UDC: 616.24-002.2-007.272:616.155.194]-08

TREATMENT OF ANEMIA OF CHRONIC INFLAMMATION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Abstract. Most extrapulmonary manifestations of chronic obstructive pulmonary disease (COPD) are now interpreted as its systemic manifestations, including anemia of chronic inflammation. If there is a sufficient number of scientific studies devoted to determining the frequency of anemia in COPD and its pathogenetic aspects, there are practically no studies about its treatment. *The aim of our work* was to compare the effectiveness of various methods of management of COPD with anemia of chronic inflammation. *Materials and methods*. The study included 52 patients with COPD in the acute phase and anemia of chronic inflammation and 62 healthy patients. During the baseline treatment all patients received treatment for exacerbation of COPD and were randomized to 3 groups: I (20 patients), II (20 patients) and III (12 patients). Group I additionally received 80 mg of Fe^{2+} 2 times per day during 21 days; Group II — 100 mg of the iron (III) hydroxide sucrose complex intravenously 3 times per week during 4 weeks, Group III — 100 mg of the iron (III) hydroxide sucrose complex intravenously and human recombinant erythropoietin 3000 IU 3 times per week during 4 weeks. The blood levels of hemoglobin, serum iron, ferritin, hepcidin and C-reactive protein were determined before treatment, after completion of treatment of COPD exacerbation, and after treatment with iron and erythropoietin. Erythropoietin was determined in all patients before treatment. Statistical analysis of the results was performed by using the SPSS-21 program. *Results.* It was established that only in patients of group III the content of ferritin in the blood was significantly reduced, and the content of serum iron was significantly increased in comparison with patients of other groups. An increase in hemoglobin and decrease in hepcidin concentration in patients of group III and a decrease in hemoglobin and increase in hepcidin in patients of groups I and II was a confirmation of the existing idea about the role of hepcidin, which is the main hormone that regulate metabolism of iron by controlling its absorption in the small intestine and its use from the depot, and thus plays a key role in the pathogenesis of anemia of chronic inflammation. After completion of treatment, it was found that in patients of group III the hemoglobin content was significantly higher ($p > 0.05$), and hepcidin and C-reactive protein — lower compared to patients in groups I and II ($p < 0.001$). *Conclusions*. In patients with COPD and anemia of chronic inflammation basic treatment in combination with iron (III) hydroxide sucrose complex intravenously and erythropoietin subcutaneously leads to suppression of the inflammatory process, specifically by a significant decrease in the content of hepcidin, C-reactive protein and ferritin simultaneously with an increase in the content of hemoglobin and serum iron, which was not observed in patients with oral or intravenous iron monotherapy.

Key words: anemia of chronic inflammation, chronic obstructive pulmonary disease, serum iron, hepcidin, ferritin, C-reactive protein, erythropoietin.

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Asthma and Allergy, 2020, 1, P. 28–36.

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www.search.crossref.org
DOI: 10.31655/2307-3373-2020-1-28-36

