The Role of Erdosteine in Reducing the Need for Bronchodilators During Acute Exacerbation of Chronic Obstructive Pulmonary Disease

Faisal Yunus,* Hadiarto Mangunmegoro,* Indah Rahmawati,* Raymond R. Tjandrawinata,** Dwi Nofiarny***

*Department of Pulmonology and Respiratory Medicine Faculty of Medicine, University of Indonesia, Jakarta
**Dexa Laboratories of Biomolecular Sciences, Dexa Medica Group, Indonesia
***Corporate Department of Scientific Research, Dexa Medica Group, Indonesia

Abstract: Bronchodilators are the mainstay in symptomatic management of stable chronic obstructive pulmonary disease (COPD). At exacerbation, bronchoconstriction may get worse and thus it is logical to increase the dose and/or frequency of administration of bronchodilator agents. This study aimed to evaluate whether erdosteine used concomitantly with levofloxacin in patients with acute exacerbation of COPD with purulent sputum could reduce the frequency of bronchodilator inhalation during exacerbation episodes. This study is a randomised double-blind placebo-controlled clinical study with the primary endpoint was the mean frequency of bronchodilator consumption per-day evaluated on day 8. Secondary endpoints were improvement of clinical symptoms and the Global Efficacy Index. Group 1 were treated with erdosteine and levofloxacin, whilst group 2 with placebo and levofloxacin. Erdosteine or its matching placebo was administered 2x 300 mg/day for seven days; while levofloxacin, 500 mg o.d. Ninety patients aged 45-80 years were enrolled. Erdosteine group needed significantly less bronchodilator than those in placebo group, p<0.001. At the end of study, a higher rate of clinical improvement was observed in erdosteine group (61.9%) than placebo group (46.7%) with a slightly greater improvement in sputum purulence and sputum viscosity in erdosteine group as well. No statistical significance found in such secondary endpoints. Majority of adverse events were mild and comparable between groups. Erdosteine in addition to levofloxacin in patients with acute exacerbation of COPD with purulent sputum provided a significant reduction in patients’ need for bronchodilators and was well tolerated.

Keywords: bacterial infections, bronchodilator, COPD, erdosteine, levofloxacin
Peran Erdosteine dalam Mengurangi Kebutuhan akan Bronkodilator pada Penyakit Paru Obstruktif Kronik

Faisal Yunus,* Hadiarto Mangunnegoro,* Indah Rahmawati,*
Raymond R. Tjandrawinata,** Dwi Nofiarny***

*Departemen Pulmonologi dan Ilmu Kedokteran Respirasi,
Fakultas Kedokteran Universitas Indonesia, Jakarta

