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Changes in biochemical and molecular parameters of blood in patients with chronic generalized periodontitis during a course of treatment with interleukin-1 receptor antagonist

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The aim of the study was to conduct a laboratory and biochemical assessment of the complex therapy of chronic generalized periodontitis (CGP) with the inclusion of an IL-1 receptor antagonist (*Anakinra*) in the therapy.

Materials and methods. Examination and treatment of 60 patients with CGP of moderate severity and 30 patients with intact periodontium aged 40 to 65 years (35 women and 25 men) were conducted. Patients were divided into 2 groups: main and control, 30 people in each. Examination and treatment were carried out with the consent of the patients in accordance with GCP standards (1996) and the principles of the Declaration of Helsinki (World Medical Association – WMA, 2013). Patients with CGP of both groups received standard complex therapy for 30 days, which included oral hygiene; vector therapy; curettage; fixation of teeth in the correct position with specialized materials; anti-inflammatory and antiseptic medications. In addition, patients in the main group were prescribed Anakinra (1 mg/day) in the form of intraoral transgingival electrophoresis on both jaws (5 sessions). Biochemical studies included monitoring of the activity of lactate dehydrogenase (LDH), succinate dehydrogenase (SDH), glutathione peroxidase (GPx), glutathione reductase (GR); enzyme immunoassay of endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), nitrotyrosine and metalloproteinase-2 (MPP-2) in the blood of patients of the control and main groups before treatment and after 30 days of treatment. Statistical processing of the results was performed using the software package Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J), as well as "SPSS 16.0", "Microsoft Excel 2003".

Results. It was found that the additional inclusion of Anakinra in the complex treatment of CGP potentiated the anti-inflammatory effect of the therapy that was manifested in a more pronounced, compared to the control group, decrease in the level of MMP-2, and clinical signs (depth of periodontal pockets, bleeding, tooth mobility, etc.); enhanced antioxidant action, which was confirmed by a more pronounced decrease in nitrotyrosine level, an increase in GR and GPx activity ($p < 0.05$) compared to similar indicators in patients in the control group. The inclusion of Anakinra enhanced the anti-ischemic effect of complex therapy that was manifested in a decrease in LDH levels and an increase in SDH concentration ($p < 0.05$); and also contributed to a decrease in iNOS expression and an increase in eNOS expression ($p < 0.05$) compared to similar indicators of patients in the control group.

Conclusions. The results obtained demonstrate a promising strategy of pharmacological blockade of IL-1β receptors, which may have new prospects for the treatment of patients with CGP.

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Зміни біохімічних та молекулярних показників крові у пацієнтів з хронічним генералізованим пародонтитом при курсовому лікуванні антагоністом рецепторів інтерлейкіну-1

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Мета роботи – здійснити лабораторно-біохімічне оцінювання комплексної терапії хронічного генералізованого пародонтиту при включенні до терапії антагоніста рецепторів IL-1 (Анакінри).

Матеріали і методи. Проведено обстеження та лікування 60 хворих на хронічний генералізований пародонтит (ХГП) середнього ступеня тяжкості та 30 пацієнтів з інтактним пародонтом у віці від 40 до 65 років (35 жінок та 25 чоловіків). Пацієнтів було поділено на 2 групи – основну та контрольну, по 30 осіб у кожній. Лікування та обстеження проводили з дозволу пацієнтів згідно зі стандартами GCP (1996 року) та принципами Гельсінської декларації (World Medical Association -WMA, 2013 року). Пацієнти з ХГП обох груп протягом 30 днів отримували стандартну комплексну терапію, що включала гігієну ротової порожнини; вектор-терапію; кюретаж; фіксацію зубів у правильному положенні спеціалізованими матеріалами; протизапальні та антисептичні препарати. Крім того, пацієнтам основної групи призначали Анакінру (*1 мг/добу*) у вигляді внутрішньоротового трансгінгівального електрофорезу на обидві щелепи (*5 сеансів*). Біохімічні дослідження включали моніторинг активності лактатдегідрогенази (ЛДГ), сукцинатдегідрогенази (СДГ),

