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PHARMACOTHERAPY AND LUNG FUNCTION DECLINE IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE : A SYSTEMATIC REVIEW

Galih Radityo Prabowo*

**Faculty of Medicine, University of Muhammadiyah Malang, Indonesia*

Corresponding Author:
galihradityo_prabowo@yahoo.com

Abstract

Chronic obstructive pulmonary disease (COPD) is a long-term condition that affects millions of individuals all over the world and is a major contributor to the rise in hospital admission rates. According to projections made by the World Health Organization (WHO), COPD would become the third greatest cause of mortality worldwide by the year 2020. These patients are also very substantial consumers of the resources made available by the health and social care systems. Because there is now no treatment that can reverse the effects of COPD, patients are responsible for their own healthcare and the management of their condition. There is a correlation between the amount of cigarettes smoked and the degree to which COPD is present. The pathophysiology of COPD is intimately tied to the impact that cigarette smoke has on the lungs. Pharmacological trials that were carried out more than three decades ago with the use of short-acting bronchodilators or inhaled glucocorticoids did not succeed in demonstrating a statistically significant slower rate of FEV1 decline in comparison to the placebo group in their intention-to-treat populations. In light of these equivocal data, the belief that smoking cessation is the only treatment that can delay the course of COPD became widespread. Unfortunately, this pessimism has had a negative impact on how the general public views COPD and has decreased interest in alternative therapeutic techniques. Tiotropium had a greater FEV1 than the placebo, and it also reduced the annual reduction in FEV1 after bronchodilator usage in individuals with COPD who were in the GOLD stage 1 or 2 range. FEV1 drop might be stopped by FF or VI. The patients expressed satisfaction with the treatment, which resulted in fewer exacerbations. It seems like fluticasone furoate or vilanterol could slow down the drop in FEV1 levels.

Keyword: *Chronic Obstructive Pulmonary Disease; FEV1; Lung Function; Pharmacotherapy;*

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a chronic disease that affects millions of people worldwide, causing a significant increase in admission rates.[1] The World Health Organization (WHO) estimates that COPD will be the third leading cause of death globally by 2020. These patients are also very large users of health and social services resources. There is no cure for COPD, so self-care and appropriate management play an important role in a patient's life.[2]

Cigarettes are the main cause of COPD in developed countries, while firewood and charcoal smoke are in developing countries. The pathogenesis of COPD is closely related to the effects of cigarette smoke on the lungs, where a relationship is found between the number of cigarettes and the severity of COPD.[2] COPD is associated with impaired pulmonary inflammatory response caused by inhalation produced by cigarette smoke, air pollution, or exposure received at work. All smokers experience lung inflammation that continues to increase and does not improve after stopping smoking.[3,4]

The Global Burden of Disease Study reported a prevalence of 251 million cases of COPD globally in 2016 and an estimated 3.17 million deaths due to COPD in 2015 (i.e., 5% of all deaths globally). More than 90% of COPD deaths occur in low- and middle-income countries.[5] COPD is the largest contributor to morbidity (35%) due to lung disease in Indonesia, followed by bronchial asthma (33%), lung cancer (30%), and others (2%).[6]

The increase in the incidence of COPD is due to demographic changes and increasing life expectancy.[7] However, COPD is also not uncommon in non-smokers. Another study found that the prevalence of COPD in people who had never smoked was 3.0-7%.[8] COPD is a lung disease that often occurs and is associated with smoking habits. The incidence of COPD tends to increase with age, but it is still often under-diagnosed and under-treated, especially in the elderly population.[2,9]

In their intention-to-treat populations, pharmacological trials conducted more than 30 years ago using short-acting bronchodilators or inhaled glucocorticoids failed to demonstrate a statistically significantly slower rate of FEV1 decline compared to placebo. Based on these inconclusive findings, the dogma became that smoking cessation was the only therapy that could slow the progression of COPD. Regrettably, this nihilism has harmed public perception of COPD and diminished interest in alternative therapeutic approaches.[10,11] Recent studies provide information that may help explain why pharmacotherapy had no effect in these early trials.[12]

First, the mean rate of FEV1 decline in COPD patients is lower than what Fletcher and colleagues initially reported. Second, nearly half of COPD patients do not have a steeper rate of decline than healthy smokers and nonsmokers without COPD. As a result, studies evaluating the average change in FEV1 of the enrolled subjects have been hampered by the inclusion of "normal decliners," who reduce the power to detect a therapeutic effect. Third, some of the older pharmacological agents used in those studies have a short duration of action, and most studies have not been long enough to determine changes in FEV1 for a chronic disease with a long natural history.[12,13]

This article review some research on pharmacotherapy and lung function decline in patients with chronic obstructive pulmonary disease (COPD).

