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Roflumilast: an experience of its use in the treatment of severe COPD

Valentyna Goncharuk, Iryna Savelikhina and Kseniia Ostrovska

Abstract
Chronic obstructive pulmonary disease (COPD) is a pathologic pulmonary condition characterized by expiratory airflow obstruction due to emphysematous destruction of the lung parenchyma and remodeling of the small airways. COPD is now recognised to be a condition of global importance because of high morbidity and risk of premature death of millions of people. Chronic inflammation and exacerbations play a central role in the progression of the disease. Roflumilast – a phosphodiesterase-4 (PDE4) inhibitor, through selective inhibition of the PDE4 enzyme, roflumilast prevents the breakdown of cyclic AMP, which plays an important role in regulating inflammatory cell activity.

Keywords: COPD, spirometry, X-Ray, clinical symptoms, roflumilast

Introduction
Our understanding of chronic obstructive pulmonary disease (COPD) has changed over the past two decades. We have moved from an airflow limitation-centric view to the recognition that COPD is a multicomponent disease with structural and functional lung effects [1, 8-11]. The research of epidemiological manifestations of the disease (chronic cough, phlegm and dyspnoea on exertion) and the pathological manifestations (enlarged and increased numbers of mucus-secreting glands, destruction of the lung parenchyma and the development of emphysema) has a big significance. Posteroanterior and lateral chest x-ray (CXR) is a standard part of the clinical evaluation of subjects with COPD. Such images are inexpensive, easily obtained, and involve minimal radiation exposure [2, 7]. Spirometry is the gold standard for making the diagnosis of COPD. It should be performed in every case of suspected COPD [3]. Spirometry is a method of assessing lung function by measuring the volume of air that the patient is able to expel from the lungs after a maximal inspiration [3-5]. It is a reliable method of differentiating between obstructive airways disorders and restrictive diseases. Spirometry is the most effective way of determining the severity of COPD.
The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has proposed 4 stages of COPD, based upon spirometric testing. These are an FEV1/VC ratio 0.70 and: FEV1 80% predicted (stage I, mild), FEV1 of 50 – 80% predicted (stage II, moderate), FEV1 of 30 –50% predicted (stage III, severe), and FEV1 30% predicted (stage IV, very severe). Based on these staging criteria, stepwise approaches to therapy are recommended [1, 6, 9].
Spirometry consists of:

- Forced Vital Capacity (FVC)-The total amount of air you can breathe out after taking the deepest breath possible.
- Forced Expiratory Volume in One Second (FEV1)-The amount of air you can forcefully exhale during the first second of the FVC test.
- Peak Expiratory Flow Rate (PEFR)-PEFR measures how fast a person can breathe out, and the estimated value depends on gender, ethnicity, height, weight and age.
- Total Lung Capacity (TLC)-The total amount of air in the lungs after a deep inhalation.
- Forced Expiratory Volume (FEV)-The amount of air forcefully blown out of the lungs during the first, second and third seconds of the FVC test.
- Maximum Voluntary Ventilation (MVV)-The amount of air a person can breathe in and out in one minute.
- Forced Expiratory Flow (FEF)-The flow or volume in the middle of an exhalation.
- Functional Residual Capacity (FRC)-The amount of air that stays in the lungs after a normal breath.
- Tidal Volume (VT)-The amount of air inhaled or exhaled while breathing normally.

- Minute Volume (MV)-The amount of air exhaled per minute.
- Vital Capacity (VC)-The total volume of air you can exhale after inhaling as much as possible.

How to prepare for the test

- Do not smoke for one hour before test
- Do not drink alcohol within four hours of test
- Do not eat a large meal within two hours of test
- Do not perform vigorous exercise within 30 minutes of test

Contraindications (main)

- Recent myocardial infarction – patients should not be tested within 1 month
- Chest or abdominal pain of any cause
- Oral or facial pain exacerbated by a mouthpiece
- Stress incontinence
- Dementia or confused state

There are three distinct phases to the FVC manoeuvre, as follows: 1. maximal inspiration 2. a ‘‘blast’’ of exhalation 3. continued complete exhalation to the end of test (EOT).

The GOLD has included roflumilast as treatment option in its COPD management guidelines. A section on the new class, phosphodiesterase 4 (PDE4) inhibitors, describes the efficacy of roflumilast in patients with COPD [1, 10].

Material and Methods

The research of clinical symptoms, X-Ray, spirometry was perfomed to 151 patiens at 30, 90 and 180 days of treatment using conventional regimens in combination with roflumilast [1, 9].

The patients were divided into groups based on the treatment assignment.

Group I - 85 patients who received maintenance treatment without roflumilast.

Group II - 66 patients was divided into:

II-a subgroup - 31 patients who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) ronce daily 30 days.