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глутатіонпероксидази (ГПР), глутатіонредуктази (ГР); імуноферментний аналіз ендотеліальної синтази оксиду азоту (eNOS), індуцибельної синтази оксиду азоту (iNOS), нітротирозину та металопротеїназ-2 (МПП-2) у крові пацієнтів контрольної та основної груп до лікування та на 30 добу лікування. Статистичну обробку результатів здійснювали за допомогою пакета програм Statistica for Windows 13 (StatSoft Inc., № JPZ804I382130ARCN10-J), а також «SPSS 16.0», «Microsoft Excel 2003».

Результати. Було встановлено, що додаткове включення Анакінри в комплексне лікування ХГП потенціювало протизапальний ефект терапії, що знаходило вияв у більш вираженому, порівняно з контрольною групою, зниженні рівня ММП-2 та клінічних ознак (глибина пародонтальних кишень, кровоточивість, рухливість зубів тощо); посилювало антиоксидантний ефект комплексної терапії, що підтверджувалося більш вираженим зниженням рівня нітротирозину, підвищенням активності ГР та ГПР ($p < 0,05$) порівняно з аналогічними показниками пацієнтів контрольної групи. Включення Анакінри посилювало протиішемічну дію комплексної терапії, що знаходило вияв у зниженні рівня ЛДГ та підвищенні концентрації СДГ ($p < 0,05$); а також сприяло зниженню експресії iNOS та підвищенню експресії eNOS ($p < 0,05$) порівняно з аналогічними показниками пацієнтів контрольної групи.

Висновки. Отримані результати демонструють перспективність стратегії медикаментозної блокади рецепторів ІЛ-1β, яка може мати нові перспективи лікування пацієнтів з ХГП.

Сучасні медичні технології. 2025. Т. 17, № 4(67). С. 306-313

It is known that among periodontal diseases, the most common is chronic periodontitis, which is found in the majority of the world's population. Chronic periodontitis is characterized by a recurrent course, and in the absence of adequate modern treatment, it can lead to tooth loss, the development of pathology of organs and systems and a decrease in the quality of life [1,2,3]. Very often periodontitis treatment begins quite late, as this periodontal disease rarely manifests in the early stages and has a sufficient latent period [4,5]. Despite the successes achieved in the treatment of chronic periodontitis, the frequency of its detection, especially among young people, is indeed increasing. Therefore, optimization of drug treatment measures for chronic periodontitis by including new medications in the complex therapy, the action of which is directed at the most important target links of this pathology, is a key task of modern dentistry. The etiology of chronic periodontitis is well studied, and, in brief, includes pathogenic microorganisms (*Porphyromonas gingivalis*, *Actinobacillus actinomycetemcomitans*, *Tannerella forsythensis, and Treponema denticola*). The waste products of pathogenic microbes initiate an inflammatory reaction in periodontal tissues, which significantly increases the expression of proinflammatory cytokines such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) leading to IL-1β-dependent activation of molecular reactions including increased expression of inducible nitric oxide synthase (iNOS), matrix metallopeptidase 9 (MMP-9), matrix metallopeptidase 1 (MMP-1), matrix metallopeptidase 3 (MMP-3), activation of nitrosative and oxidative stress that contribute to bone resorption [6,7,8,9].

The NOD-like receptor protein-3 (NLRP3) inflammasome signaling pathway promotes IL-1β activation, and NLRP3 inflammasome complex mRNA expression is increased in the blood of patients with gingivitis and chronic periodontitis [10,11].

Composite IL-1 genotype is significantly associated with periodontitis severity in adults [12]. IL-1β induces high levels of iNOS mRNA, increases iNOS expression, which, under conditions of antioxidant system deficiency, leads to an increase in cytotoxic and proinflammatory forms of NO such as peroxynitrite ($ONOO^-$) and nitrosonium ions (NO^+), as well as superoxide ($O_2^{\bullet-}$) and hydroxyl (•OH) radicals.