METHODS

This study followed to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 project guidelines for data collection, processing, and reporting. These concerns informed the adoption of the regulations. This literature review analyzes the relationship between medication and lung function deterioration in COPD patients. The following are the most important points raised by this study: 1) Papers must always be written in English and must discuss medication and loss in lung function in COPD patients. 2) Articles published after 2014 and falling within the scope of this systematic review were assessed. The anthology will remove editorials, submissions without a DOI, reviews of already published works, and major duplicates of journal articles.

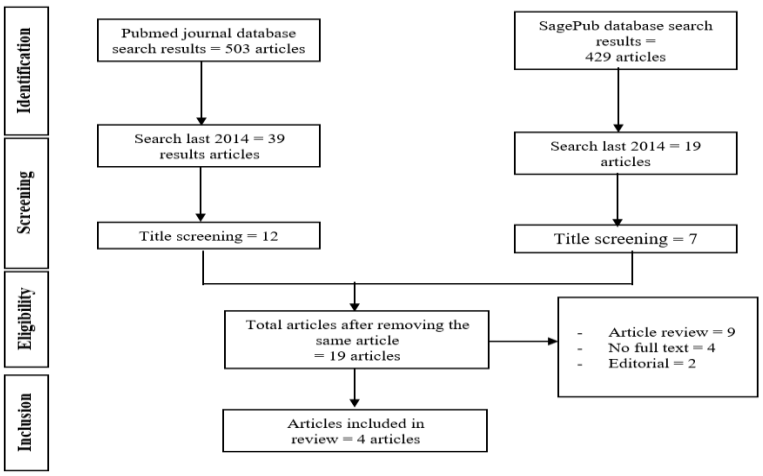

Figure 1. Article search flowchart

The search for studies to be included in the systematic review was carried out from March, 21th 2023 using the PubMed and SagePub databases by inputting the words: "pharmacotherapy", "lung function decline" and "chronic obstructive pulmonary disease". Where *("drug therapy"[MeSH Terms] OR ("drug"[All Fields] AND "therapy"[All Fields]) OR "drug therapy"[All Fields] OR "pharmacotherapies"[All Fields] OR "drug therapy"[MeSH Subheading] OR "pharmacotherapy"[All Fields]) AND ("respiratory physiological phenomena"[MeSH Terms] OR ("respiratory"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "respiratory physiological phenomena"[All Fields] OR ("lung"[All Fields] AND "function"[All Fields]) OR "lung function"[All Fields]) AND ("decline"[All Fields] OR "declined"[All Fields] OR "decliner"[All Fields] OR "decliners"[All Fields] OR "declines"[All Fields] OR "declining"[All Fields]) AND ("pulmonary disease, chronic obstructive"[MeSH Terms] OR ("pulmonary"[All Fields] AND "disease"[All Fields] AND "chronic"[All Fields] AND "obstructive"[All Fields]) OR "chronic obstructive pulmonary disease"[All Fields] OR ("chronic"[All Fields] AND "obstructive"[All Fields] AND "pulmonary"[All Fields] AND "disease"[All Fields]))* is used as search keywords.

Each study's abstract and title were used to determine eligibility. As a result, historical literature is their primary source of information. After reviewing multiple publications with identical results, submissions in unpublished English are sought. Only studies that met the inclusion criteria were included in the systematic review. This narrows the search results to only those that meet the criteria. The evaluation procedure is as follows. The study's analysis included information about the authors, publication dates, location, activities, and parameters. After saving search results in EndNote, duplicate articles were removed from the database. Two reviewers each evaluated the title and abstract of each article.

Before deciding which manuscript to study, each author read the title and abstract of each publication. Following that, we'll go over all of the papers that meet the inclusion criteria for the review. Following our investigation, we will review pertinent research articles. This rule specifies which manuscripts will be reviewed. It should be easier to determine which items to investigate further. Which previous studies were included in the review, and why were they included?

