The Pharma Innovation Journal 2018; 7(3): 512-514

www.ThePharmaJournal.com

The Pharma Innovation

ISSN (E): 2277- 7695
ISSN (P): 2349-8242
NAAS Rating: 5.03
TPI 2018; 7(3): 512-514

www.thepharmajournal.com
Received: 16-01-2018
Accepted: 17-02-2018

Kseniia Ostrovska
Department of Phtisiology and Pulmonology with the course of occupational diseases, SHEE "Ivano - Frankivsk National Medical University", Ivano-Frankivsk, Ukraine

Iryna Savelikhina
Department of Phtisiology and Pulmonology with the course of occupational diseases, SHEE "Ivano - Frankivsk National Medical University", Ivano-Frankivsk, Ukraine

Mykola Ostrovskyy
Department of Phtisiology and Pulmonology with the course of occupational diseases, SHEE "Ivano - Frankivsk National Medical University", Ivano-Frankivsk, Ukraine

Correspondence
Iryna Savelikhina
Department of Phtisiology and Pulmonology with the course of occupational diseases, SHEE "Ivano - Frankivsk National Medical University", Ivano-Frankivsk, Ukraine

The role of biomarkers and efficacy of roflumilast in the treatment of severe COPD

Kseniia Ostrovska, Iryna Savelikhina and Mykola Ostrovskyy

Abstract
Our understanding of chronic obstructive pulmonary disease (COPD) has changed over the past two decades. It is the most common inflammatory disease of the airways, and the incidence of it is increasing throughout the world. Roflumilast - a phosphodiesterase-4 (PDE4) inhibitor, through selective inhibition of the PDE-4 enzyme prevents the breakdown of cyclic AMP, which plays an important role in regulating inflammatory cell activity. Most of the clinical features of COPD are determined by cytokines, which play a key role in the chronic inflammation. This study assessed the anti-inflammatory efficacy of roflumilast, in patients with stable severe COPD.

Keywords: Chronic obstructive pulmonary disease, biomarkers, IL-4, IL-6, roflumilast

Introduction
Chronic obstructive pulmonary disease (COPD) is responsible for early mortality, high death rates and significant cost to health systems all over the world. Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless urgent action is taken to reduce the underlying risk factors, especially tobacco use. The projection for 2020 indicates that COPD will be the third leading cause of death worldwide and fifth leading cause of years lost through early mortality. COPD is associated with increase in the risk of death and is linked to multiple comorbidities, including hypertension, heart failure, ischemic heart disease, diabetes mellitus, myocardial infarction, osteoporosis, depression, and pneumonia [4].
Active smoking remains the main risk factor, but there are other factors: air pollution, occupational factors, infections. Current epidemiologic practice evaluates COPD based on self-reported symptoms of chronic bronchitis, self-reported physician-diagnosed COPD, spirometry confirmed airflow obstruction, or emphysema diagnosed by volumetric computed chest tomography (CT). This disease is also associated with significant comorbidities. COPD is a disorder that includes various phenotypes, the continuum of which remains under debate.
The pathological criterion of COPD are destruction of the lung parenchyma with pulmonary emphysema, inflammation of the small airways with respiratory bronchiolitis, and inflammation of the central airways with chronic bronchitis [7-8].
Many inflammatory cells and mediators are involved in the inflammatory process of COPD [3]. Cytokines play an important part in many pathobiological processes of chronic obstructive pulmonary disease (COPD), including the chronic inflammatory process, emphysema, and altered innate immune response.
Interleukin (IL)-4 - a pleiotropic cytokine. It mainly promotes the proliferation of T cells and induces antibody production by B cells, and can also stimulate proliferation, differentiation, and activation of fibroblasts, endothelial, epithelial cells [5-6].
Interleukin 6 (IL6) is a pleiotropic pro-inflammatory and immunomodulatory cytokine secreted by airway epithelial cells, alveolar macrophages, adipocytes and myocytes as well as other tissues and cells [8-9]. IL6 has been related to skeletal muscle weakness in COPD, as well as to exacerbations[4] and pulmonary infections in patients with COPD [10].
PDE is a generic term that describes a large superfamily of enzymes that catalyze the breakdown of cyclic adenosine-3',5'-monophosphate (cAMP) and/or cyclic guanosine-3',5'-monophosphate (cGMP) to their respective inactive nucleotide 5'-monophosphates. Phosphodiesterase-4 (PDE4) is a vital enzyme in the metabolism of cyclic adenosine monophosphate (cAMP) and inhibition of PDE4 can inactivate immune and inflammatory cells via increase cAMP [11]. It is recommended by the GOLD guideline that a combination of PDE4 inhibitor and long-acting bronchodilator can be considered as an alternative treatment

