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EXPERIENCE WITH THE USE OF REBAMIPIDE FOR THE CORRECTION OF LOW-GRADE SYSTEMIC INFLAMMATION IN PATIENTS WITH POSTCOVID SYNDROME

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Abstract

Introduction: *Despite the lack of a clear understanding of the mechanisms underlying the post-covid syndrome, a pronounced systemic inflammation that transforms into low-grade "chronic" inflammation during the process of recuperation undoubtedly plays an important role. One of the main problems of low-grade inflammation, which poses a risk to human health, is a significant increase in the risk of cardiovascular complications in the post-covid period, which include death from cardiovascular disease.*

Objective: *to evaluate the efficacy of the effect of the rebamipide on the level of C-reactive protein in patients with postcovid syndrome with severe arthralgias.*

Materials and methods. *62 patients with a postcovid syndrome and joint pain were included in the study. The patients were divided into two groups. The first group (n=34) received rebamipide and omeprazole for 28 days. Group 2 - 28 patients, received only omeprazole for 28 days. All patients underwent clinical examination, anamnestic data collection and blood tests for levels of systemic inflammation marker - C-reactive protein and basic lipopolysaccharide binding systems.*

Results. *In peripheral blood in group No. 1 a significant decrease in C-reactive protein level (mg/L) was found to 3.75 [2.82; 4.21] and post-drug 2.05 [1.85; 2.62] ($p<0.05$), respectively ($p<0.05$). In the second group no significant changes were found before drug administration 3.4 [2.56; 4.0] and after proton-pump inhibitor course 3.52 [2.68; 3.9] ($p>0.05$).*

Conclusions. *We can conclude that rebamipide has the potential to be a therapeutic agent for low-grade inflammation not only in patients with the presence of gastrointestinal diseases and metabolic disorders, but also in individuals who have undergone a new coronavirus infection and have signs of postcovid syndrome accompanied by an increase in peripheral blood C-reactive protein as part of low-grade inflammation.*

Keywords: *systemic inflammation, postcovid, coronavirus infection, rebamipide, C-reactive protein.*

Introduction

More than 669 million people worldwide had already contracted a new coronavirus infection (NCI) [*Yong S et al., 2023*]; in the Russian Federation, this figure exceeded 22.5 million, accounting for more than 15% of the total population [*Starodubov V et al., 2022*]. Patients who have undergone the acute phase of NCI are at risk of developing the so-called postcovid syndrome, which is manifested by symptoms of health impairment 12 weeks after reconsolidation, namely pain syn-

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drome, psychiatric disorders, asthenovegetative syndrome, decreased tolerance to physical activity, and a general decrease in the quality of life [*Huang L et al., 2021, Evans R et al., 2022*]. Clinical manifestations of the post-covid period develop in more than 20% of patients, and the largest studies conducted in China to date show that almost half of NCI re-convalescents a year after discharge from an infectious hospital developed symptoms characterized as manifestations of the post-covid syndrome [*Huang C et al., 2021*].

Despite the lack of a clear understanding of the mechanisms underlying the postcovid syndrome, a pronounced systemic inflammation plays an undoubtedly important role, transforming in the process of recollection into low-grade "chronic" inflammation (LGI), arising as a consequence of immune dysregulation and organ damage developed in the acute period. In the world literature, the level of C-reactive protein (CRP) in peripheral blood in the range from 3 *mg/L* to 10 *mg/L* is a common indicator characterizing LGI [*Rifai N, Ridker P, 2003; Imhof A et al., 2003*]. The data obtained in the course of research over the last few years indicate the development of LGI in patients who have undergone NCI [*Florencio L, Fernández-de-Las-Peñas C, 2022; PHOSP-COVID Collaborative Group, 2022; Maamar M et al., 2022; Beloglazov V et al., 2023*].

