УДК 616.23/.24-002.2:577.112
https://doi.org: 10.20538/1682-0363-2020-1-59–66

Eosinophilic cationic protein as a non-invasive marker of the nature of inflammatory response in patients with chronic obstructive pulmonary disease

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ABSRACT

Objective. To estimate the value of measuring plasma eosinophilic cationic protein (ECP) levels in patients with chronic obstructive pulmonary disease (COPD) as a potential biomarker for determining the activity of eosinophilic inflammation. To compare it to determining the number of blood eosinophils and predicting the severity of COPD by determining such clinical characteristics as respiratory function, exacerbation frequency and the BODE index.

Materials and methods. Based on the protocol, 161 patients with COPD participated in the study. They made 2 visits for the collection of anamnestic data and the performance of the main study procedures: respiratory function test, 6-minute step test, dyspnea assessment according to the Medical Research Council Scale questionnaire and sputum and blood analysis in order to determine the level of eosinophils and ECP. The second visit was conducted 12 months after the first to assess the dynamics of the disease. We paid particular attention to the presence of allergies in the case history, the frequency of exacerbations, the number of courses of treatment with antibacterial drugs and inhalants, and systemic glucocorticoids.

Results. The study has demonstrated that high plasma levels of ECP in patients with COPD are associated with a more severe course of disease and the development of more frequent infection-related exacerbations of the disease, which require the administration of inhaled glucocorticoids and antibiotics. We have demonstrated an inverse relationship between the ECP level and forced expiratory volume in 1 second (FEV1). This allows the use of this indicator as a predictor of the severity of COPD in patients.

Conclusion. According to the obtained data, measuring the ECP level of blood plasma can be recommended for use as a clinical marker in the prognosis of COPD and selection of personalized therapy. It is a non-invasive and a relatively easily accomplished research method.

Key words: COPD, eosinophils, eosinophilic cationic protein, phenotype, severity, glucocorticoids.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Source of financing. The study was supported by the Russian Academic Excellence Project.

Conformity with the principles of ethics. All patients participating in the study signed an informed consent. The study was approved by the local Ethics Committee SSMU.

For citation: Karnaushkina M.A., Fedosenko S.V., Danilov R.S., Komarova I.S., Petrov V.A. Eosinophilic cationic protein as a non-invasive marker of the nature of inflammatory response in patients with chronic

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obstructive pulmonary disease. *Bulletin of Siberian Medicine*. 2020; 19 (1): 59–66. https://doi.org: 10.20538/1682-0363-2020-1-59–66.

Эозинофильный катионный белок как неинвазивный маркер характера воспалительного ответа у больных хронической обструктивной болезнью легких

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РЕЗЮМЕ

Цель исследования. Установить ценность измерения уровня эозинофильного катионного протеина в плазме крови у больных хронической обструктивной болезнью легких

(ХОБЛ) как потенциального биомаркера для определения активности эозинофильного воспаления в сравнении с определением количества эозинофилов крови и прогнозирования тяжести ее течения на основании определения таких клинических характеристик, как функция внешнего дыхания, частота обострений и индекс BODE.

Материалы и методы. В исследовании приняли участие больные ХОБЛ (n = 161), для которых предусмотрено два визита, включающих сбор анамнестических данных и выполнение основных процедур исследования (функция внешнего дыхания, 6-минутный шаговый тест, оценка одышки по опроснику Medical Research Council Scale, исследование мокроты и крови с определением уровня эозинофилов и эозинофильного катионного белка). Второй визит проводился через 12 мес после первого для оценки динамики заболевания. Особое внимание уделялось наличию аллергии в анамнезе, частоте обострений, количеству курсов терапии антибактериальными препаратами и приему ингаляционных и системных глюкокортикостероидов.

Результаты. Исследование продемонстрировало, что высокий уровень эозинофильного катионного белка в плазме крови у больных ХОБЛ ассоциирован с более тяжелым течением и развитием более частых инфекционно-зависимых обострений заболевания, требующих назначения ингаляционных глюкокортикостероидов и антибиотиков. Нами была продемонстрирована обратная связь между уровнем эозинофильного катионного белка ECP и ОФВ1, что позволяет использовать данный показатель как предиктор тяжести течения ХОБЛ.