It is known that IL-1β specifically activates iNOS gene transcription. Specific IL-1β blockers have been shown to reduce iNOS mRNA expression to physiological levels [13]. High levels of IL-1β in the blood of patients with chronic periodontitis can cause systemic adverse effects such as an increased risk of developing cardiovascular diseases and diseases of the hepatobiliary system [14]. Chronic and aggressive periodontitis are both associated with significant increases in salivary NLRP3, apoptosis-associated protein containing a caspase recruitment domain (ASC), and IL-1β [15]. Currently, IL-1 family members are considered as promising new therapeutic targets for the treatment of inflammatory diseases of the oral cavity [16]. Thus, data were obtained that antibacterial medications such as minocycline, doxycycline, roxithromycin, amoxicillin and metronidazole when administered locally into periodontal pockets of microspheres had a limited effect on IL-1β. However, this limited effect of these agents disappears within 6 months [17,18,19].

IL-1β receptor/antibody antagonists are of greater interest to pharmacologists and clinicians. However, the clinical efficacy of IL-1 blockers of varying selectivity and affinity in periodontitis has hardly been studied. IL-1 blockers such as *Anakinra, Rilonacept* and *Canakinumab* exhibiting significant anti-inflammatory effects both in experimental studies and in clinical use, are of theoretical interest in the treatment of periodontitis [20].

Anakinra is a recombinant homologue of the IL-1α and IL-1β antagonist, and by blocking these receptors, prevents the cascade of inflammatory reactions in pathological conditions and during the formation of the inflammasome. Since 2001, Anakinra has been approved for the treatment of rheumatoid arthritis, autoinflammatory syndromes and idiopathic recurrent pericarditis, as well as chronic inflammatory conditions such as familial Mediterranean fever (FMF), TNF-α receptor-associated periodic syndrome (TRAPS), and gout [21]. There are a number of clinical trials underway for Anakinra in chronic inflammatory diseases, including type 1 diabetes, atherosclerosis, hepatitis (NCT01903798) and chronic kidney disease. Anakinra has a short half-life of 4–6 hours, requiring frequent dosing [22,23].

Topical application of Anakinra, both as a dental gel and by electrophoresis, appears to be very promising for the treatment of

periodontitis. Convincing experimental results have been obtained for the topical application of Anakinra in chronic generalized periodontitis in animals [23] that justifies its clinical use in the complex therapy of chronic periodontitis.

Aim

To provide a laboratory and biochemical assessment of the complex therapy of chronic generalized periodontitis with the inclusion of a recombinant IL-1 receptor antagonist (*Anakinra*).

Materials and methods

We examined 60 patients with chronic generalized periodontitis (CGP) of moderate severity aged 40 to 65 years (35 women and 25 men). The study also included 30 patients with intact periodontium who were undergoing a preventive examination by a dentist. All patients were examined and treated at the University Clinic of the Zaporizhzhia State Medical and Pharmaceutical University, and the Modern Center for Dental Implantation "Chertov Clinic" (Zaporizhzhia). Depending on the therapy, patients were divided into 2 groups: the main and control, 30 people each. The inclusion criteria were moderate chronic generalized periodontitis and informed voluntary consent to complex treatment. Exclusion criteria were the presence of acute or exacerbation of chronic infectious or autoimmune diseases, acute allergic reactions, oncological and mental illnesses, long-term hormonal therapy, diseases of the pituitary gland and thyroid gland, and hypersensitivity to therapeutic agents.

Patients with CGP in both groups received a standard treatment complex for 30 days including oral hygiene; anti-inflammatory agents; antiseptic medications in the form of gel or rinses, as well as agents based on propolis and solcoseryl. Patients in both groups also received vector therapy, curettage, and fixing teeth in the correct position using specialized materials.