One of the major problems of LGI that pose a risk to human health is a significant increase in the risk of cardiovascular complications in the postcovid period, which includes death from cardiovascular disease (CVD) [*Silva Andrade B et al., 2021*]. Having a history of NCI significantly increases the 12-month risk of CVD, making cardiovascular events one of the most common clinical manifestations and causes of death in the postcovid period [*Franceschi C et al., 2018; Elseidy S et al., 2022; Wang W et al., 2022*].

Low-grade inflammation is a polyetiologic problem, and possible causes of LGI development include the presence of single nucleotide polymorphisms of proinflammatory cytokine genes [*Collaboration IRGCERF et al., 2016*], increased intestinal permeability (IP) to potential proinflammatory agents, including lipopolysaccharide of Gramnegative flora (LPS) [*Tsounis E et al., 2023*], the presence of a focus of chronic infection [*Wang H et al., 2017*], and dysmetabolic disorders with impaired function of barrier systems (obesity and type 2 diabetes) [*Karczewski J et al., 2023*]. Based on the currently available information in the literature about the gastrointestinal tract affected by NCI virus, namely the development of local inflammation of the small intestinal mucosa, in our opinion, one of the most important ways to develop and maintain the LGI state in NCI patients may be increased IP [*Sun Z et al., 2022; Tsounis E et al., 2023; Eleftheriotis G et al., 2023*]. In this regard, it is reasonable to consider the use of drugs that can influence the state of dense contacts of the small intestine, reducing the IP [*Simanenkov V et al., 2021*], such as rebamipide, an inducer of endogenous prostaglandin E, used in gastrointestinal tract lesions against the background of taking nonsteroidal anti-inflammatory drugs (NSAIDs) [*Ostroumova O, Kochetkov A, 2020*].Considering all of the above, our study focused on the effect of rebamipide administration on the levels of CRP and the major systems that bind lipopolysaccharide (LPS), as a potential inducer of inflammatory reactions (lipopolysaccharide-binding protein (LBP) and protein of increased intestinal permeability (BPI)) in patients with postcovid syndrome manifested by severe arthralgias and required prescription of NSAIDs and proton pump inhibitors (PPIs) to protect the gastric mucosa.

Materials and methods

A prospective single-center study included 62 people aged 46±5.6 years with a history of coronavirus infection, taking nonsteroidal anti-inflammatory drugs (NSAIDs) for joint pain on the background of postcovid syndrome and living in the Republic of Crimea. The patients were divided into two groups. The first group (n=34) received rebamipide at a dose of 100 *mg* 3 times a day and omeprazole 20 *mg* daily for 28 days. Group 2 - 28 patients, received only omeprazole 20 *mg* daily for 28 days. The study included patients aged 18-75 years who had a new COVID-19 coronavirus infection and were taking NSAIDs (on average for 5±2 days) for arthralgias that occurred against the background of the new coronavirus infection.

Inclusion criteria were: presence of postcovid syndrome (moderate NCI) from 6 to 8 months before inclusion in the study. The control group

Table 1.

Characteristics of the patients included in the study

Parameters	Group 1 (n = 34)	Group 2 (n = 28)	Control group (n = 20)
Gender abs. (%)			
Male	13 (38.24)	10 (35.71)	6 (30)
Female	21 (61.76)	18 (64.29)	14 (60)
Age, (*years*)	44 [40;48]	46 [43;49]	44 [38;47]
BMI, (kg/m^2)	23.92 [20.95; 24.2]	22.77 [20.7; 24.3]	22.17 [20.8; 23.9]

Note: *There were no significant differences in the indicators between the groups (p > 0.05). BMI - body mass index.*

consisted of 20 relatively healthy respondents (14 women and 6 men) who had no history of NCI and were comparable to the study groups in terms of sex and age. The main parameters characterizing the patients included in the study are presented in Table 1.

Exclusion criteria were as follows: age over 75 years, arthralgias not related to NCI, increased uric acid according to biochemical blood analysis, increased antibodies to cyclic citrullinated peptide (ACCP) and rheumatoid factor (RF), taking glucocorticoid drugs, contraindications to the administration of rebamipide. Patients were included in the study after signing informed consent.