ЛІКУВАННЯ АНЕМІЇ ХРОНІЧНОГО ЗАПАЛЕННЯ У ХВОРИХ НА ХРОНІЧНЕ ОБСТРУКТИВНЕ ЗАХВОРЮВАННЯ ЛЕГЕНЬ

А. В. Ковчун, Л. Н. Приступа

Резюме. Більшість позалегеневих проявів хронічного обструктивного захворювання легень (ХОЗЛ) тепер інтерпретуються як його системні маніфестації, серед яких і анемія хронічного запалення. За наявності достатньої кількості наукових досліджень присвячених з'ясуванню частоти анемії при ХОЗЛ та її патогенетичних аспектів, практично відсутні дослідження стосовно шляхів її лікування. *Метою роботи* було порівняти ефективність різних методів лікування хворих на ХОЗЛ із анемією хронічного запалення. *Матеріали і методи.* У дослідження було включено 52 хворих на ХОЗЛ у фазі загострення із анемією хронічного запалення та 62 практично здорові особи. Усі пацієнти отримували комплексне лікування загострення ХОЗЛ на фоні базисного лікування та були рандомізовані на 3 групи: I (20 пацієнтів), II (20 пацієнтів) та III (12 хворих). Пацієнти I групи додатково отримували 80 мг двовалентного 2 рази на добу протягом 21 доби; II групи — 100 мг сахарозного комплексу гідроксиду заліза (III) внутрішньовенно 3 рази на тиждень протягом 4 тижнів, III групи — 100 мг сахарозного комплексу гідроксиду заліза (III) внутрішньовенно та еритропоетин людини рекомбінантний 3000 МО підшкірно 3 рази на тиждень протягом 4 тижнів. Хворим визначали вміст в крові гемоглобіну, сироваткового заліза, феритину, гепсидину та С-реактивного протеїну до початку лікування, після завершення лікування загострення ХОЗЛ та після завершення лікування препаратами заліза та еритропоетином. Визначення еритропоетину проводили всім хворим до початку лікування. Статистичну обробку проводили з використанням програми SPSS-21. *Результати.* Встановлено, що лише у хворих III групи вміст феритину в крові вірогідно знижувався, а вміст сироваткового заліза достовірно підвищувався порівняно із хворими інших груп. Зростання вмісту гемоглобіну на фоні зменшення концентрації гепсидину у хворих III групи та зниження вмісту гемоглобіну поряд із збільшенням вмісту гепсидину у пацієнтів I та II груп було підтвердженням існуючої думки про роль гепсидину, який є основним гормоном, що регулює метаболізм заліза шляхом контролю його всмоктування в тонкому кишечнику та його використання з депо, і таким чином, відіграє ключову роль в патогенезі анемії хронічного запалення. По завершенню лікування було виявлено, що у хворих III групи вміст гемоглобіну був достовірно вищим ($p < 0,05$), а гепсидину та С-реактивного протеїну — нижчим порівняно із пацієнтами I та II груп ($p < 0,001$). *Висновки.* У хворих на ХОЗЛ з анемією хронічного запалення застосування базисного лікування у поєднанні з сахарозним комплексом гідроксиду заліза (III) внутрішньовенно та еритропоетину підшкірно відбулося пригнічення запального процесу, що супроводжувалося достовірним зниженням вмісту гепсидину, С-реактивного протеїну та феритину одночасно із збільшенням вмісту гемоглобіну та сироваткового заліза, — чого не спостерігалось у пацієнтів під впливом монотерапії пероральними або внутрішньовенними препаратами заліза.

Ключові слова: анемія хронічного запалення, хронічне обструктивне захворювання легень, сироваткове залізо, гепсидин, феритин, С-реактивний протеїн, еритропоетин.

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«Астма та алергія», 2020, № 1, С. 28–36.

ЛЕЧЕНИЕ АНЕМИИ ХРОНИЧЕСКОГО ВОСПАЛЕНИЯ У БОЛЬНЫХ ХРОНИЧЕСКИМ ОБСТРУКТИВНЫМ ЗАБОЛЕВАНИЕМ ЛЕГКИХ

А. В. Ковчун, Л. Н. Приступа

Резюме. Большинство внелегочных проявлений хронического обструктивного заболевания легких (ХОЗЛ) теперь интерпретируются как его системные манифестации, среди которых и анемия хронического воспаления. При наличии достаточного количества научных исследований посвященных определению частоты анемии при ХОЗЛ и её патогенетических аспектов, практически отсутствуют исследования изучающие её лечение. *Целью работы* было сравнить эффективность различных методов лечения больных ХОЗЛ с анемией хронического воспаления. *Материалы и методы.* В исследование было включено 52 пациента с ХОЗЛ в фазе обострения и анемией хронического воспаления и 62 практически здоровых пациента. Все пациенты получали комплексное лечение обострения ХОЗЛ на фоне базисного лечения и были рандомизированы на 3 группы: I (20 пациентов), II (20 пациентов) и III (12 больных). Пациенты I группы дополнительно получали 80 мг двухвалентного железа 2 раза в сутки в течение 21 дня; II группы — 100 мг сахарозного комплекса гидроксида железа (III) внутривенно 3 раза в неделю в течение 4 недель, III группы — 100 мг сахарозного комплекса гидроксида железа (III) внутривенно и эритропо-