II-b subgroup - 24 patients, who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) once daily 90 days,

II-c subgroup - 11 patients, who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) ronce daily 180 days. There were 15 healthy persons examined (PHP).

Verification of the diagnosis and its formulation confirmed with the *Order* of *Ministry* of *Health* of *Ukraine № 555* of June, 27, 2013 [9] and GOLD 2017 [1].

Results and Discussion

The most frequent subjective manifestation of the pathology was a cough. In 39 (25.8%) patients it was dry, in 80 (53.0%) - accompanied by sputum release, in 32 (21.2%) patients, Shortness of breath in a state of rest were identified in 57 (37.7%) patients, and with normal physical activity - in 94 (62.3%) patients. General weakness, rapid fatigability and sweating were found in 140 (92.7%) patients. The presence of multiple dry wheezing and wheezing was observed in 117 (77.5%) patients, and extension of exhalation and respiratory noise was heard in 138 (91.4%) patients. Body mass index (BMI) in group C was (23.5 ± 4.4) kg / m2 and in group D - (28.0 ± 3.2) kg / m2.

The diagnostic criterion of severe COPD is a decrease of 30% <FEV1<50% from predicted together with FEV1/FVC<70% and improvement ofFEV1 not more than 12% from predicted after a test with a bronchial spasmolytic, which points at incomplete reversibility of a wheeze. The respiratory function was estimated by 151 patients through spirography, which was carried out with the help of the device “Spirocom” (the city of Kharkiv, Ukraine).

The research studies have shown that before treatment, the indices of the respiratory function amounted to: FVC, % - 72,69 ± 3,77, FEV1, % - 38,11 ± 3,43, PEF25% - 36,21 ± 3,18, PEF50% - 32,62 ± 2,21, PEF75% - 34,41 ± 3,70, FEV1/FVC, % - 52,42 ± 3,54.

According to radiography: increase in lung volume in 145 (96.0%) patients; peribronchial pneumosclerosis in 140 (92.7%) patients; increase in retrosternal air space in 140 (92.7%) patients; emphysematous changes (reduction of pulmonary image) in 145 (96.0%) subjects.

In the course of the research studies, we observed a slight improvement of indices of the respiratory function on the 30thday of treatment in patients of the 1st group. We did not note the positive dynamics of indices of FVD on the 90thand 180th days of treatment that turned out to be uncertain.

At 180 days of treatment with roflumilast in the baseline therapy in 3 patients, dyspnoea was restless and amounted to only 9.1%; in 4 patients, dyspnea was reduced during normal physical activity and amounted to only 36.4%, which is 1, 7 times less than the data before treatment. In 2 (18.2%) patients, a dry cough disappeared. The sputum disappeared in 6 patients and amounted to only 18.2%, which is 4 times less than the pre-treatment indicator. The number of multiple dry wheezing decreased in 7 patients; overall weakness, fast fatigue, sweating was maintained only in 2 patients in the II-subgroup. The extension of the exhalation and respiratory depression phase was observed in 9 (81.8%) patients in this subgroup, and, like the box-off percussion sound, remained unchanged throughout the treatment.

The treatment with roflumilast, which is included in the basic treatment of COPD has led to the most visible improvement of the indices of the respiratory function, namely, in that group of patients, who have been taking it during 180 days, compared with 30 and 90-days of the treatment period and especially compared with the group of patients to whom the roflumilast was not included in the basic therapy (Table 1).

Table 1

Indexes	Groups of investigations			p1	p2
	PHP, n=15	II –в subgroup			
		Before treatment	180 day of treatment		
FVC, %	102,3 ± 0,2	69,8 ± 3,2	75,1 ± 3,1	<0,05	<0,05
FEV_1, %	97,4 ± 0,2	37,2 ± 3,09	47,7 ± 3,8	<0,05	<0,05
MVV_{25}, %	77,1 ± 4,8	37,7 ± 2,02	48,5 ± 3,1	<0,05	<0,05
MVV_{50}, %	63,5 ± 2,7	34,4 ± 3,1	52,3 ± 3,1	<0,05	<0,05

MVV_{75}, %	56,9 ± 3,5	37,2 ± 3,3	53,3 ± 3,9	<0,05	<0,05
FEV/FVC,%	95,2 ± 1,2	53,4 ± 2,3	63,5 ± 3,7	<0,05	<0,05

P1 - the reliability of the difference between the parameters between the indicators before treatment and after the treatment;
P2 - the reliability of the difference between the study groups;
P3- is the reliability of the difference between the parameters of the study and control groups.
* - p> 0.05 difference between the indicators before and after the treatment

Conclusions

Inclusion of roflumilast in the complex of pharmacological therapy provided positive dynamics of clinical changes, spirometry data, especially in that group of patients, who have been taking it during 180 days.

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