All patients were clinically examined, anamnestic data were collected, and blood tests (ELISA) were performed for the levels of systemic inflammation marker - C-reactive protein (CRP) and basic lipopolysaccharide binding systems (LPS and BPI).

C-reactive protein content (*mg/L*) in plasma was determined by quantitative high-sensitivity enzyme-linked immunosorbent assay using ELISA test produced by Cloud Clone corp. (Wuhan, Hubei, China).

The content of LBP (*ng/mL*) in plasma was determined by quantitative high-sensitivity enzyme-linked immunosorbent assay using ELISA test manufactured by Cloud Clone corp. (Wuhan, Hubei, China).

Blood Pressure Index *pg/mL*) in blood plasma was determined by quantitative high-sensitivity enzyme-linked immunosorbent assay using ELISA test produced by Cloud Clone corp. (Wuhan, Hubei, China).

Data were analyzed using the licensed statistical software "Statistica 12" (StatSoft Inc.). Initially, all studied indicators were checked for normality of distribution using Shapiro-Wilk W-criterion, samples in which the criterion was $p \geq 0.1$ were taken as normal distribution, W-criterion value of $p < 0.1$ was taken as non-normal distribution. When processing nonparametric data, the Wilcoxon T-test for related samples was used to compare groups. The indicators were considered statistically significant at $p < 0.05$. In the case of normal distribution, the paired Student's T-test for related samples was used to process nonparametric data for comparison of groups. The indicators were considered statistically significant at $p < 0.05$.

The research was approved by the Local Ethical Committee of Vernadsky Crimean Federal University (Simferopol) on June 23, 2023 protocol (No. 7). Helsinki Declaration has been followed for involving human subjects in the study.

Results

According to the results of the study, significantly higher levels of CRP and LBP were registered in the studied groups before treatment compared to the control group ($p < 0.05$). On the contrary, BPI index was significantly lower in the groups of patients with postcovid syndrome ($p < 0.05$). In peripheral blood in group No. 1, which took rebamipide in addition to PPI, a significant decrease in CRP level (*mg/L*) was found to 3.75 [2.82; 4.21] and post-drug 2.05 [1.85; 2.62] ($p < 0.05$), respectively ($p < 0.05$). In the second group (omeprazole monotherapy), no significant changes were found before drug 3.4 [2.56; 4.0] and after PPI course 3.52 [2.68; 3.9] ($p > 0.05$) (Table 2).

Discussion

Novel coronavirus infection can directly and indirectly lead to disruption of the integrity of the blood-brain barrier by increasing intestinal translocation of LPS and other bacterial products into the lymph, portal and then systemic bloodstream, significantly potentiating the already existing inflammation in NCI patients [*Tsounis E et al., 2023*]. Studies of acute SARS-CoV-2 have demon-

Table 2.

Laboratory values before and after treatment.

Group and parameter		Before treatment Me [Q1;Q3]	After treatment Me [Q1;Q3]	Significance of differences, p
C-reactive protein (*mg/l*)	Control group (n=15)	0.5 [0.4; 0.9]	-	-
	Group №1 (n=32)	3.75 [2.82; 4.21]*	2.05 [1.85; 2.62]	p<0.05
	Group №2 (n=28)	3.4 [2.56; 4.0]*	3.52 [2.68; 3.9]	p>0.05
lipopolysaccharide-binding protein (*ng/mL*)	Control group (n=15)	8.75 [3.2; 17.9]	-	-
	Group №1 (n=32)	18.46 [14.0; 25.5]*	12.84 [8.2; 16.7]	p<0.05
	Group №2 (n=28)	16.22 [14.0; 23.0]*	17.11 [13.8; 26.0]	p>0.05
bactericidal/permeability increasing protein (*pg/ml*)	Control group (n=15)	2580 [1532; 2728]	-	-
	Group №1 (n=32)	1576 [276; 3588]*	1634 [350; 3124]	p>0.05
	Group №2 (n=28)	1440 [282; 3862]*	1551 [225; 3373]	p>0.05

