Literature review

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

Ita Octafia\textsuperscript{1}, Dwi Octamy Sari\textsuperscript{1}, Novi Wulandari\textsuperscript{1}, Sandra Annisa\textsuperscript{1}, Linda Wahyuni Wongkar\textsuperscript{1}, Ferdias kurnia Bahari\textsuperscript{1}, Faiz Farikhah\textsuperscript{1}, Moh. Firmansah\textsuperscript{1}, Erfin Midhiawati\textsuperscript{1,2}, Fauna Herawati\textsuperscript{1,2*}

1) Magister Program of Clinical Pharmacy, Faculty of Pharmacy, Surabaya University, Surabaya, Indonesia
2) Department of Clinical and Community Pharmacy, Faculty of Pharmacy, University of Surabaya, Indonesia

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\textit{*Correspondence:}
fauna@staff.ubaya.ac.id

\textbf{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.
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 mucus 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 mucus 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 (Agusti & 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 antiproteases 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,
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 drugs used in the treatment of COPD

<table>
<thead>
<tr>
<th>GENERAL MEDICINE</th>
<th>TYPE</th>
<th>NEBULIZER</th>
<th>ORAL</th>
<th>INJECTION</th>
<th>DOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BETA 2- ANTAGONIS</td>
<td>SHORT-ACTING (SABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoterol</td>
<td>MDI</td>
<td>√</td>
<td>Tablet, syrup</td>
<td>4-6 hours</td>
<td></td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>MDI</td>
<td>√</td>
<td></td>
<td>6-8 hours</td>
<td></td>
</tr>
<tr>
<td>Salbutamol (albuterol)</td>
<td>MDI &amp; DPI</td>
<td>√</td>
<td>Tablet, syrup, sustain release</td>
<td>4-6 hours</td>
<td></td>
</tr>
<tr>
<td>Terbutalin</td>
<td>DPI</td>
<td></td>
<td>Tablet</td>
<td>√</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>LONG-ACTING (LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arformoterol</td>
<td></td>
<td>√</td>
<td></td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>Formoterol</td>
<td>DPI</td>
<td></td>
<td></td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>Indaceterol</td>
<td>DPI</td>
<td></td>
<td></td>
<td>24 hours</td>
<td></td>
</tr>
<tr>
<td>Olodaterol</td>
<td>SMI</td>
<td></td>
<td></td>
<td>24 hours</td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>MDI &amp; DPI</td>
<td></td>
<td></td>
<td>12 hours</td>
<td></td>
</tr>
<tr>
<td>ANTICOLINERGİK</td>
<td>SHORT-ACTING (SAMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>MDI</td>
<td>√</td>
<td></td>
<td>6-8 hours</td>
<td></td>
</tr>
<tr>
<td>Oxitropium bromide</td>
<td>MDI</td>
<td></td>
<td></td>
<td>7-9 hours</td>
<td></td>
</tr>
<tr>
<td>LONG-ACTING (LAMA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acidinium bromide</td>
<td>DPI, MDI</td>
<td></td>
<td></td>
<td>12 hours</td>
<td></td>
</tr>
</tbody>
</table>
Diabetes insipidus in patients with traumatic severe brain injury: Case Report

ABSTRACT

Traumatic severe brain injury is a fatal injury, with definitive data on the incidence of diabetes insipidus in traumatic severe brain injury in Indonesia until now. In this report, a 45-year-old man was brought to the Dr. Soetomo General Hospital's resuscitation room after an accident. Initially, the patient was referred to the Emergency Department (IRD) after the accident and received an oxygen mask of 5 liters per minute. Blood pressure was 110/75 mmHg (MAP 86), pulse 120 times per minute. The patient was intubated and ventilated with a tidal volume of 21 cm. The ventilator used PCV mode with RR 16, PC 15, trigger 2, I:E 1:2, FiO2 50%.

In the first 2 weeks after the injury, one of the complications of severe brain injury is diabetes insipidus. (Agha and Thompson, 2006). The patient developed polyuria with a production of 300 cc/hour urine and an osmolality of 149 mmol/liter. The initial impact of systemic hypotension and physiological ADH stimulation, which is decreased, occurs in the first 2 weeks after the injury. One complication of severe brain injury is diabetes insipidus.