Заключение. Учитывая полученные нами данные, измерение эозинофильного катионного белка плазмы крови, являющееся неинвазивным и относительно легко выполнимым методом исследования, можно рекомендовать использовать в качестве клинического маркера при прогнозе ХОБЛ и персонифицированном подборе терапии.

Ключевые слова: ХОБЛ, эозинофилы, эозинофильный катионный белок, фенотип, степень тяжести, глюкокортикостероиды.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источники финансирования. Исследование поддержано «Проектом повышения конкурентоспособности ведущих российских университетов среди ведущих мировых научно-образовательных центров».

Соответствие принципам этики. Все лица, участвующие в исследовании подписали информированное согласие. Исследование одобрено этическим комитетом СибГМУ.

Для цитирования: Карнаушкина М.А., Федосенко С.В., Данилов Р.С., Комарова И.С., Петров В.А. Эозинофильный катионный белок как неинвазивный маркер характера воспалительного ответа у больных хронической обструктивной болезнью легких. *Бюллетень сибирской медицины.* 2020; 19 (1): 59–66. https://doi.org: 10.20538/1682-0363-2020-1-59–66.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the respiratory tract. The development of COPD is associated with the influence of various environmental factors. COPD is a multicomponent disease characterized by a number of pathological changes in the respiratory system, such as mucus hypersecretion, airway obstruction, bronchiolitis, and lung tissue remodeling [1]. According to the published studies, different COPD phenotypes are formed depending on the predominance of certain changes in lung tissue and the rate of their progression.

Recently, scientists have identified more and more new phenotypes of this disease. Thus, the data published in recent years have allowed us to identify a phenotype characterized by bronchial hyperresponsiveness and the presence of eosinophilic inflammation in the respiratory tract [1]. Whereas inflammatory infiltration in the respiratory tract in other COPD types is mainly represented by neutrophils and cytotoxic T-cells. The leading functional criterion for diagnosis of these types is a negative post-bronchodilator test with FEV1/FVC ratio less than 0.7 [1–3]. Scientists have suggested that in the pathogenesis of the COPD phenotype, characterized by the presence of bronchial hyperresponsiveness in the respiratory tract, the T2-dependent mechanism of inflammation prevails. This is more typical for patients with bronchial asthma with eosinophilic inflammation type [2, 3]. Eosinophils are considered to be the key effector cells damaging the mucous membrane of the respiratory tract in this mechanism of the inflammatory process. One of the main proteins that reflect the activity of eosinophilic inflammation is eosinophilic cationic protein (ECP). It is easily detected both in bronchial secretions and in peripheral blood; its level correlates with the severity of asthma and the frequency of exacerbations [4].

M. Saetta and his co-authors have found that the number of tissue eosinophils and the level of ECP increases not only in patients with asthma, but also in some patients with COPD. This increase was most often observed in sputum and bronchial lavage in severe exacerbation phases of the disease. From a pathogenic perspective, the obtained data were explained by the fact that ECP is a powerful chemoattractant for eosinophils, neutrophils and basophils, which are involved in viral and bacterial inflammatory processes in the respiratory tract [5]. A number of recently published studies have discussed that, on the one hand, an increase in ECP in the respiratory tract reflects the degree of eosinophilic inflammation. On the other hand, ECP itself acts as a powerful chemoattractant. It attracts eosinophils, neutrophils and basophils (effector cells involved in viral and bacterial inflammatory processes in the bronchopulmonary area) to the inflammation focus [6].

Today, the global guidelines of the Global Initiative for Chronic Obstructive Lung Disease GOLD and recommendations of the Russian Respiratory Society for the treatment of COPD suggest taking into account the level of eosinophils in the blood of patients who have recurrent exacerbations related to adequate single or dual bronchodilator therapy. This allows the consideration of the advisability of prescribing inhalant glucocorticoids (also called inhaled corticosteroids or ICS) [1]. The degree of inflammation correlates stronger to the blood level of ECP in patients with COPD than to the level of sputum and eosinophils in blood. Thus, it is reasonable to determine its level and use it as a marker of inflammatory activity in the airway for patients with severe COPD and as a predictor of the effectiveness of ICS in patients with eosinophilic phenotype of COPD [7–9].