DOI: 10.31655/2307-3373-2020-1-28-36 ISSN 2307-3373

этин человека рекомбинантный 3000 МЕ 3 раза в неделю в течение 4 недель. Больным определяли содержание в крови гемоглобина, сывороточного железа, ферритина, гепсидина и С-реактивного протеина до начала лечения, после завершения лечения обострения ХОЗЛ и после завершения лечения препаратами железа и эритропоэтином. Определение эритропоэтина проводили всем больным до начала лечения. Статистическую обработку проводили с использованием программы SPSS-21. *Результаты*. Установлено, что только у больных III группы содержание ферритина в крови достоверно снижалось, а содержание сывороточного железа достоверно повышалось по сравнению с больными других групп. Увеличение содержания гемоглобина на фоне уменьшения концентрации гепсидина у больных III группы и снижение содержания гемоглобина наряду с увеличением содержания гепсидина у пациентов I и II групп было подтверждением существующей мысли о роли гепсидина, который является основным гормоном, регулирующим метаболизм железа путем контроля его всасывания в тонком кишечнике и его использования из депо, и таким образом, играет ключевую роль в патогенезе анемии хронического воспаления. По завершению лечения было выявлено, что у больных III группы содержание гемоглобина был достоверно выше ($p < 0,05$), а гепсидина и С-реактивного протеина — ниже по сравнению с пациентами I и II групп ($p < 0,001$). *Выводы*. У больных ХОЗЛ с анемией хронического воспаления применение базисного лечения в сочетании с сахарозным комплексом гидроксида железа (III) внутривенно и эритропоэтина подкожно привело к подавлению воспалительного процесса, что сопровождалось достоверным снижением содержания гепсидина, С-реактивного протеина и ферритина одновременно с увеличением содержания гемоглобина и сывороточного железа, — чего не наблюдалось у пациентов под влиянием монотерапии пероральными или внутривенными препаратами железа.

Ключевые слова: анемия хронического воспаления, хроническое обструктивное заболевание легких, сывороточное железо, гепсидин, ферритин, С-реактивный протеин, эритропоэтин.

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Introduction. According to the data of The Global Burden of Disease Study, in 2016 chronic obstructive pulmonary disease (COPD) prevalence was 251 million cases globally [1]. The National Institute of Phthisiology and Pulmonology reports that at least 7 % population of Ukraine suffers from COPD, which is approximately 3 million people [2]. However, there is no accurate data on the prevalence of the disease, since there is no official statistics in the country [3]. Untimely treatment of such patients and consequent loss of working capacity leads to a high mortality rate. Taking into account the immensity of socioeconomic losses, this problem needs further study in order to improve health care services for COPD patients [1].

Over the last century, new data emerged regarding the pathogenetic mechanisms of COPD development and course, including some clinical and laboratory signs that previously seemed to be independent of the lung disease. Due to this, the majority of extrapulmonary symptoms are interpreted as systemic manifestations of COPD [4]. The data obtained eventually were reflected in The Global Initiative for Chronic Obstructive Lung Disease (GOLD): «Inflammatory mediators in the circulation may contribute to skeletal muscle wasting and cachexia, and may initiate or worsen comorbidities such as ischemic heart disease, heart failure, osteoporosis, normocytic anemia, diabetes, depression and metabolic syndrome» [10].

COPD has long been associated with polycythemia, which used to be attributed to chronic hypoxia. But recent epidemiological studies demonstrated that only 6–10 % of patients have polycythemia, while anemia is observed in 17–27 % of patients with COPD [5, 7, 8, 11, 12, 21]. One of the few studies of anemia in patients with COPD [8], which included a study of its etiology, showed that approximately 70 % of anemia cases are pathogenetically associated with COPD and regarded as anemia of chronic inflammation (or anemia of chronic disease, ACD), while the rest of cases are iron-deficiency anemia or acute posthemorrhagic anemia, which could be regarded as comorbid conditions.

The pathogenesis of ACD is complex enough, but it was found that hepcidin is a universal humoral regulator of iron metabolism [17]. Proinflammatory cytokines (IL-6, IL-8, TNF-α) and acute phase proteins (C-reactive protein (CRP), fibrinogen) were proved to cause hepcidin overproduction by the liver which prevents iron from exiting cells and inhibits its redistribution from bone marrow into macrophages; as a result, it leads to impaired utilization of iron by erythroid cells for hemoglobin formation [6]. At the same time, cytokines (IL-6, IL-8, TNF-α) inhibit secretion of erythropoietin (EPO) and suppress its response, which leads to impaired

ISSN 2307-3373 DOI: 10.31655/2307-3373-2020-1-28-36

proliferation of erythroid progenitor cells and shortening of erythrocyte life [17].

Though there are a lot of scientific studies related to the incidence of anemia in COPD patients and its pathogenetic aspects, there are practically no studies regarding its treatment. Based on the data of Cote C. et al. (2007) [7], who indicated a more severe course of COPD in patients with anemia, it is suggested that correction of anemia will improve the functional state of patients (i. e. reduce shortness of breath and increase exercise tolerance). It was shown in a study involving patients with chronic heart failure and anemia [16]: as a result of treatment with EPO for 3 months the hemoglobin content in the blood increased as well as exercise tolerance.