The patient was unconscious since the accident occurred. First aid was given in the previous health facility; RSUD Tuban, thus the patient was referred to the IRD Dr. Soetomo. The patient experienced severe brain injury in the United States. There were more than 50,000 deaths and 500,000 permanent neurological sequelae. About 85% of mortality occurred within 2 weeks. Traumatic brain injury is a fatal injury, with a mortality rate of 50%. About 1.5 million people with severe brain injury in the United States have more than 50,000 deaths and 500,000 permanent neurological sequelae. (Agha and Thompson, 2006).

INTRODUCTION

There is no certain data about the occurrence of diabetes insipidus in patients with traumatic severe brain injury. One of the complications of traumatic severe brain injury is diabetes insipidus. There are no definite data on the incidence of diabetes insipidus in traumatic severe brain injury in Indonesia. In the previous health facility, the patient was brought to the IRD Dr. Soetomo hospital. The patient is unconscious since the accident occurred. First aid was given in the previous health facility; RSUD Tuban, thus the patient was referred to the IRD Dr. Soetomo. The patient experienced severe brain injury in the United States. There were more than 50,000 deaths and 500,000 incidences of ganglia neurological permanent.

The initial impact of systemic hypotension and physiological ADH stimulation, which is decreased, occurs in the first 2 weeks after the injury. One complication of severe brain injury is diabetes insipidus. There are no definite data on the incidence of diabetes insipidus in traumatic severe brain injury in Indonesia until now. In this report, a 45-year-old man was brought to the Dr. Soetomo General Hospital's resuscitation room after an accident. Initially, the patient was referred to the Emergency Department (IRD) after the accident and received an oxygen mask of 5 liters per minute. Blood pressure was 110/75 mmHg (MAP 86), pulse 120 times per minute. The patient was intubated and ventilated with a tidal volume of 21 cm. The ventilator used PCV mode with RR 16, PC 15, trigger 2, I:E 1:2, FiO2 50%.

Aminophyllin solution √ Up to 24 hours
Teofilin SR Tablet √ Up to 24 hours

For the treatment of diabetes insipidus, the drugs used were Tiotropium DPI, SMI and Umeclidinium DPI. The initial treatment for diabetes insipidus required complicated treatment. Therefore, if not handled properly, it can cause death. The initial impact of systemic hypotension and physiological ADH stimulation, which is decreased, occurs in the first 2 weeks after the injury. One complication of severe brain injury is diabetes insipidus. (Agha and Thompson, 2006).

COMPARISON SHORT-ACTING BETA2-AGONISTS AND ATIKOLINERGIK (SABA/SAMA)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Form</th>
<th>RFC</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenoterol/Iproteronium</td>
<td>SMI</td>
<td>√</td>
<td>6-8 hours</td>
<td></td>
</tr>
<tr>
<td>Salbutamol/ Iproteronium</td>
<td>SMI, MDI</td>
<td>√</td>
<td>6-8 hours</td>
<td></td>
</tr>
</tbody>
</table>

COMPARISON SHORT-ACTING BETA2-AGONIS AND ANTICOLINERGIK (LABA/LAMA)

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Form</th>
<th>RFC</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol/Aclidinium</td>
<td>DPI</td>
<td>12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol/ Glycopironium</td>
<td>MDI</td>
<td>12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indacaterol/Glycopironium</td>
<td>DPI</td>
<td>12-24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vilahterol/umeclidinium</td>
<td>DPI</td>
<td>24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olodaterol/Tiotropium</td>
<td>SMI</td>
<td>24 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

METHYLMXANTIN

<table>
<thead>
<tr>
<th>Drug</th>
<th>Form</th>
<th>RFC</th>
<th>Route</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminophyllin</td>
<td>solution</td>
<td>√</td>
<td>Up to 24 hours</td>
<td></td>
</tr>
<tr>
<td>Teofilin SR</td>
<td>Tablet</td>
<td>√</td>
<td>Up to 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

**ARTICLE INFO**

1) Resident of Anesthesiology and Intensive Care of RSUD Dr. Soetomo, Medical Faculty of Airlangga University.

Cedera otak berat trauma adalah cedera fatal, dengan tingkat kematian hingga 50%. Sekitar 1,5 juta orang mengalami cedera otak berat di Amerika Serikat. Terdapat lebih dari 50,000 kematian.

**ABSTRAK**

Pada kasus ini, pasien yang berusia 45 tahun, laki-laki, datang ke Instalasi Darurat (IRD) setelah mengalami kecelakaan lalu lintas 12 jam sebelum dirawat. Setelah hospitalisasi, pasien mengalami polyuria sebesar 300 cc/hour dan natrium tubuh sebesar 149 mmol/liter.