**Dexa Laboratories of Biomolecular Sciences, Dexa Medica Group, Indonesia

***Corporate Department of Scientific Research, Dexa Medica Group, Indonesia


Kata Kunci: infeksi bakteri, bronkodilator, PPOK, erdosteine, levofloksasin

Introduction

Chronic obstructive pulmonary disease (COPD) is one among the other major causes of morbidity and mortality. It is currently the fourth leading cause of death and the 12th leading cause of disability worldwide. The prevalence, mortality and morbidity rates are predicted to rise within the next decade.1,2 COPD is defined as a disease state characterized by irreversible airflow obstruction. The airflow obstruction is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases.2,3 Exacerbation of COPD is characterized by a marked increase in the number of neutrophile in the airway, associated with sputum purulence. Neutrophil secrete elastase and proteinases which may contribute to epithelial damage, decrease ciliary beat frequency, stimulate goblet cells to secrete mucus, improve bronchial permeability against mucus preventing oedema and protein exudation to the airway.3–5 The most common causes of exacerbation in COPD are bacterial (approximately 40-60%) and viral infections (about 15-25%) and air pollution.6–23 Two independent studies by Stockley et al24 and Allegra et al.25 stated that sputum purulence on exacerbation of COPD was a predictor of the presence of a high bacterial concentration (with 94.4% sensitivity and 77% specificity). Thus, in such exacerbation, in particular when they show clinical signs of airway infection (e.g. increased volume and/or change of sputum color/viscosity and/or fever), use of an antibacterial agent would be beneficial. Other studies discovered that sputum puru-
lence was related to bacterial growth during exacerbation period. COPD patients with more frequent exacerbations and/or greater severity require appropriate antimicrobial therapy.6,26–29 Furthermore, therapeutic strategies involving agents that inhibit mucus production, increase the mucus hydration and prevent infectious exacerbations such as through reducing bacterial adherence or limiting cellular damage in the presence of microorganisms, should also be pursued.29 Addition of mucolytic agents may considerably reduce the frequency and length of the exacerbation episodes in COPD, which may in turn contribute to the improvement of pulmonary function.6,26,27,29–33 Poole and Black32 in their systematic analysis on several clinical studies with mucolytics in COPD patients found that treatment with such agents was associated with a small reduction in acute exacerbations and a reduction in total number of days of disability. Benefit may be greater in individuals who have frequent or prolonged exacerbations, and in patients with moderate or severe COPD in whom inhaled corticosteroids are not prescribed.

Erdosteine [N-(carboxymethylthioacetyl) homocysteine thiolactone] is a favorable choice of mucolytics in COPD therapy. More than just a mucolytic, it also provides anti-inflammatory, anti-bacterial-adhesion, and antioxidant activities.14–35 Studies in animals and human showed erdosteine might improve viscosity, elasticity, and biochemical composition of mucus as well as decrease mucus hypersecretion and expectorant volume. In vitro studies36 exhibited erdosteine effect in inhibiting bacterial adhesion resulting in clinical trials in a higher local antibiotic concentration, thus decreased bacterial growth more effectively.34–37 Several clinical studies suggested that erdosteine had the ability to decline exacerbations, hence increased COPD patients’ productivity as demonstrated also in long term treatment of COPD patients.38

The studies also confirmed that erdosteine combined with antibiotics would increase antibiotic concentration in sputum but not in serum of patients with exacerbation of chronic bronchitis.34,37,39,40 In several randomized-clinical trials, erdosteine improved the efficacy of antibiotic therapy in patients with exacerbation of chronic bronchitis.34,37 Those studies clearly indicated that the clinical picture of infective exacerbations in chronic obstructive bronchitis is modified earlier and to a deeper degree by the synergistic activity of erdosteine and the antibiotics without risk of augmenting the side-effects.14,37,39,40 Inhaled bronchodilators may produce considerable symptomatic benefit in COPD therapy through mechanisms including an effect on dynamic hyperinflation.41 Currently, β-2 agonists, anticholinergic agents, theophylline and a combination of these drugs are the standard, frontline bronchodilators in the symptomatic management of COPD exacerbations.29 At exacerbation there may be worsened bronchoconstriction, due to complex inflammatory neural interactions that results in further hyperinflation.42 It is thus logical to increase the dose and/or frequency of administration of bronchodilator agents the patients usually use. To date, there is no study which evaluating whether the use of mucolytic agents such as erdosteine may reduce such frequent bronchodilator consumption from the usual dose needed at exacerbation of COPD.

The objectives of the current study were to investigate whether erdosteine given concomitantly with levofloxacin to subjects with acute exacerbation of COPD could: reduce the frequency of bronchodilator inhalation during the exacerbation episodes, accelerate COPD clinical symptoms improvement, decrease sputum viscosity and purulence, and to observe whether unexpected adverse events might occur after concomitant use of erdosteine with levofloxacin, the standard therapy of acute infective exacerbation of COPD.