RESULT

First study conducted with 841 patients who underwent randomization, 388 patients in the tiotropium group and 383 in the placebo group were included in the full analysis set. The FEV1 in patients who received tiotropium was higher than in those who received placebo throughout the trial (ranges of mean differences [MD] = 127-69 ml before bronchodilator use and 71-133 ml after bronchodilator use; P<0.001 for all comparisons). There was no significant amelioration of the mean ± SE annual decline in the FEV1 before bronchodilator use: the decline was 38±6 ml per year in the tiotropium group and 53 ± 6 ml per year in the placebo group (difference = 15 ml per year; 95% confidence interval [CI] = -1 to 31; P=0.06). In contrast, the annual decline in the FEV1 after bronchodilator use was significantly less in the tiotropium group than in the placebo group (29 ± 5 ml per year vs. 51 ± 6 ml per year; difference = 22 ml per year [95% CI = 6 to 37]; P=0.006). The incidence of adverse events was generally similar in the two groups.[14]

Calverley, et al (2018)[15] conducted a study with 16,485 patients with moderate COPD and heightened cardiovascular risk. They showed adjusted rates of FEV1 decrease were -46 ml/year (-30% of baseline) with placebo, -47 ml/year (-3.0% of baseline) with VI, -38 ml/year (-2.5%) with FF, and -38 ml/year (-2.3%) with FF/VI. FF-containing regimens had lower decline rates than placebo (P 0.03), whereas FF/VI exhibited lower decline rates than VI alone (P 0.005). The drop in FEV1 was accelerated in current smokers, individuals with a lower body mass index, men, and patients with preexisting cardiovascular disease.

The standard deviation amongst patients for the rate of decline was 59 ml per year. 38% of patients had an estimated decline in FEV(1) of more than 40 ml per year over the 3-year study period, 31% had a decline of 21 to 40 ml per year, 23% had a change in FEV(1) ranging from a decrease of 20 ml per year to an increase of 20 ml per year, and 8% had an increase of more than 20 ml per year. The mean rate of decline in FEV(1) was 2.4 ml per year higher in current smokers than in current nonsmokers, 1.4 ml per year higher in patients with emphysema than in patients without emphysema, and 1.7 ml per year higher in patients with bronchodilator reversibility than in patients without reversibility.[16]

Siler, et al (2017)[17] showed FF/VI 100/25 µg group had a 34 mL adjusted mean treatment difference over the VI 25 µg group in change from baseline trough FEV1 (95% CI 14-55; p = 0.001) at day 84. The percentage of rescue medication-free 24-hour periods did not differ significantly between groups. In terms of time to first moderate/severe COPD exacerbation, the FF/VI 100/25 µg group showed a 42% risk reduction compared to the VI 25 µg group (95% CI 22-57; nominal p <0.001). The incidence of adverse events during treatment was comparable between groups.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Agent	Conclusion
Zhou, 2017[14]	China	Multicenter, randomized, double-blind, placebo-controlled trial	841 patients who underwent randomization, 388 patients in the tiotropium group and 383 in the placebo group	Once-daily inhaled dose (18 µg) of tiotropium	Tiotropium resulted in a higher FEV1 than the placebo after 24 months, and it mitigated the annual reduction in the FEV1 after bronchodilator usage in patients with COPD who were in GOLD stage 1 or stage 2.
Calverley, 2018[15]	United Kingdom (UK)	Prespecified analysis of the key secondary outcome in SUMMIT (Study to Understand Mortality and Morbidity)	16,485 patients with moderate COPD and heightened cardiovascular risk	Inhaled corticosteroid fluticasone furoate (FF; 100 µg), the long-acting β-agonist vilanterol (VI; 25 µg), or their combination (FF/VI)	It appears that either FF alone or in combination with VI can slow down the rate of FEV1 decline in patients who have moderate COPD and an increased risk of cardiovascular complications.
Vestbo, 2016[16]	United State of America (USA), United Kingdom (UK)	Double-blind randomised controlled trial	23,835 COPD patients	Inhaled fluticasone furoate (100 µg), vilanterol (25 µg), or the combination of fluticasone furoate (100 µg) and vilanterol (25 µg).	Treatment with fluticasone furoate and vilanterol did not change mortality or cardiovascular outcomes in patients with moderate COPD who had an increased risk of cardiovascular disease. However, the treatment did minimize exacerbations and was well accepted by the patients. It appeared that fluticasone furoate, either on its own or in combination with vilanterol, could slow the drop in FEV1 levels.
Siler, 2017[17]	United State of America (USA), United Kingdom (UK), Japan	Randomized, three-way, incomplete block, crossover study	1,620 patients	fluticasone furoate (FF) / vilanterol (VI) 100/25 µg or VI 25 µg once daily	On a statistical scale, the effect of FF in the combination of FF and VI at 100/25 µg on lung function in COPD was found to be significant.