in patients with severe COPD due to the effective improvement of lung functions [13-15]. Roflumilast, a phosphodiesterase (PDE) 4 inhibitor, is a novel oral anti-inflammatory agent that, in clinical studies, has been shown to reduce exacerbations in patients with severe and very severe COPD who have symptoms of chronic bronchitis and a history of exacerbations [15, 18].

Roflumilast and its main metabolite roflumilast N-oxide are selective PDE4 inhibitors which act to decrease immune and inflammatory cell activation [15-17]. Roflumilast targets the PDE4A, 4B and 4D splicing variants with similar potency in the nanomolar range. The affinity to the PDE4C splicing variants is 5 to 10-fold lower. This mechanism of action and the selectivity also apply to roflumilast Noxide, which is the major active metabolite of roflumilast. Phosphodiesterase-4 (PDE4) inhibitors are a new class of anti-inflammatory drugs that have shown efficacy and acceptable tolerability in preclinical and clinical studies in patients with COPD [13, 14]. The first large clinical trial involved 1411 patients with moderately severe disease (mean post-bronchodilator FEV1 1.5 L, 54% predicted) with a lack of reversibility to 400 μg albuterol and compared the effect of daily treatment with roflumilast 250 μg or 500 μg for 24 weeks with placebo62 [13-14, 17, 19]. The only other respiratory medications allowed during the study were short-acting β2-agonists (SABAs) and short-acting anticholinergics (SAACs). Approximately a quarter of the patients were treated with xanthines, 20% with ICSs, and 15% with long-acting β2 agonists (LABAs) prior to study entry. At the end of the study, roflumilast-treated patients experienced greater improvements in post bronchodilator FEV1 (74 mL and 97 mL for the 250 μg and 500 μg dose, respectively) and health-related quality of life, although the difference from baseline did not reach the clinically significant threshold of −4 units. In addition, exacerbations, primarily of mild intensity, were decreased but adverse events were similar in the two groups [13, 19].

Materials and Methods of Research

The levels of CRP and collagen IV were studied in 61 patients in bronchoalveolar fluid (BALF) in patients with severe COPD. The patients were divided into groups based on the treatment assignment.

Group I: 12 patients who received maintenance treatment without roflumilast.

Group II: 66 patients was divided into:

a) 23 patients who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) once daily 30 days.
b) 15 patients, who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) once daily 90 days,
c) 11 patients, who as a part of maintenance treatment used roflumilast 500 micrograms (one tablet) once daily 180 days. There were 15 healthy persons examined (PHP). Maintenance treatment included: M-long-acting anticholinergics, β-2 agonists, short-acting inhaled and systemic glucocorticosteroids.

Verification of the diagnosis and its formulation confirmed with the Order of Ministry of Health of Ukraine № 555 of June, 27, 2013 [1] and GOLD 2017 [3].

Results

The use of treatment regimens for patients with COPD without roflumilast at the time of treatment completion (group I), the IL-6 concentration had a slight positive dynamics. The indicator dicreased only in 5.55% (p1 <0.05). The best tendencies of the dynamics of levels of IL-6 are identified in patients who used roflumilast within 30 days (II-a subgroup study). Thus, we noted a more complete normalization of the levels of IL-6, which decreased by 1.12 times (p1 <0.05), compared to the rates before treatment, which was 5.88% (p2 <0.05) higher than indicators of I group.

However, we would like to note that prolonged to 90 days roflumilast use (II-b subgroup study) was more effective in improvement of IL-6 levels. At the time of the treatment completion the parameter decreased by 1.57 times and amounted to (88.52 ± 4.94) pg / ml (p1 <0.05), which was 48.84% higher than in the I group (p2 <0,05) and 40,58% - in the II-a subgroup of the study (p2 <0,05). Nevertheless, IL-6 levels, in spite of the favorable dynamics, in the 2nd subgroup still remained 1.91 times higher than the control group values (p3 <0.05).