Patients of the main group, in addition to the main treatment, received Anakinra (Kineret) (Sobi – Swedish Orphan Biovitrum, Sweden) at the beginning of the entire course of treatment in the form of 5 sessions (10 days) of intraoral two-jaw transgingival electrophoresis (1 mg/day). For electrophoresis, the device "ZAPOVIT" POTOK-01M LLC "BIOMED" (Ukraine) was used. Anakinra was diluted in a physiological solution with the addition of 0.5 M phosphate buffer at pH 6.8. Gingival electrodes of the "Jumper cables" type were used with disposable conductive pads made of carbon paper. The current strength was 5 mA for 15 min. The medication was administered from the negative pole.

Bioethical aspects of research. The study was conducted with the consent of the patients in accordance with the basic standards of GCP (1996), the European Convention on Human Rights and Biomedicine of 04.04.1997, and in accordance with the principles of the Declaration of Helsinki in its latest version, adopted at the 64th General Assembly of the World Medical Association (WMA), Fortaleza, Brazil, October 2013 [24,25,26]. This study was approved by the Bioethics Committee of Zaporizhzhia State Medical and Pharmaceutical University (Protocol No 3 dated 12.06.2023). All patients were explained the nature of the examination and treatment. All participants in this study gave their consent or refused it.

Blood collection and preparation of biological material. Before and after 30 days of treatment, blood was taken from the cubital vein of patients in all groups, and placed in a test tube with the anticoagulant ETDA. Blood plasma and lymphocytes were isolated by centrifugation in an Eppendorf-5804R centrifuge (Eppendorf, USA) using Hanks' solution and a Ficoll-P gradient with a specific density of 1.077 g/cm^3 (Merck KGaA, Germany).

Biochemical research. In blood lymphocytes, the activity of lactate dehydrogenase (LDH) was determined using a kit from Cormay (Poland) on an ACCENT-200 biochemical analyzer (Poland). Succinate dehydrogenase (SDH) activity was also determined in lymphocytes using the Succinate Dehydrogenase Activity Assay Kit (Colorimetric; Cat. No.: ab228560, Abcam Company, UK). Glutathione peroxidase (GPX) activity was determined in blood plasma using the Glutathione Peroxidase Assay Kit (Colorimetric) (Cat. No.: ab102530, Abcam Company, UK).

Glutathione peroxidase (GPX) activity was determined in blood plasma using the Glutathione Peroxidase Assay Kit (Colorimetric; Cat. No.: ab102530, Abcam Company, UK). Glutathione reductase (GR) activity in blood plasma was determined spectrophotometrically by monitoring the rate of NADPH oxidation at 340 nm [27]. Measurements were carried out on an Eppendorf BioSpectometr spectrophotometer (USA).

Enzyme immunoassay. The concentration of endothelial nitric oxide synthase (eNOS) was determined in blood plasma using the ELISA Kit for eNOS (cat. No. SEA868Hu; Cloud-Clone Corporation, USA). In blood plasma, the concentration of inducible nitric oxide synthase (iNOS) was determined using the ELISA Kit for Nitric Oxide Synthase 2, Inducible (NOS2) (Cat. No. HEA837Hu; Cloud-Clone Corporation, USA). In blood plasma, the concentration of nitrotyrosine was determined using the ELISA Kit for Nitrotyrosine (NT) (Cat. No. CEB863Ge Cloud-Clone Corporation, USA). The concentration of metalloproteinase-2 (MPP-2) was determined in blood plasma using the Human MMP-2 ELISA Kit (Cat. No. KE00077; Proteintech, Germany). All parameters were determined using an Immunochem-2200 analyzer, USA.

Statistical analysis. All obtained research data were statistically processed using the software package Statistica for Windows 13 (StatSoft Inc., No. JPZ804I382130ARCN10-J), "SPSS 16.0", and "Microsoft Excel 2003". The arithmetic mean (M), and the error of the arithmetic mean (m) were calculated. To identify intergroup and intragroup differences, Student's t-test and Fisher's angular transformation were used. Selected statistical procedures and algorithms were implemented as specially written macros in the corresponding programs. For all types of analysis, differences at $p < 0.05$ were considered statistically significant.