Notes: *The table presents quantitative (Me [Q1; Q3]) signs. Differences in quantitative signs were identified using the Wilcoxon test. * - reliability of differences compared to the control group p<0.05.*

strated altered levels of zonulin, one of the major markers of intestinal barrier permeability [*Okuyucu M et al., 2022*], and patients who died from severe NCI had higher levels of zonulin. It is also known that patients with evidence of postcovid syndrome have significantly higher mean plasma zonulin concentrations than patients without postcovid syndrome [*Mouchati C et al., 2023*].

Recent work suggests a potential role of bacterial LPS in immune hyperactivation in NCI [*Teixeira P et al., 2021; Huang L et al., 2022*]. The interaction of LPS with toll-like receptor type 4 (TLR4), which recognizes it, leads to activation of the whole cascade of proinflammatory reactions, and in our previous studies we demonstrated more than 15-fold increase in the level of LPS compared to the control group in the acute period of severe NCI [*Yatskov I et al., 2022*].

The results obtained in our study demonstrated a statistically significant decrease in the level of CRP and LBP in peripheral blood in patients who underwent NCI and took rebamipide in addition to PPIs to prevent the development of NSAID-gastropathies against the background of severe joint syndrome. BPI level in peripheral blood in patients of groups 1 and 2 did not change significantly. The described changes can be explained by multifactorial influence and pleiotropic effects of rebamipide presented in the literature.

First of all, the anti-inflammatory effect may be related to the beneficial effect of rebamipide on the state of intestinal permeability, preventing the translocation of proinflammatory agents into the systemic bloodstream. This ability was demonstrated in a comparative study by Kovalyova A. et al. in which sixty patients were randomized into three groups taking trimebutin, trimebutin + rebamipide or rebamipide for 2 months [*Kovaleva A et al., 2023*]. Serum zonulin levels were significantly reduced in the group taking rebamipide. In addition, rebamipide reduced the severity of enterocyte damage and inflammation in the intestine, reducing the level of lymphocytic infiltration of the mucosa [*Kovaleva A et al., 2023*]. Comparable results were obtained in another study. Statsenko et al. reported a significant decrease in the level of zonulin in patients taking rebamipide at a dose of 100 mg 3 times a day against the background of functional dyspepsia. In this group of patients, serum zonulin decreased almost twofold from the initial level (Δ% - 49%) [*Kovaleva A et al., 2023*].

Rebamipide is also a potential factor in reducing the risk of cardiovascular complications. Thus, Jhun et al. suggested that rebamipide suppresses the development of atherosclerosis due to reciprocal regulation of Th17/Treg. To determine the therapeutic activity of rebamipide, the authors induced atherosclerosis in apolipoprotein E (ApoE) knockout mice and determined the activity of rebamipide in the context of retarding atherogenesis. by assessing inflammatory cytokine and lipid levels in serum in vivo or in vitro [*Jhun J et al., 2017*]. Oral administration of rebamipide reduced plaque for-

mation in atherosclerotic foci, levels of markers of metabolic disorders and atherosclerosis in ApoE-deficient mice, as well as decreased Th17 population and increased Treg. Rebamipide also reduced the severity of obesity-induced arthritis and was able to reduce the development of atherosclerosis by controlling the balance between Th17 and Treg cells. The authors also reported the ability of rebamipide to reduce the levels of proinflammatory cytokines such as interleukin 6 and tumor necrosis factor-α [*Jhun J et al., 2017*].

Conclusion

Considering the findings in our study, we can conclude that rebamipide has the potential to be a therapeutic agent for LGI not only in patients with the presence of gastrointestinal diseases and metabolic disorders, but also in individuals who have had a new coronavirus infection and have signs of postcovid syndrome accompanied by an increase in peripheral blood CRP as part of LGI.

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