DISCUSSION

The goal of COPD management is to reduce symptoms and the risk of acute exacerbations. Indicators of decreasing symptoms are increasing symptoms, improving tolerance to activity, and improving health status. While indicators of reducing risk are preventing disease exacerbation, preventing and treating exacerbations, reducing mortality. By inhalation (MDI), unless preparations are not available/unaffordable and given routinely (if symptoms persist) or only when needed (intermittent symptoms). Three classes can be given, including: β-2 agonists (fenopterol, salbutamol, albuterol, terbutaline, formoterol, salmeterol), anticholinergics: (ipratropium bromide, oxytroprium bromide), and methylxanthin (slow-release theophylline, if the combination of □-2 and steroids are not satisfactory).[2]

Folmetrol and salmeterol are LABAs given 2 times a day, which significantly improve FEV1 and lung volume, tightness, exacerbation rates and the number of hospital admissions, but there is no effect on improving mortality or lung function. Indacaterol or LABA consumed once a day can improve tightness, health status, and the rate of exacerbations. Some patients with a history of coughing will be followed by indacaterol inhalation. Oladaterol and vilanterol are additional LABAs that can be consumed once a day and can improve symptoms and lung function.[2]

COPD that shows a response to steroid testing is given with VEP1 <50% predicted (grades III and IV) and acute exacerbations. Treatment with ICS has shown a limited response. Several drugs including beta2-agonists, theophylline or macrolides can affect corticosteroid sensitivity in COPD. Treatment with ICS alone does not modify the decrease in FEV1. In patients with moderate-severe COPD, the combination of ICS with LABA is more effective in improving lung function, health status and reducing exacerbations. In addition, treatment with LABA / ICS fixed dose combination (FDC) has a significant effect compared to LABA alone, in patients with exacerbations a maximum of once a year.[2]

ICSs lower the rate of deterioration in lung function compared to placebo when administered alone or in conjunction with a LABA, according to research by Calverley et al. These findings have implications for the treatment of COPD patients and the study of disease progression.[15] Unlike the TORCH experiment, LABA monotherapy had no effect on the rate of FEV1 reduction. Although the other therapeutic effects of once-daily VI, such as exacerbation prevention, are comparable to those of twice-daily salmeterol, this may be related to the medication chosen.[18] Other study showed alone or in combination with vilanterol, fluticasone furoate seems to attenuate FEV1 decline.[16]

Other drugs that can be given include mucolytics (mucokinetics, mucoregulators): ambroxol, carbocysteine, glycerol iodide. Antioxidants: N-Acetyl-cysteine. Immunoregulators and antitussives, although they are not given routinely.[2] Antimuscarinics are drugs that block the bronchoconstrictive effect of acetylcholine at M3 muscarinic receptors in the smooth muscles of the respiratory tract. Short-acting antimuscarinics (SAMAS) such as ipratropium and oxitroprium also block M2 neuronal receptors, potentially triggering bronchoconstriction. Long acting muscarinic antagonists (LAMAS) such as tiotropium, aclidinium, glycopyrronium bromide and umeclidinium, bind to M3 muscarinic receptors with faster dissociation than M2 muscarinic receptors which prolongs the duration of the bronchodilator effect.[19]

Zhou, et al (2017)[14] examined the efficacy and safety of tiotropium in a large cohort of individuals with GOLD stage 1 or 2 COPD. At 24 months, tiotropium produced a significantly greater FEV1 than placebo and improved the yearly fall in FEV1 assessed after bronchodilator use but not in FEV1 assessed before bronchodilator use. Moreover, tiotropium reduced the frequency of acute COPD exacerbations compared to placebo and enhanced the quality of life in patients with GOLD stage 1 or 2 COPD. Comparable outcomes were observed in patients with a CAT score of fewer than ten.
Study used a FEV1:FVC ratio of less than 0.70 following bronchodilator administration plus respiratory symptoms, a history of exposure to risk factors (e.g., smoking, air pollution, biomass burning), or both as the case criteria for COPD.[2]

Early-stage COPD patients are asymptomatic but experience a rapid loss in lung function. In our study, all individuals satisfied the diagnostic criteria for COPD based on risk factors and spirometric data.[20,21] Among patients with a CAT score of less than 10, tiotropium was associated with a smaller yearly reduction in FEV1 after bronchodilator usage than placebo. It is unknown whether tiotropium's ability to prevent COPD-related loss of lung function has any influence on the underlying disease mechanisms in COPD. If so, then the advantage we found may only delay the onset of a more severe disease, as opposed to preventing it.[22,23]

CONCLUSION

Tiotropium had a higher FEV1 than the placebo and reduced the annual FEV1 decrease after bronchodilator use in GOLD stage 1 or 2 COPD patients. FF or VI may halt FEV1 decline. Patients liked the treatment, which reduced exacerbations. Fluticasone furoate or vilanterol appeared to reduce FEV1 decline.