Results

Examination of patients before the start of treatment revealed the following features in patients with intact periodontium (relatively healthy): no signs of bleeding, tooth mobility or gum inflammation were found, while patients in the control and main groups had visual changes in the gums, such as swelling, bluish tint, thickened edges, poor fit to the teeth, and changes in gum contour, the presence of pathological pockets (up to 5 mm) with serous and serous-purulent exudate, dental plaque, tartar, tooth

Table 1. Molecular parameters of blood from patients with CGP before and after 30-day drug treatment

Groups of patients	eNOS, pg/ml	iNOS, pg/ml	MMP-2, ng/ml	Nitrotyrosine, ng/ml
Relatively healthy (intact periodontium), n = 30	61.8 ± 4.7	12.8 ± 0.8	0.8 ± 0.03	2.8 ± 0.11
Control group at admission, n = 30	18.3 ± 4.5[1]	34.3 ± 2.7[1]	14.8 ± 1.5[1]	23.4 ± 2.1[1]
Control group after treatment for 30 days, n = 30	22.4 ± 3.5[1]	32.4 ± 6.5[1]	8.2±0.5*[,1]	18.3 ± 1.9*[,1]
Main group at admission, n = 30	17.9 ± 2.1[1]	36.3 ± 2.7[1]	15.9 ± 1.7[1]	24.7 ± 2.1[1]
Main group (*Anakinra*) after treatment, n = 30	55.6 ± 5.2*[,1#]	15.2 ± 2.1*[,1#]	3.2 ± 0.1*[,1#]	6.8 ± 0.5*[,1,#]

[1]: the indicators are statistically significant compared to the data of the intact group ($p < 0.05$); *: compared to the data before treatment ($p < 0.05$); #: compared to the control group ($p < 0.05$).

Table 2. Biochemical blood parameters of patients with CGP before and after 30-day drug treatment

Groups of patients	GR, μM/l	GPx, pg/ml	SDH, nM/ml/min	LDH, IU/L
Relatively healthy (intact periodontium), n = 30	4.8 ± 0.7	7.8 ± 0.3	26.8 ± 1.3	342.8 ± 34.1
Control group at admission, n = 30	2.3 ± 0.5[1]	3.3 ± 0.7[1]	17.2 ± 2.4[1]	545.4 ± 62.1[1]
Control group after treatment for 30 days, n = 30	2.5 ± 0.5[1]	3.7 ± 0.5[1]	19.8 ± 3.5[1]	427.3 ± 51.2*
Main group at admission, n = 30	2.1 ± 0.1[1]	3.3 ± 0.5[1]	17.2 ± 1.5[1]	553.3 ± 47.8[1]
Main group (*Anakinra*) after treatment, n = 30	4.0 ± 0.6*[,#]	4.2 ± 0.2*[,#,1]	19.2 ± 2.3[1]	355.8 ± 37.5*

[1]: the indicators are statistically significant compared to the data of the intact group ($p < 0.05$); *: compared to the data before treatment ($p < 0.05$); #: compared to the control group ($p < 0.05$).

mobility, and signs of inflammation. Thus, the main signs of CGP of moderate severity were identified and clinically confirmed in patients.

Analysis of biochemical and enzyme immunoassay studies of blood from patients with CGP in the control and main groups before the start of treatment revealed signs of ischemia, significant inflammation, and activation of oxidative stress against the background of disturbances in the nitroxidergic system and deprivation of the antioxidant enzymatic system. Thus, before the start of treatment in the blood of patients with CGP of both groups were detected an increase in the concentration of nitrotyrosine by 8.3–8.8 times ($p < 0.05$) against the background of a decrease in the activity of GR (by 52–56.2 %) and GPR (on average by 57.7 %) ($p < 0.05$) compared with the values of the intact group *(Tables 1* and *2)*.

