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Effect Of Roflumilast On Clinical Features In Patients With Severe Chronic Obstructive Pulmonary Disease

Iryna Savelikhina [1*], Myckola Ostrovskyy [1]

1. Department of Phtisiology and Pulmonology with the course of occupational diseases, Ivano-Frankivsk National Medical University Ukraine
[E-mail: iryna.savelikhina@gmail.com]

Chronic obstructive pulmonary disease (COPD) is the fifth cause of morbidity and mortality in the developed world and represents a substantial economic and social burden.

Phosphodiesterase-4 (PDE4) inhibitors are a new class of anti-inflammatory drugs that have shown efficacy in preclinical and clinical studies in patients with COPD.

This review is focused on the indication that roflumilast, which offers a unique anti-inflammatory mechanism of action in an oral formulation, is effective in decreasing symptoms associated with COPD stage III, and may possess clinical potential in the management of the disease.

There were 151 participants in the study. Verification of the diagnosis and its formulation confirmed by the order MH of Ukraine № 128 from 19.03.2007 "On the approval of medical care clinical protocols for «Pulmonology» [14]. Clinical examination was conducted including 151 patients before and at 30, 90 and 180 days of treatment with roflumilast.

Keyword: Roflumilast, Phosphodiesterase 4 Inhibitor, Chronic Obstructive Pulmonary Disease, Clinical Symptoms.

1. Introduction:

Chronic obstructive pulmonary disease (COPD) is a heterogeneous, multi-component disease associated with significant clinical burden. Chronic obstructive pulmonary disease (COPD) is a major global health problem that is now a leading cause of death worldwide [20]. COPD is associated with a chronic inflammatory response, predominantly in small airways and lung parenchyma, which is characterized by increased numbers of T lymphocytes, macrophages, neutrophils [20].

COPD is responsible for high death rates and significant cost to health systems. COPD is currently the 5th cause of morbidity and mortality in the developed world and represents a

substantial economic and social burden [18-19,20].

It has been predicted that COPD will be the world's fifth-ranking cause of disability by 2020 [19-20]. According to the WHO, in 2002 in Europe 260 thousand people died from COPD. The condition was the cause of 2.7% of all deaths, although, according to experts, mortality from COPD is clearly underestimated. The WHO experts say that for the past 30 years, mortality from COPD in the world has increased by 163% [6]. This disease occurs in 4-6% of the adult population of Europe. Moreover, the number of patients is 2.7 million – in Germany, in Italy and France - 2.6 million in Spain - 1.8 million [2]. There are approximately 900,000 people diagnosed with COPD in the UK and a further 2 million are estimated to have the disease but remain undiagnosed [12]. It is the second most common reason for emergency hospital admissions in the UK, with 1 in 8 emergency admissions each year being due to COPD [13].
In Ukraine the problem of COPD is extremely pointed. In particular, over the last decade, the incidence rate of COPD (before 2004 - chronic obstructive bronchitis) has increased by 6.9%, while the proportion among newly diagnosed diseases was about 38.0% [2,4].
According to official statistics, in Ukraine, the incidence of COPD is 10 times higher than in bronchial asthma. In percentage terms, COPD (62.4%) is far ahead of other respiratory diseases for the duration of periods of disability in the structure of bronchopulmonary disease (compared to asthma - 21.4%, pneumonia - 7.6%) [1,2,5,8].

Consequently, the mortality from COPD increases (41.2 per 100,000 population), 3.2 times higher than the rate for pneumonia (12.8) and 34 times (1.2) in asthma [1,2-3]. However, the mortality and disability are quickly growing, especially among men of working age [1,2,7]. It is estimated that patients with COPD suffer from one to four or more exacerbations during the year [1,9].

COPD leave people disabled and an increasing burden on society. COPD lead to significant social impact on society. According to the forecast of the WHO (2003), this ailment in 2020 will occupy the fifth leading cause of disability [2,10]. COPD is one of the main causes of death among females. According to researchers worldwide, increased mortality from COPD among women soon will continue to grow and outpace the same rate among males.