The use of roflumilast in COPD patients of II-c subgroups had a clear effect on the positive dynamics of the IL-6 in BALF: at the end of treatment, the level significantly decreased by 1.97 times (p1 <0.05). The achieved effect by 76.66% exceeded the similar indices in the II-a subgroup of the study (p2 <0.05), 25.67% in the II-b subgroup (p2 <0.05) and 87.05% in the I group.

After 90 days and 180 days treatment with roflumilast the level of IL-4 increased in 2.44 times (p1 <0.05) and 2.71 times (p1 <0.05), respectively. And we did not find such a significant effect on the dynamics of IL-4 level in the I group. It was estimated that the level of IL-4 in BALF at the time of the completion of the observation was only - (3.16 ± 0.21) pg / ml (p1 <0.05), which was 2.95 times (p3 <0, 05) below the same indicators in the control group

Conclusions

Inclusion of roflumilast in the complex of pharmacological therapy provided positive dynamics IL-6 and IL-4 level concentration. These arguments allow us to recommend the proposed therapies for intensive distribution in the clinical practice.

References

1. The Order of Ministry of Health of Ukraine № 555 of June 27, 2013.
2. From the Global Strategy for Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2017.
3. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? Lancet. 2007; 370(9589):797-799.
4. Ställberg B, Janson C, Johansson G, *et al*. Management, morbidity and mortality of COPD during an 11-year period: an observational retrospective epidemiological register study in Sweden (PATHOS) Prim Care Respir J. 2014; 23(1):38-45.
5. Shen H, Xia L, Lu J. Interleukin-4 in rheumatoid arthritis patients with interstitial lung disease: A pilot study. Indian J Med Res. 2013; 138:919-21.
6. Luzina IG, Lockatell V, Todd NW, *et al*. Alternatively spliced variants of interleukin-4 promote inflammation

differentially. J Leukoc Biol. 2011; 89:763-70.
7. Di Stefano A, Caramori G, Ricciardolo FL, Capelli A, Adcock IM, Donner CF. Cellular and molecular mechanisms in chronic obstructive pulmonary disease: an overview. Clin Exp Allergy. 2004; 34:1156-1167.
8. Caramori G, Pandit A, Papi A. Is there a difference between chronic airway inflammation in chronic severe asthma and chronic obstructive pulmonary disease? Curr Opin Allergy Clin Immunol. 2005; 5:77-83.
9. Walston JD, Fallin MD, Cushman M, *et al*. IL-6 gene variation is associated with IL-6 and C-reactive protein levels but not cardiovascular outcomes in the Cardiovascular Health Study. Hum Genet 2007; 122:485-94.
10. Yende S, Tuomanen EI, Wunderink R, *et al*. Preinfection systemic inflammatory markers and risk of hospitalization due to pneumonia. Am J Respir Crit Care Med. 2005; 172:1440-6.
11. Rabe KF, *et al*. Roflumilast-an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 2005; 366:563-71.
12. Yan JH, Gu WJ, Pan L. Efficacy and safety of roflumilast in patients with stable chronic obstructive pulmonary disease: a meta-analysis. Pulm Pharmacol Ther. 2014; 27:83-9.
13. Antoniu SA. New therapeutic options in the management of COPD-focus on roflumilast / S.A. Antoniu // International Journal of COPD. 2011; 6:147-155.
14. Rabe KF. Roflumilast - an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial [Text] / KF Rabe [*et al*.] // Lancet, 2005.
15. Hermann R, Nassr N, Lahu G, *et al*. Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. Clin Pharmacokinet. 2007; 46(5):403-416.
16. Gauvreau GM, Boulet LP, Schmid-Wirlitsch C, *et al*. Roflumilast attenuates allergen-induced inflammation in mild asthmatic subjects. Respir Res. 2011; 12:140.
17. Schick MA, Wunder C, Wollborn J, *et al*. Phosphodiesterase-4 inhibition as a therapeutic approach to treat capillary leakage in systemic inflammation. J Physiol. 2012; 590(Pt 11):2693-2708.
18. Hermann R, Nassr N, Lahu G, *et al*. Steady-state pharmacokinetics of roflumilast and roflumilast N-oxide in patients with mild and moderate liver cirrhosis. Clin Pharmacokinet. 2007; 46(5):403-416.
19. Bateman ED, Jardim J, Goehring UM, Brose M, Calverly P. Effect of roflumilast on hospitalizations in COPD patients. Eur Resp J. 2012; 40(Suppl 56):P2109.