**KESIMPULAN**


**DATA**

- **Formoterol/Beclomethasone** MDI
- **Formoterol/Budesonide** MDI, DPI
- **Formoterol/Mometasone** MDI
- **Salmeterol/Fluticasone** MDI, DPI
- **Vilanterol/Fluticasone furoate** DPI

**TRIPEL COMBINATION LAMA/LABA/ICS**

- **Fluticasone/Beclomethasone/Vilanterol** MDI
- **Umeclidinium/Vilanterol** DPI
- **Beclometasone/Formoterol/Glycopirronium** MDI

**PHOSPODIESTERASE-4 INHIBITOR**

- **Roflumilast** Tablet

**MUCOLITIC**

- **Erdostine** Tablet

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

![Roflumilast](image)

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

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

Source: Lee et al., 2016
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).

Table 3. Cost-Effectiveness of Roflumilast Addition

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LAMA+ Roflumilast</th>
<th>LA MA</th>
<th>Incremental</th>
<th>LAB A/ICS+ Roflumilast</th>
<th>LAB A/ICS</th>
<th>Incremental</th>
<th>LAMA+ LABA/ICS+ Roflumilast</th>
<th>LA MA +LABA/ICS</th>
<th>Incremental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost of CHF</td>
<td>86.754</td>
<td>83.364</td>
<td>3390</td>
<td>91.470</td>
<td>88.161</td>
<td>3308</td>
<td>99.364</td>
<td>95.564</td>
<td>3799</td>
</tr>
<tr>
<td>Maintenance costs, CHF</td>
<td>35.857</td>
<td>25.481</td>
<td>10.376</td>
<td>40.917</td>
<td>30.279</td>
<td>10.638</td>
<td>43.533</td>
<td>37.682</td>
<td>10.851</td>
</tr>
<tr>
<td>Exacerbation treatment costs, CHF</td>
<td>2039</td>
<td>2.331</td>
<td>-292</td>
<td>2024.85</td>
<td>2331</td>
<td>-306</td>
<td>2036</td>
<td>2331</td>
<td>-295</td>
</tr>
<tr>
<td>Ex-hospital maintenance fees</td>
<td>48.858</td>
<td>55.552</td>
<td>-6694</td>
<td>9.642</td>
<td>55.552</td>
<td>-7024</td>
<td>48.795</td>
<td>55.552</td>
<td>-6757</td>
</tr>
<tr>
<td>Life year (LY)</td>
<td>9.625</td>
<td>9.278</td>
<td>0.347</td>
<td>6.479</td>
<td>9.278</td>
<td>0.364</td>
<td>9.628</td>
<td>9.278</td>
<td>0.351</td>
</tr>
<tr>
<td>QALY</td>
<td>6.466</td>
<td>6.191</td>
<td>0.275</td>
<td>11.456</td>
<td>6.191</td>
<td>0.289</td>
<td>6.468</td>
<td>6.191</td>
<td>0.278</td>
</tr>
<tr>
<td>ICER,CHF per QALY</td>
<td>12.313</td>
<td>9078</td>
<td>13.671</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICER,CHF per LY</td>
<td>9.757</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10.833</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Type of research</th>
<th>Horizon</th>
<th>Pudin</th>
<th>Drug therapy</th>
<th>Different total cost</th>
<th>Different ICER</th>
<th>Author’s conclusion</th>
<th>QHES score</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Samyshkin et al., 2014) (UK)</td>
<td>(CUA) model</td>
<td>lifetime</td>
<td>takeda</td>
<td>LABA + Roflumilast</td>
<td>£3197 (+£3656) Ys</td>
<td>+0.164 QAL</td>
<td>(€19,505) per QALY</td>
<td>91</td>
</tr>
<tr>
<td>(Samyshkin et al., 2014) (UK)</td>
<td>(CUA) model</td>
<td>lifetime</td>
<td>takeda</td>
<td>LABA</td>
<td>several years research</td>
<td>+0,175 LY</td>
<td>€22.305 per QALY</td>
<td></td>
</tr>
</tbody>
</table>