COPD is a costly disease. In the U.S. the direct costs of treating patients with this pathology in 2002 amounted to more than $ 18 billion, and total costs associated with the disease - more than 32 billion [11]. However, a significant portion of costs are so-called inefficient costs [2].

For example, in European countries about 74% of all costs associated with COPD are wasting on disability patients and less than 20% are the direct costs of their treatment (about 12% for outpatient, and 7% - Landline) [1-2] . According to prognostic data on the socio-economic costs in 2020 COPD will take the 5th place in the world [2,8,10]. However, today the cost of COPD in general is three times higher than the cost of bronchial asthma (BA).

Increasing evidence indicates that chronic obstructive pulmonary disease (COPD) is a complex disease involving more than airflow obstruction [25]. Systemic inflammation may also initiate or worsen comorbid diseases, such as ischaemic heart disease, heart failure, osteoporosis, normocytic anaemia, lung cancer, depression and diabetes [25].

Comorbid diseases lead to increased hospitalizations and mortality, complicate the management of COPD.
In the Lung Health Study 12.8% of the 5,887 smokers were hospitalized, with 42% of the hospitalizations secondary to cardiovascular events or pulmonary complications [26].
Between 1970 and 2002, death rates due to stroke and heart disease decreased (63% and 52%,

respectively), while death rates due to COPD increased 100% [26].

In fact, most COPD patients are reported to die of extrapulmonary diseases, including cardiac ischemia, cardiac arrhythmias, and heart failure [27]. Others die of complications like pneumonia or septicemia that may not have developed or have been fatal without the burden of COPD [27]. In the Towards a Revolution in COPD Health (TORCH) trial, 35% of deaths were due to pulmonary causes, 27% to cardiovascular disease, and 21% to cancer. Ten percent were attributed to other causes, whereas the primary cause of death could not be determined by the clinical end-point committee in 7% of cases [27].

COPD is characterized by a mild or asymptomatic course, followed by a progressive increase in the severity of the condition, and a steadily growing decline of a respiratory function, and it is the most specific and predictive signs of the disease. Unfortunately, this pathology is often diagnosed at later stages, when the most advanced treatment programs do not allow slow steady progression. According to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines, COPD is characterized by airflow limitation that is not fully reversible. This airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases. Important symptoms of COPD are chronic cough, sputum production and dyspnea [14]. The single most important risk factors are a history of exposure to tobacco smoke, occupational exposure to dusts and chemicals, genetic predisposition and lower socio-economic status [14]. A diagnosis of COPD should be considered if any of these key indicators are present and confirmed by spirometry [14]. Acute exacerbations of COPD (AECOPD) are major clinical events [15]. They are associated with a more rapid decline in lung function and an increased risk of dying. Exacerbations that require hospitalization are particular significant. Approximately 40% of the AECOPD patients who require hospitalization will die in the subsequent year [15]. Treatment with long-acting bronchodilators and combination inhaled corticosteroid/long-acting bronchodilator inhalers reduces but does not eliminate AECOPD [15]. A phosphodiesterase (PDE) IV type - roflumilast and its active metabolite (roflumilast N-oxide) are selective inhibitors of phosphodiesterase 4 (PDE4) reduces the frequency of AECOPD when given in combination with short-acting bronchodilators, long-acting bronchodilators, or inhaled corticosteroids. Roflumilast and roflumilast N-oxide inhibition of PDE4 (a major cyclic-3',5'-adenosine monophosphate (cyclic AMP)-metabolizing enzyme in lung tissue) activity leads to the accumulation of intracellular cyclic AMP. Roflumilast is indicated as maintenance treatment in severe COPD (i.e. in patients with post-bronchodilator FEV1 <50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as an add-on to bronchodilator treatment [17]. Clinical trials have demonstrated that roflumilast improves lung function and reduces exacerbation frequency in COPD. Roflumilast is effective when used concomitantly with all forms of bronchodilator and with inhaled corticosteroids [16].