All this indicates a significant activation of oxidative stress reactions during periodontal inflammation. Also, in the blood of patients with CGP of both groups before treatment, a decrease in the activity of SDH (on average by 35.8 %), and an increase in the activity of LDH (by 55.8–59.3 %) were found compared with the values of the intact group ($p < 0.05$), which indicates the manifestation of ischemia in periodontitis *(Tables 2)*.

Before the start of treatment, an increase in the concentration of MMP-2 (by 18.5–19.8 times; $p < 0.05$) in the blood from patients with CGP of both groups was recorded compared with the values of the intact group, which indicated significant inflammation *(Table 1)*. The identified pathological processes occurred against the background of an increase in the expression of iNOS (by 2.7–2.8 times) and a decrease in the expression of eNOS (by 70.4–71.0 %, $p < 0.05$) compared with the values of the intact group *(Table 1)*.

After a one-month course of CGP complex therapy (including removal of dental deposits and plaque, rational hygiene, curettage of periodontal pockets, vector therapy, pharmacotherapy), an improvement in the clinical picture was revealed, such as reduction of hyperemia, bleeding gums, and bad breath. However, the benefits identified were more pronounced in patients with CGP in the main group, who additionally received Anakinra (1 mg/day) via electrophoresis.

Thus, in patients of the main group, additional prescription of IL-1 antagonist in the complex treatment of CGP led to a more significant reduction in the depth of periodontal pockets (up to 1–2 mm, whereas in the control group – up to 3–4 mm), cessation of discharge from them and epithelialization of their bottom, as well as minimization of bleeding from the gums. A more pronounced decrease in tooth mobility was also noted in the main group 30 days after complex therapy against the background of a more pronounced improvement in the gum picture than in patients in the control group (the mucous membrane was denser; the gums were more tightly attached to the neck of the tooth, less edematous, and did not differ in color from the intact gum).

Biochemical and enzyme immunoassay studies of the blood from patients of the control and main groups one month after complex treatment of CGP also revealed improvements, such as reduced inflammation, inhibition of oxidative stress, normalization of the nitrogen monoxide system. Thus, in patients of the main group, with the additional administration of Anakinra in the complex therapy of CGP, a significant decrease in the concentration of MPP-2 in the blood (by 80 %) was observed compared to the start of treatment. In the control group, the level of MMP-2 decreased by 44.6 % compared to baseline values ($p < 0.05$).

The concentration of MMP-2 in the blood of patients in the main group was lower than the concentration of MPP-2 in the control group ($p < 0.05$), which indicates a significant increase in the anti-inflammatory action of complex therapy due to the inclusion of Anakinra.

A decrease in nitrotyrosine (by 72.5 %) was also observed 30 days after treatment compared to the initial values ($p < 0.05$). The concentration of nitrotyrosine in the blood of patients in the main group was lower than the concentration of nitrotyrosine in patients of the control group after 30 days of treatment ($p < 0.05$). Also, in patients of the main group, after 30 days of treatment, an increase in the activity of antioxidant enzymes was observed: GR – by 1.9 times, and GPX – by 1.27 times ($p < 0.05$) compared to the initial values, which indicated an increase in the antioxidant action of the therapy with the inclusion of Anakinra.

In the blood of patients of the control group, no significant changes in the activity of GR and GPX were detected before and after 30-day treatment. Also, in the blood of patients in the main group after 30-day treatment, a decrease in iNOS expression by 58.1 % was detected compared to the initial levels ($p < 0.05$), and an increase in eNOS expression by 3.1 times was detected compared to the baseline data.

In patients of the control group, no significant changes in the expression of NOS isoforms were detected before and after treatment. Thus, the inclusion of Anakinra in the complex therapy of CGP leads to normalization of the expression of NOS isoforms and, possibly, enhances its anti-inflammatory effect by interrupting NO-dependent proinflammatory mechanisms. No significant changes in SDH activity were observed in the blood of patients from either the control or main group before and after treatment. However, a significant decrease in LDH activity was detected, indicating a mild reduction in ischemic disturbances in the periodontium after 30 days of treatment.