**Methods**

This was a two-arm, randomised, double-blind, parallel and placebo-controlled clinical study. The study was conducted from October 2004 to April 2006, at Asthma Out-patient Clinic and Emergency Installation, Persahabatan Hospital, Jakarta. Patients from both sexes who were diagnosed with acute exacerbation of COPD with purulent sputum and were not participating in other clinical trials were included. Purulent sputum was used as a diagnostic predictor for exacerbations due to bacterial infection.32 Exclusion criteria were history of asthma or FEV1 with reversibility of >12% under spirometry test, using mucolytic agents and/or antibiotics within 2 weeks before screening, under long-term corticosteroid treatment either systemic or inhalation, known or suspected hypersensitivity to the trial products, suffered from hepatic function disorder, indicated by elevated SGOT/SGPT levels by more than 3 times upper normal range and/or elevated bilirubin by more than 1.5 times upper normal range, and subjects with severe renal dysfunction as indicated by creatinin clearance of <25 mL/min. COPD patients due to other cause such as bronchiectasis, tuberculosis, cystic fibrosis, and malignancies were also excluded from the study. For females of childbearing potential, pregnancy, breast-feeding, the intention of becoming pregnant, or judged not to be using adequate contraceptive measures were also excluded. Subject’s participation was discontinued when he/she considered as having no compliance with the trial procedures, uncooperative, experiencing serious adverse events, or might be withdrawn on his/her own decision.

**Treatments**

At visit 1 (day 0, screening), prospective subjects were checked against the inclusion and exclusion criteria. After the informed consent were obtained from each subject, they led physical examination, routine blood and urine tests, chest X-ray photograph, spirometric test to measure the 1st-second forced expiratory volume (FEV1), and measurement of peak expiratory flow rate using peak flow meter (Aimed, Clem-
by at least one of the following symptoms, such as upper symptoms, respectively. Exacerbation is also accompanied as type II (moderate) and type III (mild) are those with 2 and dyspnea, increased sputum production and purulence), where exacerbation is marked by at least 3 exacerbation symptoms (dyspnea according to Anthonisen classification). Of those evaluable subjects, 8 subjects took erbosteine group, could not be analyzed as they provided no single post-baseline data. Thus, a total of 81 and 87 subjects were evaluable for primary and secondary efficacy analyses. For the secondary endpoints, only 3 of them, who were in placebo group. Two subjects experiencing serious adverse events, each one was in each group. They both needed hospitalization due to worsened clinical symptoms.

All the 9 withdrawn subjects could not be analyzed for the primary endpoint as they had no available data recording bronchodilator consumption during the study. However, for the secondary endpoints, only 3 of them, who were in erdosteine group, could not be analyzed as they provided no single post-baseline data. Thus, a total of 81 and 87 subjects were evaluable for primary and secondary efficacy analysis, respectively. Of those evaluable subjects, 8 subjects took the study product (erdosteine) for less than 80% of the total planned study medication.
Demographic and Other Baseline Characteristics

The demographic and baseline characteristics of patients are shown in Table 1.

Efficacy Evaluation

The primary efficacy endpoint was the daily frequency of bronchodilator used by the subjects during their participation in the study. On comparing 41 subjects in placebo group and 40 subjects in erdosteine group who needed bronchodilator inhalation and recorded their usage in the patient diary, subjects in placebo group needed bronchodilator puffs nearly twice (p<0.001, 95% CI 1.624-2.720) as much those in erdosteine group (Table 2).

Six parameters included in Global Efficacy Index were used to evaluate the clinical efficacy of acute exacerbation of COPD. They were sputum purulence, sputum viscosity, difficulty to expectorate, catarrh at auscultation, cough frequency and quality, and dyspnoea intensity. These parameters were all evaluated at every visit. The efficacy evaluation results are tabulated in Table 3 and mean total score of the Global Efficacy Index are figured out in Figure 2.

There was no significant difference in the mean score of each individual exacerbation parameters between groups after treatment (Visit-2 and Visit-3). Referring to Figure 2; there was no significant difference in mean of total global score between erdosteine and placebo group.