Roflumilast thus represents an important addition to current therapeutic options for COPD patients with chronic bronchitis, including those who remain symptomatic despite treatment [16]. PDE4 inhibitor roflumilast has been shown to provide effective inhibition of chemotaxis, leucocyte activation, and cytokine production in vitro and in animal models of COPD, and reduce the number of neutrophils and eosinophils in the sputum of patients with COPD [21]. In two large, randomised clinical studies undertaken in patients with COPD that was moderate to severe or severe to very severe, roflumilast consistently improved lung function. In two randomised trials in symptomatic patients with severe COPD and a history of exacerbations, Calverley and colleagues confirmed after 1 year the positive effects of roflumilast on both lung function and exacerbations independent of the patient's smoking status or use of concomitant medication such as inhaled longacting β2 agonists [21-22].

The most common adverse effects of roflumilast are diarrhea, nausea, headaches, weight loss. In clinical trials, patients treated with roflumilast experienced weight loss that averaged just over 2 kg but was primarily due to the loss of fat tissue [15]. Weight loss was least in underweight patients and obese patients experienced the greatest weight loss. An unexpected benefit of treatment with roflumilast was that fasting blood glucose and hemoglobin A1c levels improved in patients with comorbid type 2 diabetes mellitus [15,21-22]. The two pivotal, one year studies (M2-124 and M2-125), which assessed the efficacy of roflumilast in the patient population for which it is now licensed, showed that roflumilast significantly reduced the rate of moderate or severe exacerbations by 16.9% compared to placebo (rate ratio 0.83 [95% CI 0.75 to 0.92]; p=0.0003) [21]. In patients who received concomitant LABA therapy during the trials, the addition of roflumilast reduced the rate of moderate or severe exacerbations by 20.7% compared to LABA alone (RR 0.79 [95% CI 0.69 to 0.91]; p=0.0011), which demonstrates that the efficacy of roflumilast is consistent with or without concomitant bronchodilator therapy [21].
The change from baseline in pre-bronchodilator FEV1 was a co-primary endpoint in the pivotal trials, and a mean improvement of 48 ml (95% CI 35 to 62 ml; p<0.0001) was observed with roflumilast compared to placebo in the pooled data set. A similar improvement of 46 ml (95% CI 29 to 64 ml; p<0.0001) was also observed in patients who received concomitant LABA therapy compared to LABA alone [21-22].

2. Material and Methods

The patients were divided into 2 groups according to their treatment. I group - 85 patients who received therapy according to GOLD without roflumilast. II group - 66 patients who received therapy according to GOLD using roflumilast were divided into: a subgroup II-a - 31 patients who used roflumilast 500 mcg 1 tablet 1 time daily 30 days. II-b subgroup - 24 patients received roflumilast 500 mcg 1 tablet 1 time daily 90 days, subgroup II-c - 11 patients received roflumilast 500 mcg 1 tablet 1 time daily 180 days. COPD treatment included inhaled corticosteroid therapy, oral corticosteroids, M-long-acting anticholinergics, short-acting β-2 agonists.
There were 151 participants in the study. Verification of the diagnosis and its formulation confirmed by the order MH of Ukraine № 128 from 19.03.2007 " On the approval of medical care clinical protocols for «Pulmonology» [14]. Clinical examination was conducted including 151 patients before and at 30, 90 and 180 days of treatment with roflumilast.

3. Results

The main symptoms of COPD are: shortness of breath that gets worse when patients exercise, as COPD gets worse, patients may be short of breath even, at rest severely limit their activities; most morning coughs, coughing throughout the day, sometimes at night, small amounts of mucous sputum when they cough, expiratory wheeze.
As you know, one of the first places in the diagnosis of disease is the physical examination. The characteristic physical signs are lengthening of exhalation phase, dry sibilant rales and weezing, weakening of respiratory sound (due to hyperinflation and emphysema), box-shaped sound during percussion.
Prior to the treatment in the first study group we observed: dyspnea during usual physical activities - in 52 (61.2%) patients; dyspnea at rest - in 33 (38.8%) patients, and cough with sputum production - in 63 (74 1%), dry cough - in 22 (25.8%) patients (Table 1). On the 30th day of the treatment we saw no changes in the symptoms listed above: shortness of breath during usual physical activities in 52 (61.2%) patients, at rest - in 33 (38.8%) patients, and cough with sputum - in 64 (75.3%), dry cough - in 21 (24.7%) patients. After 90 days of treatment only in 2 patients of this group reduced dyspnea at rest and was - 36.5%, dry cough changed to productive in 2 patients and was - 22.3%. After 180 days of treatment clinical changes were not significant: dyspnea at rest reduced in 1 patient and was - 35.3%, unproductive cough reduced in 2 patients, and was - 75.3% (Table.1).