A study of the effectiveness of ACD treatment using erythrocyte transfusion in COPD patients during exacerbation period showed that administration of erythrocyte mass led to an increase in hemoglobin and improved respiratory function [18]. Another study reported that patients with COPD and anemia had decreased dyspnea and increased values of hemoglobin, hematocrit, erythrocyte count and ferritin in response to treatment with EPO-stimulating agents and intravenous iron [19].

The objective of the study was to determine efficacy of different treatment strategies in patients with COPD and ACD.

Materials and methods. The study included 52 patients with exacerbation of COPD and ACD, including 9 patients from group B, 40 patients from group C and 3 patients from group D; patients had stage II–IV obstruction by GOLD [10]. The control group consisted of 62 apparently healthy individuals. The study was carried out at the Pulmonary Unit of Municipal Institution of Sumy Regional Council «Sumy Regional Clinical Hospital» and Therapeutic Unit of Municipal Institution «Sumy Municipal Clinical Hospital No. 4».

COPD was diagnosed according to the Order of the Ministry of Health of Ukraine No. 555 dated 27 June 2013 and GOLD 2014 recommendations [10]. Anemia was diagnosed according to WHO recommendations (hemoglobin < 130.0 g/L in men and < 120.0 g/L in women) and the Unified Clinical Protocol of Primary and Secondary (Specialized) Medical Care No. 709 dated 02 Nov 2015. ACD was diagnosed if hemoglobin < 130.0 g/L in men and < 120.0 g/L in women and soluble transferrin receptors content within reference range (8.7–28.1 nmol/L). The exclusion criteria were: severe concomitant diseases (pulmonary tuberculosis, oncopathology, alcohol and/or drug addiction, AIDS, heart failure (stages IIB–III), and decompensated liver failure, kidney failure, or other failures); a defined source of bleeding (complications of peptic ulcer, nonspecific ulcerative colitis, chronic hemorrhoids, etc.); prediagnosed true anemias (megaloblastic, aplastic, hemolytic); use of angiotensin-converting enzyme inhibitors; pregnancy or lactation; chronic administration of systemic corticosteroids.

In order to study treatment effectiveness for ACD in COPD patients, all patients were randomized into 3 groups: group I (20 patients), group II (20 patients), and group III (12 patients), who were representative of sex, age, and severity of COPD. All patients in groups I–III received background therapy, namely: long-acting β_2-agonists (salmeterol or formoterol), long-acting anticholinergic drugs (tiotropium bromide) and inhaled corticosteroids (inhaled GCs). For the period of exacerbation (7 days) systemic corticosteroids were prescribed (30 mg in terms of equivalent amount of prednisolone), short-acting bronchodilators were used as needed, antibacterial therapy (aminopenicillins, macrolides or fluoroquinolones) were given to patients with COPD bacterial exacerbation. After exacerbations had been treated, the patients in all groups continued to receive background therapy: patients in group I additionally received tablets of divalent iron 80 mg ("Tardiferon") twice a day for 21 days; patients in group II received iron(III)-hydroxide sucrose complex 100 mg intravenously ("Sufer") 3 times a week for 4 weeks, patients in group III received iron(III)-hydroxide sucrose complex 100 mg intravenously ("Sufer") and recombinant human erythropoietin 3000 IU ("Emaveil") subcutaneously 3 times a week for 4 weeks. Patients were assessed for hemoglobin, serum iron (SI), ferritin, hepcidin, and CRP in the blood prior to initiation of treatment (visit 1), after completion of exacerbation treatment (visit 2, Day 8), and after completion of iron and EPO treatment (visit 3, Day 36); EPO content analysis was performed during visit 1. Assessment of patient's risk of deep vein thrombosis and pulmonary embolism was determined by Wells criteria during visit 1 and at the end of each week of EPO treatment (after the third infusion onwards).

Statistical analysis of the results was performed using SPSS-21 program. Mean values were presented as (M ± m), where 'M' is the mean value and 'm' is the standard error. The differences in median values of 3 or more linked samples were estimated by nonparametric techniques, namely Friedman's two-way analysis of variance by ranks, and for 2 samples the Wilcoxon test was used. Kruskal–Wallis test was used for comparing three or more independent samples. All tests were two-sided, value of $p < 0.05$ was considered statistically significant.