The aim of the study was to estimate the value of measuring plasma eosinophilic cationic protein (ECP) levels in patients with chronic obstructive pulmonary disease (COPD) as a potential biomarker for determining the activity of eosinophilic inflammation. To compare it to determining the number of blood eosinophils and predicting the severity of COPD by determining such clinical characteristics as respiratory function, exacerbation frequency and the BODE index.

MATERIALS AND METHODS

To achieve this goal, a prospective non-interventional study was planned and conducted. The study involved 161 patients with COPD (average age of 63 [55; 70] years old, smoking index of 40 [25; 60] pack-years). All the patients had a confirmed diagnosis of COPD, according to the GOLD criteria [1], established at least 12 months before inclusion in the study, with the smoking index of more than 10 pack-years.

The study included two visits to COPD patients. During the first visit, all the patients underwent a clinical examination and medical history taking. Exercise tolerance was determined by a 6-minute step test. The degree of dyspnea was assessed by a modified MRC (Medical Research Council Dyspnea Scale) in points. All the patients underwent a study of respiratory function with a bronchodilator test. The study was carried out with the use of the MasterScreen Body equipment (Erich Jaeger, Germany). The obtained data were compared to the proper values, calculated according to the formulas recommended by the European respiratory and American thoracic societies [10]. All the patients underwent a clinical study of blood and induced sputum to determine the number of eosinophils. As a criterion of eosinophilic inflammation outside exacerbation of the disease, the level of eosinophilia ≥300 cells/μl in peripheral blood and ≥3% of eosinophils in induced sputum was used [6, 7, 11]. Also, the level of eosinophilic cationic protein (ECP) in the peripheral blood was assessed for all the patients. The level of ECP > 24 ng/ml in peripheral blood was used as a criterion for increasing ECP outside exacerbation period [4]. The second visit was carried out 12 months after the first one to assess the dynamics of the disease.

The patients were stratified by the level of eosinophils and ECP in peripheral blood during the remission period of the disease. Stratification was based on the clinical, functional, and laboratory criteria obtained during the examination. The formed groups were comparable in age and smoking history. The data are presented in Tables 1 and 2.

Table 1

Characteristics of COPD patients with different levels of eosinophils in peripheral blood during remission, $n = 161$, $Me\ [Q_{25}; Q_{75}]$

Level of eosinophils in peripheral blood	Average age, years	Smoking history
≥ 300 cells/mcl	62 [54; 69]	40 [24.5; 53.3]
< 300 cells/mcl	64 [56; 72]	45 [40.0; 52.2]

Table 2

Characteristics of COPD patients with different levels of eosinophilic cationic protein in peripheral blood during remission of the disease, $n = 161$, $Me\ [Q_{25}; Q_{75}]$

Level of ECP in peripheral blood	Average age, years	Smoking history
> 24 ng/ml	63 [53; 72]	42 [26.0; 54.5]
≤ 24 ng/ml	65 [55; 70]	44 [38.5; 52.0]

The average age in the COPD group with elevated levels of eosinophils was 62 [54; 69.25], the smoking index was 40 [24.5; 53.25]. The average age in the COPD group with normal indicators of eosinophils was 64 [56; 72], the smoking index was 45 [40; 52.5].

Data processing. Statistica software package for Windows 10.0 was used for statistical processing of anamnesis data, clinical, functional and laboratory parameters. The χ^2 criterion was used for comparing the frequencies of qualitative features. The Mann – Whitney *U*-test was used to estimate the difference of means in pairwise unrelated samples. Qualitative data are presented in the form of absolute or relative (%) frequencies, and quantitative data are presented in the form of Mediana $[Q_{25}; Q_{75}]$. The difference of values at $p < 0.05$ was considered statistically significant. The Spearman coefficient was used in the correlation analysis. The correlation strength was estimated as follows: strong: ± 0.7 to ± 1; medium: ± 0.3 to ± 0.699; weak: 0 to ± 0.299.

