ac +0.347 LY/+0,275 1b vs 2b +0,364 LY/0,289 QALY 1c vs 2c +0,351 LY/+0,278 QALY	1a vs 2ac 12.313 CHF (€10.225) per QALY 1b vs 2b 11.456 CHF (€ 9511) per QALY 1c vs 2c 13.671 CHF (€11.353) per QALY	Roflumilast in combination with PROFIT becomes a cost effective with exacerbation frequency	94
(Hertel et al., 2012a) (UK)	Marcov model (CUA)	lifetime	MSD	1. The addition of Roflumilast on: LAMA +LABA /ICS 2. LAMA+LABA/ICS For ICS tolerant and intolerant separately	ICS tolerant +£414 (£447) ICS intolerant + £ 408 (£470) (2011)	ICS tolerance: +0,03 LY/+0,003 QALY ICS intolerant: +0,04 LY/+0,003 QALY	ICS tolerant £16,566 (€19.087) per QALY ICS intolerant £36,764 (€15.859) per QALY	Roflumilast for standard treatment is cost effective for patients who continue bronchodilator exacerbation	85
(Nowak et al., 2013) (Germany)	Marcov model (CUA)	lifetime	Nycomed	1.Roflumilast + LABA 2. LABA	+64500 (2011)	+0,234 QALY +0,257 LY -2,43	€19,457 per QALY get €1852 per reduction in exacerbation	Cost effective Roflumilast added LABA in patients with COPD symptoms with the addition of several additional treatments	83,5

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According to (Samyshkin et al., 2014) (UK), it was explained that in the administration of therapy with LABA combined with Roflumilast compared with therapy only with LABA giving a difference in treatment costs of + £ 3197 with different results of +0.164 QALYs and a value of + 0.175 Lys with an ICER value of £ 19.505 per QALY. In concluding that Roflumilast's addition to the PROFIT can increase the effectiveness and cost of diagnosing severe COPD. According to (Samyshkin et al., 2013) in Switzerland, it was explained that in the administration of therapy with LAMA (1) or LABA / ICS (2) or LAMA + LABA / ICS (3) combined with Roflumilast compared to therapy with only LAMA (1) or LABA / ICS (2) or LAMA + LABA / ICS (3) alone gives a difference in treatment costs of +3390 CHF (1), +3308 CHF (2), +3799 CHF (3). Give a difference in results +0.275 QALY (1), +0.289 QALY (2), +0.278 QALY (3). Gives ICER 12,313 CHF per QALY (1), ICER 11,456 CHF per QALY (2), ICER 13,671 CHF per QALY (3). It concludes that the addition of Roflumilast is more cost-effective in patients with frequent exacerbations.

According to (Hertel et al., 2012b) (UK) explained that the provision of LAMA + LABA / ICS therapy combined with Roflumilast compared to LAMA + LABA / ICS therapy alone gives a difference in treatment costs of + £ 414 in patients tolerant of ICS and + £ 408 in patients intolerant of ICS. Furthermore provides a difference with results of +0.03 QALY in patients who are tolerant of ICS and +0.03 QALY in patients who are intolerant of ICS. Patients who were tolerant of ICH gave ICER results of £ 16,566 per QALY, whereas patients who were intolerant of ICH gave ICER results of £ 13,764 per QALY. The addition of Roflumilast therapy to the standard of care is a cost-effective way for patients with severe COPD and worsens despite the use of bronchodilators. According to (Nowak et al., 2013) (Germany) was explained in the administration of therapy with LABA + Roflumilast compared with LABA giving a difference in + € 4500. The conclusion is the cost-effectiveness of adding Roflumilast to LABA therapy in patients with severe and very severe COPD is comparable to other therapy. Roflumilast preparations already exist in Indonesia with the trade name DAXAS 500 micrograms film-coated (Takeda) but there is no data on the use of roflumilast in Indonesia.

CONCLUSION

Roflumilast is PDE4 inhibitor as an anti-inflammation and anti-remodeling. Roflumilast can be used single or in combination. In a review of efficacy, it can prevent exacerbations and improve FEV1 and vital capacity to force. The frequent side effects of Roflumilast are diarrhea and digestive disorders. The cost-effectiveness, using Roflumilast can enhance the quality of life patients compared to the group without additional Roflumilast.

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JURNAL KEDOKTERAN
FK UM SURABAYA

QANUN MEDIKA
JURNAL KEDOKTERAN FK UM SURABAYA

diterbitkan oleh:
Fakultas Kedokteran
Universitas Muhammadiyah Surabaya

2021

Vol.05 | No.01 | Hal.01-139 |January 2021 | p-issn 2581-2173 e-issn 2548-9828

Qanun Medika is an official scientific journal of the Faculty of Medicine Muhammadiyah Surabaya University in collaboration with Asosiasi Pendidikan Kedokteran dan Kesehatan Muhammadiyah (APKKM). This journal contains writing and scientific articles that are made as a realization of tri dharma college. The purpose of the publication is to contribute actively to enhancing the quality and accessibility of scientific information related to medical science information in the global era.

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Journal of Qanun Medika is registered in LIPI and has ISSN as follows:

p-ISSN: 2541-2272

e-ISSN: 2548-9526

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DOI: http://dx.doi.org/10.30651/jqm.v5i1

Table of Contents

Literature Review

Articles

Case Report