Results and discussion

Assessment of EPO content in patients with COPD and ACD showed the following results: in the patients of group I the average EPO content was 6.775±0.74 IU/mL, in group II — (7.255 ± 0.919) IU/mL, in group III — (6.850 ± 0.96) IU/mL; no significant differences were observed for these results ($p = 0.979$). The control group had significantly ($p < 0.001$) higher EPO content (13.65 ± 1.47) IU/mL compared to patients of groups I–III. Detailed analysis of EPO content in patients with COPD and ACD showed that content of EPO was below the lower reference limit in 7 patients (35 %) in group I, in 5 (25 %) patients in group II, and in 4 (33 %) patients in group III. Given that the mean EPO content in patients of all groups was within the reference values, and patients of group III were assigned recombinant human

DOI: 10.31655/2307-3373-2020-1-28-36 ISSN 2307-3373

T a b l e 1. Changes in ferritin and serum iron content in COPD patients in groups I–III during treatment

Group	Parameter		Visit 1	Visit 2	Visit 3	Control group
I	Ferritin, μg/L	m	471,76 ± 19,38	395,85 ± 4,77	409,38 ± 4,8	262,02 ± 3,38
			$\chi^2 = 26,0$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
		f	215,84 ± 11,10	170,43 ± 14,27	185,57 ± 12,76	104,99 ± 1,51
	SI, μmol/L		10,95 ± 0,59	12,87 ± 0,78	10,83 ± 2,04	21,64 ± 0,39
			$\chi^2 = 27,7$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
II	Ferritin, μg/L	m	442,52 ± 18,27	373,67 ± 30,30	399,42 ± 29,0	262,02 ± 3,38
			$\chi^2 = 20,66$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
		f	213,6 ± 18,34	166,5 ± 5,12	184,38 ± 5,70	104,99 ± 1,51
	SI, μmol/L		11,58 ± 0,97	12,78 ± 0,85	11,44 ± 2,73	21,64 ± 0,39
			$\chi^2 = 15,7$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
III	Ferritin, μg/L	m	463,76 ± 9,24	404,33 ± 7,6	351,17 ±9,25	262,02 ± 3,38
			$\chi^2 = 14,00$; $P_1 = 0,001$; $P_2 < 0,001$; $P_3 < 0,001$; $P_4 < 0,001$; $P_5 = 0,011$			
		f	195,90 ± 15,38	187,76 ± 18,44	131,33 ± 7,76	104,99 ± 1,51
	SI, μmol/L		10,92 ± 0,61	12,98 ± 0,86	18,27 ± 0,56	21,64 ± 0,39
			$\chi^2 = 20,00$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$; $P_4 < 0,001$; $P_5 = 0,001$			

R e m a r k s :
P_1 — statistical significance in a group throughout the treatment period; P_2 — statistical significance between visit 1 parameters of a study group and the control group; P_3 — statistical significance between visit 3 parameters of a study group and the control group; P_4 — statistical significance between visit 3 parameters of groups I and III; P_5 — statistical significance between visit 3 parameters of groups I and II; χ^2 — Friedman's test.

EPO, which is known to increase the risk of thrombosis [21], we assessed the risk of deep vein thrombosis and thrombosis pulmonary artery by Wells criteria. The results of each evaluation of patients equaled 0.

We evaluated the main parameters of iron metabolism in the three study groups: ferritin content was assessed to evaluate the concentration of iron in the depot and SI for the analysis of free circulating iron (Table 1).

Analysis of ferritin content, which characterizes depot iron concentration and activity of inflammatory process, demonstrated significantly higher values of ferritin in all patients regardless of sex (for all $p < 0.05$). It should be noted that due to the assigned therapy, there was a decrease in ferritin content in patients of groups I and II at visit 2, but at visit 3 its content increased again. In contrast to the results of patients in groups I and II, analysis of ferritin content in men and women of group III showed a significant decrease in its content throughout the treatment period, which may indicate a decrease in the activity of the inflammatory process. The analysis of SI content at visit 1 showed that patients in all groups ($p < 0.05$) had a significantly lower content of SI as compared to the control group, but in patients of groups I and II its content increased by visit 2 and returned to baseline levels by visit 3. However, in patients of group III, the content of SI probably was increasing throughout the treatment period, indicating that it was sufficient for hemoglobin formation. It should be mentioned that the content of ferritin and SI in patients of all groups, regardless of sex, did not reach the values of the control group. However, by comparing the laboratory parameters of the patients in the studied groups at visit 3, it was found that in group III patients ferritin content was significantly lower compared to patients of groups I and II (for all $p < 0.05$), while SI content was significantly higher compared to patients in groups I and II ($p < 0.001$ and $p = 0.001$).