Regression analysis was performed to identify the relationship between the level of eosinophil-

ic cationic protein and clinical and functional features of COPD. The level of eosinophilic cationic protein was used as a dependent variable, and clinical and functional parameters were integrated as independent variables. The p values are given after the Benjamini-Hochberg adjustment. The threshold level of significance is less than 0.05.

RESULTS

In the course of the examination of COPD patients with different eosinophils and ECP levels in peripheral blood during remission of the disease, a comparative analysis of the main clinical and functional indicators of severity and phenotypic features of the disease was performed.

No significant differences have been found when comparing the clinical and functional parameters of COPD patients with elevated and normal levels of eosinophils in peripheral blood and induced sputum.

We analyzed the obtained data based on published studies that showed a significant increase in the level of eosinophils in COPD patients during exacerbation of the disease [12, 13]. It should be noted that there were patients with a transient increase in the level of eosinophils in periods of exacerbation of COPD in the group of patients with normal eosinophils level in peripheral blood during remission of the disease. During further analysis of the data from the medical history archive, we noticed that an increase in eosinophils in the peripheral blood with a level of ≥300 cells/μl was detected not at each exacerbation in the same patient. This did not allow us to identify the group with a transient increase in eosinophils in peripheral blood correctly and to conduct a comparative analysis.

We used the determination of the level of eosinophilic cationic protein in peripheral blood as a marker of the activity of eosinophilic inflammation. The average level of eosinophilic cationic protein in patients in the study was 15 [9; 23] mg/l. The comparative analysis revealed significant levels of difference in the content of ECP between groups of patients with the eosinophils level in peripheral blood ≥300 cells/μl and < 300 cells/μl (p = 0.029). However, the correlation analysis showed significant positive correlations of the average strength of the ECP level only with the frequency of exacerbation of COPD (p = 0.035, r = +0.06).

No significant differences were found when comparing the clinical and functional parameters of COPD patients with elevated and normal levels of eosinophils in induced sputum. Therefore, at the next stage of the study, COPD patients were divided into 2 groups depending on the presence of increased ECP in peripheral blood.

To assess the differences between the groups, a comparative assessment of clinical and functional parameters was performed in the groups of patients with COPD with elevated ECP levels and the group with its normal values. Table 3 presents the clinical and functional characteristics of these groups of patients.

Table 3

Comparative characteristics of clinical and functional parameters of COPD patients with different levels of eosinophilic cationic protein in peripheral blood, *Me* [Q_{25}; Q_{75}]

Parameters	COPD patients, n = 161		p
	with elevated levels of eosinophilic cationic protein (>24 ng/ml) n = 38	with normal levels of eosinophilic cationic protein (≤24 ng/ml) n = 123	
Exacerbations within 12 months, n	3.00 [2.00; 3.75]	1 [1; 2]	0.024
ICS +LABA+LAAC therapy (12 months), n (% of patients)	14 [36; 84]	14 [11; 38]	–
ICS (12 months), n (% of patients)	20 [52; 63]	24 [19; 51]	–
Course ABT frequency (12 months), n	1.5 [1.0; 3.0]	1 [0; 1]	0.042
Smoking index, pack/years	46.50 [26.75; 75.00]	40.0 [25.5; 60.0]	0.34
BODE index, points	3 [2; 4]	1 [0; 2]	0.031
mMRC, points	3 [2; 4]	1 [0.5; 2.0]	0.046
6-minute step test, meters	450.0 [302.5; 637.5]	540 [372; 670]	0.23
Sputum production, points	1.5 [1.0; 2.0]	1 [1; 2]	0.83
Pneumonias within 12 months, %	50	22	–

Table 3 (continued)

Parameters	COPD patients, n = 161		p
	with elevated levels of eosinophilic cationic protein (>24 ng/ml) n = 38	with normal levels of eosinophilic cationic protein (≤24 ng/ml) n = 123	
FEV1, % of the norm (after a bronchodilator test)	69.0 [53.75; 75.00]	67.0 [57.0; 76.5]	0.34
Level of eosinophils in blood (outside exacerbation), 10^9/l	0.35 [0.34; 0.41]	0.17 [0.11; 0.25]	0.026

Note. ICS – inhaled corticosteroids; ABT – antibacterial therapy; LAAC – long-acting anticholinergics; LABA – long-acting beta-agonists; FEV1 – forced expiratory volume in 1 second (here and in Table 4).