Table 1: Clinical Symptoms (%) In Chronic Obstructive Pulmonary Disease Stage III of I Study Group, II-A, II-B, II-C Subgroups of Treatment

Clinical symptom	I group n=85				II-a subgroup n=31		II-b subgroup n=24		II-c subgroup n=11	
	Before treatment	30 days of treatment	90 days of treatment	180 days of treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
dyspnea during usual physical activities	61,2	61,2	63,5	58,8	64,5	58,1	62,5	41,6	63,6	36,4
dyspnea at rest	38,8	38,8	36,5	35,3	35,5	29,0	37,5	20,8	36,4	9,1
Cough with sputum production	74,1	75,3	77,6	75,3	74,2	64,5	75,0	20,8	72,7	18,2
dry cough	25,8	24,7	22,3	22,3	25,8	25,8	25,0	0	27,3	0
box-shaped percussion	100	100	100	100	100	100	100	100	100	100
General weakness, fatigue, sweating	90,6	90,6	90,6	90,6	90,3	90,3	100,0	62,6	100,0	18,2
dry sibilant rales and wheezing	77,6	77,6	75,3	71,8	77,4	67,7	79,2	50,0	72,7	18,2
exhalation phase lenthening, weakening of respiratory sound	100	100	100	100	100	100	100	100	100	100

There was no change in the physical signs: exhalation phase lengthening, weakening of respiratory sound – in 85 (100%) patients, box-shaped percussion – in 85 (100%) patients were observed throughout the study. The presence of dry sibilant rales and wheezing was heard before treatment in 66 (77.6%) patients of I study group. We have noted that indicator have remained stable for 30 days of treatment, only on the 90th day in 2 patients, and on the 180th day - in 3 patients we heard no rales on auscultation these indicators were respectively - 75, 3% and 71.8%. General weakness, fatigue, sweating were available - in 77 (90.6%) patients throughout the study.

In all patients, of the second (II) study group were available: dyspnea at rest - in 24 (36,4%) patients, shortness of breath during normal physical activities - in 42 (63,4%), dry cough - in 17 (25,7%) patients, cough with sputum production - in 49 (74,3%) patients. Frequent signs: weakness, fatigue, sweating were observed in almost all patients (100.0%). The characteristic physical signs were box-shaped percussion and / or blunting percussion recorded in 66 (100.0%) patients. Other objective signs of COPD stage III during primary examination were the presence of dry sibilant rales and wheezing, exhalation phase lengthening and the weakening of the respiratory

sounds. We identified that auscultation varied during different periods of the treatment.
So, we saw slight improvements of clinical dynamics in patients of II-a subgroup who used roflumilast during 1 month. In this subgroup dyspnea at rest was in 11 (35,5%) patients, dyspnea during normal physical activities - in 20 (64,5%) patients and dry cough - in 8 (25,8%) patients, cough with sputum - in 23 (74,2%) patients (Table 1.).

It was found out that dyspnea at rest decreased in 2 patients, dyspnea during usual physical activities - in 4 patients of this subgroup, and reducing unproductive cough - in 2 patients of II-a subgroup was: 29.0%, 58.1% and 64.5%. Typical physical signs, such as: the exhalation phase lengthening, weaking of respiratory sound (due to hyperinflation and emphysema), box-shaped percussion observed in all patients before and after 30-day treatment with roflumilast. The presence of dry sibilant rales and wheezing were identified in 24 (77.4%) patients of this subgroup, and were decreased after treatment in 3 patients, this rate was - 67.7%, weakness, fatigue, sweating in this subgroup were - in 28 (90.3%) patients before and after treatment.
Treatment of patients with COPD according to GOLD using roflumilast for 90 days led to more positive rates than in the previous subgroup. In this subgroup the rate of dry cough was in 6 (25.0%) patients, cough with sputum production - in 18 (75.0%) subjects. The rate of dyspnea at rest was in 9 (37.5%), during normal physical activities - in 15 (62.5%) patients (Table 1).