In order to evaluate the effectiveness of anemia treatment, hemoglobin content was assessed; hepcidin and CRP content was assessed to determine the course of the inflammatory process, which is shown in Table 2.

The analysis of hemoglobin content in the blood, which is the main indicator of anemia treatment effectiveness, showed that all patients in groups I and II had their hemoglobin content increased at visit 2, but at visit 3 there was a decrease in hemoglobin content regardless of patient's sex. A study of hepcidin and CRP content in groups I and II showed significant changes in the values throughout the treatment period, but a detailed analysis of the results demonstrated a temporary decrease in hepcidin and CRP content at visit 2 and an increase at visit 3. It should be mentioned that after the treatment hepcidin and CRP content remained significantly higher in the patients of groups I–II as compared to the control group. Therefore, the above increased values of hepcidin and CRP content may indicate persistence of inflammatory process. Given that hepcidin and CRP values were higher and, accordingly, hemoglobin values were lower than those in the control group, the above results may indicate that assigned treatment regimens for patients in groups I and II were not effective.

Analyzing the parameters of patients in group III, it should be noted that 2 patients discontinued from the study after 2 weeks of treatment due to their unwillingness to continue participation, as well as occurrence of ossalgia which was attributed by the patients to EPO treatment. Hemoglobin content was found to increase significantly ($p = 0.001$) in men of group III throughout the treatment period, and in women of group III there

ISSN 2307-3373 DOI: 10.31655/2307-3373-2020-1-28-36

T a b l e 2. The content of hemoglobin, hepcidin and CRP in COPD patients n groups I–III with regard to treatment duration

Group	Parameter		Visit 1	Visit 2	Visit 3	Control group
I	Hemoglobin, g/L	m	105,00 ± 3,0	111,00 ± 1,29	108,84 ± 2,11	143,89 ± 1,44
			$\chi^2 = 21,16$, $P_1 < 0,001$; $P_2 < 0,001$			
		f	103,43 ± 2,57	110,29 ± 1,89	109,42 ± 2,43	130,8 ± 0,77
	Hepcidin, ng/dL		32,47 ± 2,07	24,18 ± 0,52	27,56 ± 1,10	13,62 ± 2,29
			$\chi^2 = 40,0$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
	CRP, mg/dL		2,90 ± 0,18	2,05 ± 0,10	2,94 ± 0,06	0,467 ± 0,14
			$\chi^2 = 28,7$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
II	Hemoglobin, g/L	m	104,92 ± 2,84	111,33 ±0,98	109,33 ± 4,86	143,89 ± 1,44
			$\chi^2 = 16,56$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
		f	103,13 ± 2,9	111,75 ± 0,88	107,62 ± 2,19	130,8 ± 0,77
	Hepcidin, ng/dL		31,94 ± 1,8	24,51 ± 0,68	27,45 ± 2,81	13,62 ± 2,29
			$\chi^2 = 34,3$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$			
	CRP, mg/dL		2,94 ± 0,31	2,04 ± 0,11	2,86 ± 0,13	0,467 ± 0,14
III	Hemoglobin, g/L	m	105,43 ± 2,69	114,86 ± 1,06	123,85 ± 6,7	143,89 ± 1,44
			$\chi^2 = 14,0$; $P_1 = 0,001$; $P_2 < 0,001$; $P_3 < 0,001$; $P_4 < 0,001$; $P_5 = 0,002$			
		f	106,0 ± 3,6	112,67 ± 2,5	125,6 ± 1,15	130,8 ± 0,77
	Hepcidin, ng/dL		32,14 ± 1,16	25,17 ± 0,79	22,55 ± 2,64	13,62 ± 2,29
			$\chi^2 = 15,8$; $P_1 < 0,001$; $P_2 < 0,001$; $P_3 < 0,001$; $P_4 < 0,001$; $P_5 < 0,001$			
	CRP, mg/dL		2,95 ± 0,25	2,08 ± 0,18	1,89 ± 0,12	0,467 ± 0,14

R e m a r k s : P_1 — statistical significance in a group throughout the treatment period; P_2 — statistical significance between visit 1 parameters of a study group and the control group; P_3 — statistical significance between visit 3 parameters of a study group and the control group; P_4 — statistical significance between visit 3 parameters of groups I and III; P_5 — statistical significance between visit 3 parameters of groups I and II; χ^2 — Friedman's test.

was a reliable tendency (p = 0.05) to hemoglobin content increase. The content of inflammatory markers, such as hepcidin and CPR which are key elements in ACD pathogenesis, decreased throughout the treatment period. It should be noted that hepcidin is the major hormone that regulates iron metabolism by controlling absorption of iron in the small intestine and its use from depot; thus, it plays a key role in the pathogenesis of ACD [14]. The changes of laboratory parameters found in patients of group III, i. e. increased hemoglobin content against the background of decreased hepcidin concentration and decreased hemoglobin content vs. increased hepcidin content in patients of groups I and II confirm the existing opinion about the role of hepcidin in pathogenesis of ACD.