REFERENCE

[1]. Lumb AB. Nunn's Applied Respiratory Physiology. 8th ed. Philadelphia: Elsevier; 2017.
[2]. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for diagnosis, management, and prevention of COPD. 2017.
[3]. Broaddus VC; Mason RJ; Ernst JD; et al. Murray & Nadel's Textbook of Respiratory Medicine. Philadelphia: Elsevier Saunders; 2016.
[4]. Price SA LM. Patofisiologi Konsep Klinis Proses-Proses Penyakit. Jakarta: EGC; 2016.
[5]. World Health Organization's. Chronic obstructive pulmonary disease (COPD). Geneva; 2017.
[6]. Kementerian Kesehatan Republik Indonesia. Riset Kesehatan Dasar [Internet]. Jakarta; 2018. Available from: http://www.depkes.go.id/resources/download/infoterkini/materi_rakorpop_2018/Hasil Riskesdas 2018.pdf
[7]. Adeloye D; Chua S; Lee C; et al. Global and Regional Estimates of COPD Prevalance: Systematic Review and Meta-analysis. J Glob Health. 2015;5(2):17–23.
[8]. Currie GP. ABC of COPD. London: Blackwell Publishing; 2011.
[9]. Fishman JA, Grippi MA, Kotloff RM, et al. Fishman's Pulmonary Disease and Disorders Fifth Edition. New York: Elsevier Saunder; 2016.
[10]. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA. 1994 Nov;272(19):1497–505.
[11]. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000 May;320(7245):1297–303.
[12]. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. Am J Respir Crit Care Med. 2009 Jul;180(1):3–10.
[13]. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011 Sep;365(13):1184–92.
[14]. Zhou Y, Zhong N-S, Li X, Chen S, Zheng J, Zhao D, et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017 Sep;377(10):923–35.
[15]. Calverley PMA, Anderson JA, Brook RD, Crim C, Gallot N, Kilbride S, et al. Fluticasone Furoate, Vilanterol, and Lung Function Decline in Patients with Moderate Chronic Obstructive Pulmonary Disease and Heightened Cardiovascular Risk. Am J Respir Crit Care Med. 2018 Jan;197(1):47–55.
[16]. Vestbo J, Anderson JA, Brook RD, Calverley PMA, Celli BR, Crim C, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. Lancet (London, England). 2016 Apr;387(10030):1817–26.
[17]. Siler TM, Nagai A, Scott-Wilson CA, Midwinter DA, Crim C. A randomised, phase III trial of once-daily fluticasone furoate/vilanterol 100/25 µg versus once-daily vilanterol 25 µg to evaluate the contribution on lung function of fluticasone furoate in the combination in patients with COPD. Respir Med. 2017 Feb;123:8–17.
[18]. Thomsen LH, Dirksen A, Shaker SB, Skovgaard LT, Dahlbäck M, Pedersen JH. Analysis of FEV1 decline in relatively healthy heavy smokers: implications of expressing changes in FEV1 in relative terms. COPD J Chronic Obstr Pulm Dis. 2014;11(1):96–104.
[19]. Badan Pengawas Obat dan Makanan Republik Indonesia. Antimuskarinik. pionas.pom.go.id.
[20]. Zhou Y, Zou Y, Li X, Chen S, Zhao Z, He F, et al. Lung function and incidence of chronic obstructive pulmonary disease after improved cooking fuels and kitchen ventilation: a 9-year prospective cohort study. PLoS Med. 2014;11(3):e1001621.
[21]. Guan W-J, Zheng X-Y, Chung KF, Zhong N-S. Impact of air pollution on the burden of chronic respiratory diseases in China: time for urgent action. Lancet. 2016;388(10054):1939–51.
[22]. Tantucci C, Modina D. Lung function decline in COPD. Int J Chron Obstruct Pulmon Dis. 2012;95–9.
[23]. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2016;194(2):178–84.