A comparative analysis of clinical and functional parameters of patients with different levels of eosinophilic cationic protein in blood plasma has revealed that patients with high content of ECP received courses of antibacterial therapy significantly more often. They were characterized by significantly more severe course of the disease, a higher frequency of exacerbations, more significant dyspnea and a higher value of the BODE index. Patients with high plasma ECP tended to have a higher risk of developing pneumonia (50% of patients in this group had a history of pneumonia). They also tended to need a higher volume of basic treatment (36% received dual bronchodilator therapy in combination with ICS). At the same time, these indicators did not differ statistically significantly between groups of patients stratified by the ECP level.

Regression analysis was performed to identify the relationship between the level of ECP and clinical and functional features of COPD. The significance of the ECP level for the severity of COPD and its connection with the inflammatory genesis of the disease exacerbation was proved by the method of multiple linear regression. The content of eosinophilic cationic protein was used as a dependent variable, and other clinical and functional factors were integrated as independent variables. The data obtained are presented in Table 4.

Table 4

Eosinophilic cationic protein level and associated clinical and functional parameters in COPD patients

Parameter	SLC	SLC std. dev.	p	adj. p
Sputum production, points	5.385	2.022	0.009	0.02
Exacerbations within 12 months	2.765	0.42	0.006	0.01
Level of eosinophils in blood (outside exacerbation), $\times 10^9/л$	8.64	3.232	0.008	0.022
Number of ABT courses within 12 months	2.808	0.441	0.002	0.03
ICS (12 months), n (% of patients)	5.538	1.428	0.0002	0.0007
LABA±LAAC (12 months), n (% of patients)	3.573	1.375	0.01	0.03
ICS +LABA+LAAC therapy (12 months), n (% of patients)	6.169	1.687	0.0003	0.001
FEV1, % of the norm (after a bronchodilator test)	4.782	1.421	0.003	0.02

* SLC – slope of line coefficient adj.p.
* p – value after the Benjamini – Hochberg adjustment.

The presented table shows that clinical and functional parameters in COPD patients with higher ECP levels in peripheral blood were characterized by a greater frequency of exacerbation of the disease, higher sputum production, more frequent courses of antibacterial therapy. The regression analysis has revealed a connection between the increase in ECP and the increase in the volume of treatment. COPD patients with elevated levels of eosinophilic cationic protein in peripheral blood were significantly more likely to receive continuous triple inhaled therapy, which

includes inhaled long-acting beta-2-agonist and muscarinic antagonist in combination with ICS. This indicates a more severe course of the disease. It is noteworthy that maintenance therapy of the patients in this group included inhaled corticosteroids, the need for the prescription of which was associated with the level of ECP and was reliable ($p = 0.0002$; adj. $p = 0.0007$).

DISCUSSION

The performed work confirms that the high level of eosinophilic cationic protein in blood plasma in patients with COPD is associated with a more severe course of COPD and the development of more frequent infection-dependent exacerbations of the disease requiring the prescription of inhaled corticosteroids and antibiotics. We have demonstrated an inverse relationship between the level of ECP and FEV1, which allows us to use this indicator as a predictor of the severity of COPD. A small number in the sample of patients with extremely severe course of the disease (GOLD3-4) can explain the absence in our study of the relationship between the level of eosinophils in induced sputum and peripheral blood and the clinical and functional features of COPD in remission (identified in other studies) [14–16]. Our study will be continued in order to confirm the findings that, compared to the level of blood and sputum eosinophils, EPC is a more accurate marker of the nature of inflammation in COPD, a prognostic criterion for the severity of the disease and one of the leading criteria for the necessity to prescribe glucocorticoids to COPD patients.

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Authors contribution

Karnaushkina M.S. – conception and design. Fedosenko S.V. – analysis and interpretation of the data. Danilov R.S. – critical revision for important intellectual content. Komarova I.S. – justification of the manuscript. Petrov V.A. – final approval of the manuscript for publication.

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Received 16.05.2019
Accepted 25.12.2019