In order to summarize the results obtained for ACD treatment in COPD patients we provide a figure demonstrating the changes in hemoglobin content over time with regard to gender (Figure 1). In order to assess the effectiveness of assigned treatment regimens, we analyzed and compared CRP and hepcidin content in the study groups throughout the treatment period (Figures 2 and 3).

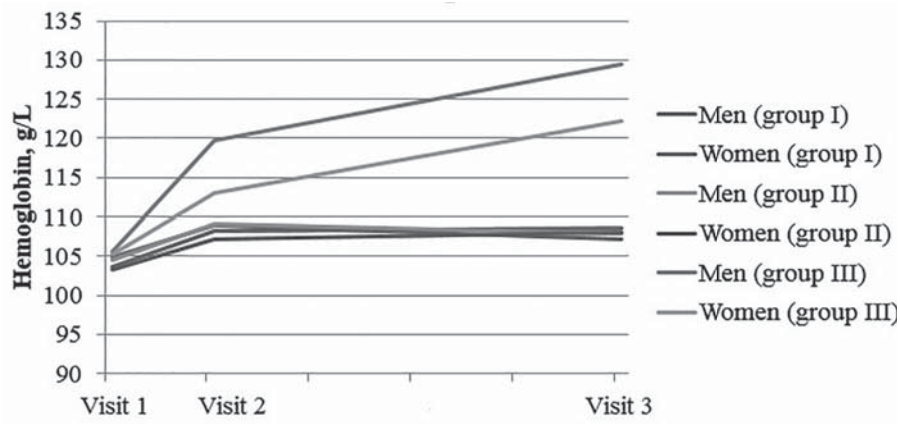

Fig. 1. Hemoglobin content in patients with COPD in groups I–III during treatment depending on sex characteristics.

DOI: 10.31655/2307-3373-2020-1-28-36 ISSN 2307-3373

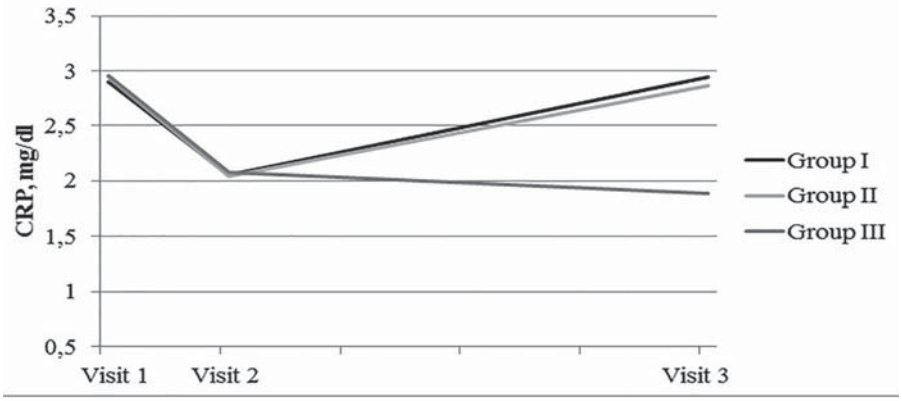

Figure 2. CRP content in patients with COPD in groups I–III during treatment.