Clinical responses in both erdosteine and placebo groups would be assessed at the end of treatment (Visit 3, Enter Figure 1. Disposition of Study Subjects

**Table 2. Mean Puff/Day of Bronchodilator Usage**

<table>
<thead>
<tr>
<th></th>
<th>Erdosteine (SD) n = 40</th>
<th>Placebo (SD) n = 41</th>
<th>p-value 95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchodilator usage **</td>
<td>2.72 (1.332)</td>
<td>4.89 (1.140)</td>
<td>&lt; 0.001 (1.624-2.720)</td>
</tr>
</tbody>
</table>

*: Analysis of the difference by Independent Sample T-test, t(= 0.05
**: Bronchodilator used were ipratropium 20 mcg/puff and fenoterol HBr 200 mcg/puff
Peran Erdosteine dalam Mengurangi Kebutuhan akan Bronkodilator pada Penyakit Paru

Table 3. Mean Scores of Each Clinical Parameters in Global Efficacy Index

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Erdosteine (mean)</th>
<th>Placebo (mean)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum purulence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit-1</td>
<td>2.07</td>
<td>2.00</td>
<td>0.601</td>
</tr>
<tr>
<td>Visit-2</td>
<td>1.52</td>
<td>1.42</td>
<td>0.363</td>
</tr>
<tr>
<td>Visit-3</td>
<td>1.17</td>
<td>1.27</td>
<td>0.456</td>
</tr>
<tr>
<td>Sputum viscosity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit-1</td>
<td>2.24</td>
<td>2.24</td>
<td>0.959</td>
</tr>
<tr>
<td>Visit-2</td>
<td>1.50</td>
<td>1.64</td>
<td>0.221</td>
</tr>
<tr>
<td>Visit-3</td>
<td>1.29</td>
<td>1.33</td>
<td>0.640</td>
</tr>
<tr>
<td>Difficulty to expectorate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit-1</td>
<td>2.13</td>
<td>2.22</td>
<td>0.528</td>
</tr>
<tr>
<td>Visit-2</td>
<td>1.79</td>
<td>1.62</td>
<td>0.280</td>
</tr>
<tr>
<td>Visit-3</td>
<td>1.48</td>
<td>1.42</td>
<td>0.846</td>
</tr>
<tr>
<td>Catarrh at auscultation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit-1</td>
<td>1.87</td>
<td>1.76</td>
<td>0.527</td>
</tr>
<tr>
<td>Visit-2</td>
<td>0.95</td>
<td>1.13</td>
<td>0.251</td>
</tr>
<tr>
<td>Visit-3</td>
<td>0.57</td>
<td>0.89</td>
<td>0.074</td>
</tr>
<tr>
<td>Frequency and quality of cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit-1</td>
<td>1.82</td>
<td>1.71</td>
<td>0.561</td>
</tr>
<tr>
<td>Visit-2</td>
<td>1.40</td>
<td>1.29</td>
<td>0.477</td>
</tr>
<tr>
<td>Visit-3</td>
<td>1.14</td>
<td>1.09</td>
<td>0.503</td>
</tr>
<tr>
<td>Dyspnea intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit-1</td>
<td>1.89</td>
<td>1.73</td>
<td>0.148</td>
</tr>
<tr>
<td>Visit-2</td>
<td>1.50</td>
<td>1.51</td>
<td>0.763</td>
</tr>
<tr>
<td>Visit-3</td>
<td>1.24</td>
<td>1.27</td>
<td>0.887</td>
</tr>
</tbody>
</table>

*Mann-Whitney test on each individual parameter between groups

Table 4. Clinical Response

<table>
<thead>
<tr>
<th>Clinical response</th>
<th>Erdosteine n (%)</th>
<th>Placebo n (%)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved (Improvement rate)</td>
<td>26 (61.9%)</td>
<td>21 (46.7%)</td>
<td>0.154</td>
</tr>
<tr>
<td>Not improved</td>
<td>16 (38.1%)</td>
<td>24 (53.3%)</td>
<td></td>
</tr>
</tbody>
</table>

*: Analysis by Chi-square test

Day-8) as the improvement rate of two main clinical parameters (sputum purulence and viscosity). The improvement rate was the proportion (percentage) of subjects who showed clinically significant improvement (defined as the attainment of score 1 or 0) in both clinical parameters. Generally, erdosteine group showed a higher rate of clinical improvement than placebo group (Table 4). There was 15.2% difference in clinical response (improvement rate) between erdosteine and placebo groups.