General weaknesses, fatigue, sweating, were observed in 24 (100.0%) patients, the presence of dry sibilant rales and wheezing in 19 (79.2%) patients. Lenthening of exhalation phase and weakening of respiratory sound, also box-shaped percussion were in 24 (100.0%) patients of II-b subgroup.

After treatment, it was explored that dyspnea at rest disappeared in 4 patients and was - 20.8%, which is in 1.8 times less compared to the data before treatment, dyspnea during physical exercise decreased in 5 patients and was - 41.6%, which is in 1.5 times lower compared with the rate before treatment.

In particular, we want to point out that in 3 (12.5%) patients of II-b subgroup dry cough has changed into a more productive, and in 1 (4.2%) patient - disappeared completely. We also observed a reduction of unproductive cough in this subgroup, at the end of treatment (20.8%). We have seen reduction of wheezing in 7 patients, their rate was - 50.0%. General weakness, fatigue, sweating, preserved in 9 patients of II-b subgroup, the data was - 62.6% and was lower in 1.6 times compared with the data before treatment. Lenthening of exhalation phase and weakening of respiratory sound, box-shaped percussion were unchanged throughout the entire period of study. (Table 1).
Long-term use of roflumilast provided the most positive clinical dynamics in II-c subgroup, where the drug used within 180 days. In this group of subjects dry cough occurred in 3 (27.3%) patients, cough with sputum production - in 8 (72.7%) subjects. Dyspnea at rest was - in 4 (36.4%), during normal physical activities - in 7 (63.6%) patients (Table 1). Lenthening of exhalation phase and weakening of respiratory sound, box-shaped percussion were observed in all patients before and after 180-day treatment with roflumilast. The presence of dry sibilant rales and wheezing heard in 8 (72.7%) patients of this sub-group, and general weakness, fatigue, sweating were in 11 (100.0%) patients before and after treatment.

After 180 days of treatment using roflumilast in 3 patients dyspnea at rest disappeared and the rate was only - 9.1%, dyspnea during usual physical activities reduced in 4 patients and was only 36.4%, it is 1, 7 times lower compared to the data before treatment. Cough disappeared in all 3 (27.3%) patients. Cough with sputum disappeared in 6 patients and was only 18.2%, which is in 4 times lower compared with the rate before treatment (Table 1).

Dry sibilant rales and wheezing decreased in 9 patients, the rate was - 18.2%. General weakness, fatigue, sweating, reduced only in 2 patients of this subgroup, the rate was - 18.2% and it was lower 5.5 times compared with the rate before treatment. Lenthening of exhalation phase and weakening of respiratory sound, box-shaped percussion were unchanged during the entire period of treatment (Table 1).

4. Conclusions

1. Roflumilast serves as a safe and effective option in the treatment of COPD. The addition of roflumilast to COPD treatment according to GOLD in patients with severe COPD reduces the clinical symptoms.
2. These datas demonstrate the potential of roflumilast in treating patients taking this drug for the long-term.