Thus, in the blood of patients in the main group, there was a decrease in LDH by 33.4 % compared to the initial values of this group ($p < 0.05$), and by 21.6 % – in the control group ($p < 0.05$). We found a significant difference in the LDH activities of the main and control groups of patients with CGP after 30 days of complex therapy. Thus, the additional inclusion of the IL-1 receptor antagonist Anakinra in the complex treatment of CGP led to a significant improvements in therapy results compared to basic therapy, as evidenced by the results of clinical examination and the results of biochemical and enzyme immunoassay studies, namely a reliable decrease in the levels of markers of inflammation, oxidative stress, ischemia, and disturbances in the NO production system.

Discussion

CGP is a disease with complex causal mechanisms, which includes both the interaction of pathogenic microorganisms and human immune-inflammatory reactions, as well as genetic and environmental factors [28]. The IL-1 family of interleukins, more than any other cytokine family, includes key signaling molecules that initiate and maintain periodontal inflammation [29]. IL-1β is mainly expressed by macrophages, dendritic cells, and can also be expressed by gingival fibroblasts, periodontal ligament cells, and osteoblasts. IL-1β triggers numerous inflammatory reactions, contributes to the development of periodontitis, and can disrupt local blood circulation, leading to generalized periodontal ischemia. IL-1β acts as a powerful stimulant of bone tissue resorption and affects the mechanisms of pyroptosis in the periodontium [30]. IL-1β increases the expression of collagenolytic enzymes, matrix metalloproteinases (MMPs) promoting the degradation of the extracellular matrix and leading to bone resorption and tissue destruction [31].

Our data are consistent with the results of other studies, which also showed significant expression of MMP-2 under the influence of IL-1β, and which plays a role in modeling the extracellular matrix, including periodontal tissues, and is associated with the progression of periodontitis [23,24]. In addition, IL-1β stimulates the production of other MMPs, such as MMP-1, MMP-3, and MMP-9, in osteoblasts, human periodontal ligament cells, and gingival fibroblasts. Increased concentrations of MMP-2 have been detected in blood and saliva samples, and increased expression of MMP-2 mRNA has been detected in fibroblasts, and connective tissue, adjacent to the sulcular epithelium in patients with aggressive periodontitis [32]. Elevated levels of MMP-2 were detected in blood and saliva samples, and increased expression of MMP-2 mRNA was detected in fibroblasts of connective tissue adjacent to the sulcular epithelium in patients with aggressive periodontitis [33]. IL-1β increases the synthesis of proinflammatory and vasoconstrictor prostaglandins, stimulates osteoclastogenesis [12,16].

Our results on the nitroxidergic system disorder in patients with CGP are confirmed by other studies, which demonstrate that IL-1β enhances expression of iNOS in periodontal tissue cells during inflammation and increases the production of NO and its cytotoxic products. It was shown that an increase in the gingival bleeding index, inhibition of platelet aggregation and adhesion, a decrease in alveolar bone height, and an increase in absorption were mediated by increased production of cytotoxic NO products [30,34].

Increased production of cytotoxic forms against the background of antioxidant deficiency leads to the initiation of nitrosative stress, a specific marker of which is nitrotyrosine. We and other researchers found significant increase of nitrotyrosine levels in the blood of and saliva of patients with CGP. Nitrosative stress plays an important role in the progression of periodontitis and directly, due to reactions of oxidative modification and nitrosylation of active sites of proteins, and nucleic acids, leads to tissue damage, impaired regeneration, and increased inflammation in the periodontium [35,36,37].

The activity of nitrosative stress and the resulting aggravation of inflammation in the periodontium occurs against the background of deprivation of the glutathione system characterized by a deficiency of reduced glutathione in the blood of patients with CGP [38,39], as well as a decrease in the activity of GR and GPX, which we identified in this research, and in the experiment [40]. Reduced GPX expression results in upregulation of the NF-kB pathway playing a critical role in inflammation, acting as a central regulator of the immune response; and oxidative stress activation in periodontitis [41]. GSH regulates IL-1β-induced NO production by modulating iNOS mRNA expression, and also regulates the expression of prostaglandins, proinflammatory cytokines, and is

able not only to limit the negative effects of nitrosative stress, but also to reduce inflammation [42,43].