Safety

Adverse events occurred during the study are listed in Table 5. There were 5 subjects (11.1%) in erdosteine group and 7 subjects (15.6%) in placebo group experiencing adverse events during their study participation. Among them, 1 patient in erdosteine group and 1 patient in placebo group were hospitalized due to heart failure and severe sinusitis, respectively, thus serious adverse event. Yet, no adverse event was regarded as related to study medication and all were resolved at the end of study.

As measured by laboratory parameters (hematology, clinical chemistry, urinalysis and vital signs), there was no statistical difference in physiological tolerability between erdosteine and placebo groups.

Discussion

Levofloxacin was chosen as the baseline therapy in this study as many evidences showed its effectiveness in chronic bronchitis ambulatory patients with exacerbation, with a cure rate as high as 68–79%. Subjects in the study concomitantly used a combination of bronchodilators (ipratropium 20 mcg/puff and fenoterol HBr 200 mcg/puff) on an as-needed basis. Several studies have shown that combinations of anticholinergics and β2-agonists produce an additive bronchodilator effect. The analysis of bronchodilator usage in this study showed a significant difference between groups. The frequency of bronchodilator inhalation by subjects in placebo group (4.89±1.140 puffs/day) is in line with one previously reported by Sin D et al2 that ipratropium is generally given 4 to 6 times a day. Erdosteine group needed significantly less bronchodilator (2.72±1.332 puffs/day) than placebo group (p<0.001). This result, at least in part, was attributed to the faster reduction of dyspnea intensity in erdosteine group. Mean score of dyspnea intensity in erdosteine group at day 8 (end of study) was relatively better than that of placebo group, though it was not statistically significant (Table 3). One possible explanation of this benefit effect of erdosteine is that the mucolytic agent reduced sputum viscosity and elasticity so that it was easily expectorated, and thus reduced the cough frequency as well as the risk for developing more severe bronchoconstriction. Altogether, these effects finally resulted in the reduction of subjects’ need for bronchodilators during exacerbation. In economic aspect, this result may also be seen as pruning the therapeutic costs of COPD therapy.

With regard to the clinical improvement, this study showed that after day 8 the improvement rate of sputum purulence (appearance) in erdosteine group was greater than that of placebo group, although it was not statistically significant (p = 0.456). At study entry, there had been 22.2% of subjects in erdosteine group had purulent sputum, 62.2% still with purulent sputum and 77.8% of the subjects (compared to 4.4% of subjects in placebo group) were not expected to receive bronchodilator 2x300 mg daily or placebo was given.
for 7 days. The study showed that erdosteine significantly reduced the frequency of cough (-63%), sputum purulence (-69.2%) and viscosity (-49.7%).

The improvement rate of sputum viscosity in erdosteine group after day 8 was also greater than that of placebo group, although, as that seen with the sputum purulence, the difference between the two groups was not statistically significant (p=0.640). At study entry, there were 31.1%, 62.2% and 6.6% of study subjects in erdosteine group compared to 33.3%, 57.8% and 8.8% of those in placebo group had had solidly thick (or viscous) sputum, thick sputum, and diluted sputum respectively. At day 8, no more solidly thick sputum was observed in both groups. In erdosteine group, 31.1% of study subjects had thick sputum, 57.8% had diluted sputum, and 4.4% had no longer expectorated sputum. Whereas in placebo group, the corresponding percentages were 40%, 53.3% and 6.6%.