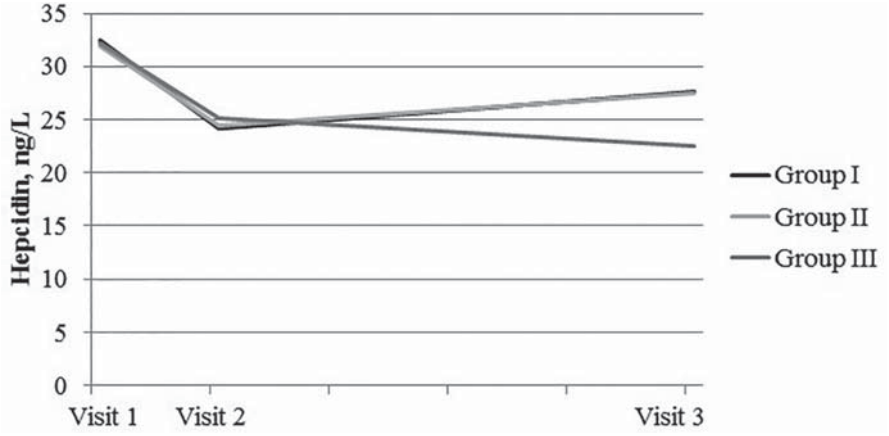

Figure 3. Hepcidin content in patients with COPD in groups I–III during treatment.

As shown in Figure 1, the increase in hemoglobin content throughout the treatment period occurred only in the patients that received intravenous iron (III)-hydroxide sucrose complex and subcutaneous EPO in addition to the background therapy. Patients in other groups had an increase in hemoglobin content only at visit 2 and a decrease in hemoglobin content at visit 3. It should be noted that the increase in hemoglobin content in patients of groups I and II occurred against the background of temporary suppression of inflammatory process due to active treatment of COPD exacerbation, which may serve as an explanation for the positive changes in hemoglobin content at visit 2.

Hepcidin and CRP are informative markers for assessment of inflammatory process and, consequently, of ACD development in COPD patients [14]. The results of our study showed that the content of hepcidin and CRP in the blood decreased in group III throughout the treatment period. In contrast to the data obtained in group III patients, the content of CRP and hepcidin in groups I and II patients decreased only at visit 2, while at visit 3 there was an increase in CRP and hepcidin content and, subsequently, inflammatory process persistence was observed.

Obviously, high content of acute phase protein ferritin and the persistent increased level of CRP and, as a consequence, high content of hepcidin in patients of groups I and II may account for ineffectiveness of the assigned regimens for ACD, which is related to its major, iron-regulatory function. Due to the influence of inflammatory mediators or high concentrations of free iron, hepcidin inhibits ferroportin, limiting iron transport into cells by intestinal villi and blocking iron exit from macrophages that leads to impaired iron homeostasis and the development of anemia. Apart from influencing iron processes, proinflammatory cytokines lead to direct inhibition of erythropoiesis and relative EPO deficiency [9, 20]. Thus, ACD treatment requires erythropoiesis stimulation, as well as maintenance of adequate level of iron in order to form hemoglobin; this can be achieved by simultaneous use of EPO and iron. On the other hand, there is a number of experimental studies that confirm the effect of EPO on inflammatory reactions, i. e. increased expression of endothelial nitric oxide synthase and induced production of nitric oxide in cardiomyocytes were demonstrated in myocardial ischemia-reperfusion under the influence of this factor, which led to a decrease in oxidative stress, in transendothelial migration of neutrophils and myeloperoxidase activity [14]. Another

ISSN 2307-3373
DOI: 10.31655/2307-3373-2020-1-28-36

experimental study of chronic heart failure signs showed a decrease in the content of proinflammatory cytokines (TNF-α, IL-1β, IL-6, and transforming growth factor-β1) in the blood nearly to control levels after four weeks of treatment with EPO [13]. An experimental study showed a high anti-inflammatory effect of EPO, namely, a decrease in blood levels of TNF-α and IL-1β and an increase in the anti-inflammatory cytokine, IL-10 [15]. Therefore, the effectiveness of ACD treatment in patients with COPD using a combination of EPO and iron supplements can be explained not only by the major, erythropoiesis-stimulating function of EPO, but also by probable pleiotropic, namely, anti-inflammatory effect of EPO.

Conclusions

In patients with COPD and concomitant anemia of chronic disease, the use of background therapy for COPD and oral and intravenous iron supplements did not lead to an increase in blood levels of hemoglobin and serum iron and a decrease in levels of hepcidin, C-reactive protein and ferritin.

Under the influence of background therapy combined with intravenous iron (III)-hydroxide sucrose complex and subcutaneous erythropoietin in COPD patients, the levels of hepcidin, C-reactive protein and ferritin decreased, which contributed to suppression of chronic inflammatory process, as well as hemoglobin and serum iron content increase.

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DOI: 10.31655/2307-3373-2020-1-28-36 ISSN 2307-3373

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Надійшла до редакції 06.12.2019 р.
Прийнято до друку: 14.02.2020 р.

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ISSN 2307-3373
DOI: 10.31655/2307-3373-2020-1-28-36