5. References

1. Feshchenko, YI. COPD control – is it possible today?. Health of Ukraine - December 2010 - № 1 (13) - S. 10 - 11.
2. Feschenko, YI. Leading experts analyzed the current situation of COPD in Ukraine and outlined ways to solve it [text]. Health of Ukraine - gruden2010 - № 24 (253) - S. 31 - 33.
3. Avdeev, S. Current approaches to the diagnosis and treatment of pulmonary hypertension in patients with chronic obstructive pulmonary disease [Text]. - 2009. - № 1. - S. 90-101.
4. Kubysheva N. Soluble antigens ICAM-1 and ICAM-3 in patients with chronic obstructive pulmonary disease.Immunology. - 2009. - № - S. 55-57.
5. Zaitsev AA, Kulahyna T, Puchnyna T. Modern modes of antibiotic treatment of infections of the lower respiratory tract. SRI. physician. - 2011. - № 9.http :// www.lvrach.ru/2011/09/7312597/
6. Butorac Petanjek B. Antibiotic therapy for exacerbations of chronic obstructive pulmonary disease (COPD). Chemother. – 2010;22 (5): 291-297.
7. Feschenko YI. Current issues of diagnosis and treatment of chronic obstructive pulmonary disease [Materials IV Congress of TB and Lung of Ukraine, Kyiv, October 20-22, 2008.]. Ukr. pulmon. Journ. - 2008. - № 2. Appendix. - P.7-1
8. Feshchenko YI. COPD in Ukraine: problems and solutions. Health of Ukraine. -2009. - № 9/1. - S. 3-4.
9. Lysenko HI. The role of the family physician in the treatment and prevention of exacerbations of chronic obstructive pulmonary disease. Ukrainian Pulm. Journal 2008. - № 3. - S. 56-58.
10. Feshchenko Y. The current approach to managing COPD. Health of Ukraine. -2006. - № 4. - S. 20-24
11. Fabbri L.M. Rofl umilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet 2009; 374: 695–703.
12. Healthcare Commission. Cleaning the air: A national study of chronic obstructive pulmonary disease. Available from http://www.cqc.org.uk/_db/_documents/COPD_report1_200607272728.pdf (Last accessed November 2010). 2006.
13. NICE Clinical Guideline 101. Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care. Update Guideline. 2010.
14. Mannino D. Changing the burden of COPD mortality. Int J Chron Obstruct Pulmon Dis. 2006 September; 1(3): 219–233.
15. Field S K. Roflumilast, a Novel Phosphodiesterase 4 Inhibitor, for COPD Patients with a History of Exacerbations. Clin Med Insights Circ Respir Pulm Med. 2012 August 13; 6: 51.
16. Rabe, KF. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. Br J Pharmacol. 2011 May;163(1):53-67.
17. Price D, Chisholm A, Ryan D, Crockett A, Jones R. The use of roflumilast in COPD: a primary care perspective. Prim Care Respir J. 2010 Dec;19(4):342-51.
18. Mannino D, Buist S. Global burden of COPD: risk factors, prevalence, and future trends. The Lancet, -Volume 370,- Issue 9589, -Pages 765 - 773, 1 September 2007.
19. National Institute for Clinical Excellence. National clinical guidelines on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax 2004; 59 (Suppl. 1): 1–232.
20. Barnes P.J. Mediators of Chronic Obstructive Pulmonary Disease. Pharmacol Rev. 2004 Dec;56(4):515-48.
21. Fabbri L M., Calverley P., Izquierdo-Alonso, José Luis et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two

randomised clinical trials. Lancet 2009;374:695-703.
22. Calverley P, Rabe K, Goehring Udo-Michael, Kristiansen S, Fabbri L, Martinez F J. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374:685-694
23. Spina D. PDE4 inhibitors: current status. Br J Pharmacol 2008; 155: 308–15.
24. Grootendorst DC, Gauw SA, Verhoosel RM., Sterk PJ, Hospers JJ, et al. Reduction in sputum neutrophil and eosinophil numbers by the PDE4 inhibitor rofl umilast in patients with COPD.Thorax 2007; 62: 1081–87.
25. Barnes P.J, Celli B.R. Systemic manifestations and comorbidities of COPD. ERJ May 1, 2009 vol. 33no. 5 1165-1185.
26. Chatila W.M, Thomashow B.M, Minai O.A, Criner G.J. Comorbidities in Chronic Obstructive Pulmonary Disease. Proc Am Thorac Soc. 2008 May 1; 5(4): 549–555.
27. Yawn B.P, Kaplan A. Co-morbidities in people with COPD: a result of multiple diseases, or multiple manifestations of smoking and reactive inflammation? Primary Care Respiratory Journal (2008); 17(4): 199-205.