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).
ABSTRACT

Traumatic severe brain injury is a fatal injury, with mortality rate of up to 50%. About 1.5 million people die and 500,000 incidents of permanent neurological sequelae occur. About 85% of deaths occur within the first 2 weeks after the injury, which exhibits one of the complications of trauma such as diabetes insipidus. In patients with traumatic severe brain injury, diabetes insipidus requires adequate rehydration and desmopressin administration. Correction of hypovolemic, polyuric and hypernatremia occurs in the first 2 weeks after the injury. One of the complications of brain injury is diabetes insipidus. There are no main treatments for diabetes insipidus in traumatic severe brain injury. Therefore, the adequate treatment of diabetes insipidus in patients with traumatic severe brain injury needs to be applied to the patient. The use of desmopressin in patients with diabetes insipidus after traumatic severe brain injury needs to be done either alone or combined with other drugs. The management of diabetes insipidus in patients with traumatic severe brain injury is important in order to reduce the complications of brain injury.

CASE REPORT

A male patient, 45 years old, was brought to the Emergency Installation (IRD) after experiencing trauma. The patient was admitted to the Intensive Care Unit (ICU) with signs of hyperventilation and respiratory distress. The patient was diagnosed with traumatic severe brain injury and diabetes insipidus. The patient received adequate rehydration and desmopressin administration. The patient was discharged from the hospital with improved symptoms and a diagnosis of diabetes insipidus.

REFERENCES


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Keywords: Traumatic severe brain injury, Diabetes insipidus, Desmopressin.

Correspondence: yud180987@yahoo.com

1. The addition of Roflumilast to standard of care:
   a. LAMA
   b. LABA/ICS
   c. LAMA + LABA / ICS

   1. The addition of Roflumilast to standard of care:
      a. LAMA
      b. LABA/ICS
      c. LAMA + LABA / ICS

   ICS tolerant
   ICS intolerant +
   £414 (£447)
   £408 (£470)
   £408 (£470)
   £414 (£447)

   ICS tolerance:
   +0,03
   +0,003
   +0,04
   +0,003
   +0,003
   QALY
   QALY
   QALY
   QALY
   QALY

   ICS tolerant
   ICS intolerant +
   £16,566 (£19,087)
   £36,764 (£15,859)
   £16,566 (£19,087)
   £36,764 (£15,859)
   £16,566 (£19,087)
   QALY
   QALY
   QALY
   QALY
   QALY

   Cost effective
   85
   83,5

   Roflumilast added LABA in patients with COPD

   Reduction in exacerbation
   2. LABA
   -2,43
   symptoms with the addition of several additional treatments

   Roflumilast for standard treatment is cost effective for patients who continue bronchodilator exacerbation

   PROFIT can increase the effectiveness and cost of diagnosing severe COPD. According to (1), ICER 11,456 CHF per QALY (2), ICER 13,671 CHF per QALY (3). It concludes that PROFIT provides a difference 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, the addition of Roflumilast therapy to the standard of care is a cost effective with PROFIT becomes a cost effective with PROFIT for patients who continue bronchodilator exacerbation frequency.
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.

REFERENCES


Traumatic severe brain injury is a fatal injury, with a mortality rate of up to 50%. About 1.5 million people experience severe traumatic brain injury in the United States. There are more than 50,000 deaths and 500,000 incidents of neurologic sequelae (Agha and Thompson, 2006). Traumatic severe brain injury is a fatal injury, with a mortality rate of up to 50%. About 1.5 million people experience severe traumatic brain injury in the United States. There are more than 50,000 deaths and 500,000 incidents of neurologic sequelae (Agha and Thompson, 2006).


Penelitian ini diterbitkan dalam jurnal Qanun Medika dengan judul “Diabetes Insipidus in Patients with Traumatic Severe Brain Injury”. Penulisnya adalah Yudha Adi Prabowo dan Prananda Surya Airlangga. 

Penelitian ini menemukan bahwa diabetes insipidus dapat terjadi pada pasien dengan cedera otak serius trauma. Diabetes insipidus adalah kondisi medis di mana otak tidak dapat membuat hormon anti-dehidrasi yang penting untuk menjaga keseimbangan cairan di tubuh. 

Sementara itu, epidemiologi cedera otak serius trauma di Indonesia juga memiliki karakteristik tersendiri. Menurut data yang diperoleh, sekitar 85% kematian terjadi dalam 2 minggu sejak kejadian kecelakaan. 

Penelitian ini memberikan pemahaman yang lebih dalam tentang kondisi diabetes insipidus dan menegaskan pentingnya penanganan yang tepat terhadap pasien dengan cedera otak serius trauma.