Overall clinical evaluation demonstrated that erdosteine produced an improvement rate of 15.2% greater than placebo (Table 5). However, the difference was not statistically significant since our study power had not particularly been designed to detect such a significant difference in clinical response.

The results are in line with several previous studies. Mohanty et al\textsuperscript{34} found that on the 3\textsuperscript{rd} day of erdosteine administration, there were apparent changes of sputum volume and viscosity in patients with chronic bronchitis exacerbation. Marchioni et al\textsuperscript{35} also found that erdosteine administration at a dose of 3x300 mg daily for 2 weeks could reduce sputum viscosity by 36.3% better than placebo.

### Table 5. Adverse Events

<table>
<thead>
<tr>
<th>Events</th>
<th>Erdosteine n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Heart Failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>1 (2.2%)*</td>
<td>-</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>-</td>
</tr>
<tr>
<td>Moderate</td>
<td>-</td>
<td>2 (4.4%)</td>
</tr>
<tr>
<td>Common cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>1 (2.2%)</td>
<td>1 (2.2%)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>-</td>
<td>1 (2.2%)*</td>
</tr>
</tbody>
</table>

Each subject might experience more than one events

*Serious Adverse Events (SAE)

In our body, the sulphhydril (-SH) group of active metabolite of erdosteine breaks disulfidobonds of mucous glycoprotein, reducing its viscosity and elasticity, thus facilitating mucociliary transport and clearance. Studies in animals and human indicated that erdosteine may modulate mucus production and tracheo-bronchial transport and has direct effect on ciliary movement.\textsuperscript{14,34,37,49,51,52} A study by Olivieri et al\textsuperscript{53} in 16 smokers with chronic bronchitis demonstrated the beneficial effect of erdosteine 3x300 mg for 8 days in improving mucociliary transport. A further study\textsuperscript{35} also showed that reduction in sputum adhesiveness by erdosteine 2x300 mg (50% and 88% on day 3 and 7 respectively) was faster and more consistent than the ambroxole did (36.7% and 60% on day 3 and 7 respectively).

In all study subjects, no statistically significant modification of laboratorial safety parameters was found. The majority of adverse events observed were mild. None of them were considered related to the study products (as the adverse drug reactions). There was no discontinuation of treatment due to adverse events in all remaining patients. Most subjects experiencing abdominal pain, nausea, and vomiting had confirmed previous gastritis disturbances. Such adverse events were probably owing to the irregular diet style or taking the study drugs before meals. Such abdominal complaints might also be related to the concomitant medication used, such as theophyllin and levofloxacin which have gastrointestinal irritating effects. Insomnia occurred in 3 subjects was considered not related to erdosteine. It was probably related to levofloxacin. Two subjects (one with concomitant CHF and the other with chronic sinusitis at baseline) had their clinical conditions worsened and needed hospitalization (regarded as SAE), thus withdrawn from the study. The pattern of adverse events reported in this study was similar with one reported by Ghiringhelli et al\textsuperscript{40} that common adverse events occurred after 4 weeks erdosteine administration were gastrointestinal disturbances and headache. All adverse events were mild and not related to the study. Other studies also reported mild epigastralgia, nausea, vomiting, erythema, pruritus, and diarrhea.\textsuperscript{6,18,14} At the end of the study, all the subjects were fully recovered (their clinical condition were stable).

### Conclusions

This study concluded that administration of erdosteine in addition to levofloxacin to patients with acute exacerbation of COPD with purulent sputum provided a significant reduction in patients’ need for bronchodilators, as compared to those who received no additional treatment with erdosteine. Erdosteine in combination with levofloxacin was well tolerated by patients with acute exacerbation of COPD.

### Acknowledgments

The study was supported by PT. Dexe Medica, Indonesia. We are deeply indebted to Prof. Arini Setiawati, PhD
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