In periodontitis, IL-1β-mediated hypoxia results in decreased SDH activity and a reversal of electron flow; and allows fumarate to serve as the final electron acceptor in the electron transport chain that subsequently leads to succinate accumulation. Excess succinate stabilizes HIF-1α, inhibits prolyl hydroxylases, and interacts with succinate receptor 1 (SUCNR1) on immune cells, increasing periodontal inflammation. Increased expression of SUCNR1 in the periodontium enhances the severity of periodontitis through an inflammatory response. High levels of succinate against the background of SDH inhibition impair ATP synthesis and oxidative phosphorylation, and increase ROS production [44,45,46].

Excessive levels of IL-1β, a pro-inflammatory cytokine, along with periodontal bacteria, such as *P. gingivalis, T. forsythia,* and *F. nucleatum,* are directly involved in the formation of mitochondrial dysfunction in periodontitis leading to increased hypoxia, oxidative stress, apoptosis of periodontal ligament stem cells and gingival epithelial cells [47,48].

Taking into account the above, as well as experimental data, the strategy of blocking IL-1β may have new prospects in the treatment of CGP. Anakinra blocks both IL-α and IL-1β, and suppresses the production of TNF- α, MMP-9, MMP-2, MMP-8, which trigger the inflammatory cascade. Thus, blockade of IL-1β inhibits increased expression of the nuclear transcription factors AP-1 and NF-κB, changes the behavior of target cells, and leads to suppression of the acute inflammatory response, expression of iNOS, MMP-2, NADPH oxidase, reduces the initiation of oxidative stress, and mitochondrial dysfunction [49,50].

By inhibiting MMP-2 expression, Anakinra helps to slow down the destruction of connective tissue, and bone loss associated with periodontitis. By blocking IL-1β, Anakinra reduces not only the inflammatory response, but also ROS production, and decreases IL-1β-induced deprivation of glutathione-dependent enzyme expression, and glutathione synthesis [51]. Increasing antioxidant and cytoprotective components of the complex therapy of CGP with the inclusion of Anakinra may be due to an increase in the expression of HSP70 during the blockade of IL-1, as well as the activation of redox-sensitive transcription factors AP-1, NF-κB and NF-1, which increase the expression of GPX [52]. Anakinra has some unique advantages over other biological medications blocking IL-1. Anakinra has demonstrated an excellent safety profile in long-term use in patients of all ages [53,54,55,56]. The short half-life of Anakinra allows flexible dosing and reduces excessive immunosuppression. In addition, rapid elimination of the drug after discontinuation allows for more effective control of adverse effects, such as hepatotoxicity, particularly in critically ill patients [57].

Conclusions

1. Based on the conducted molecular-biochemical and clinical studies, it was established that additional inclusion of the IL-1β receptor antagonist (Anakinra, 1 mg/day, 5 sessions of electrophoresis) is effective in the treatment of chronic generalized periodontitis.

2. Additional inclusion of Anakinra in the complex treatment of CGP potentiates the anti-inflammatory effect of therapy, such as a decrease in MMP-2 ($p < 0.05$) compared to the indicators of patients in the control group.

3. The inclusion of Anakinra led to the development of an antioxidant effect during complex therapy of CGP characterized by a decrease in nitrotyrosine levels, an increase in the activity of GR and GPX ($p < 0.05$) compared to the data of patients in the control group, and an anti-ischemic effect characterized by a decrease in LDH levels and an increase in SDH concentration ($p < 0.05$) compared to the values of patients with CGP in the control group.

4. Additional inclusion of Anakinra led to a decrease in iNOS expression, and an increase in eNOS expression ($p < 0.05$) compared to the data of patients in the control group.

Prospects for further research. The results obtained demonstrate a promising strategy of pharmacological blockade of IL-1β, which may have new prospects for the treatment of patients with CGP.

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