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# THE COURSE OF RHEUMATIC DISEASES ASSOCIATED WITH CORONAVIRUS INFECTION

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**Abstract:**

The main pathophysiological mechanisms underlying the potential use of anti-rheumatic therapy in case of the new coronavirus infection COVID-19 in patients with rheumatic diseases (RD) are described, as well as current data on the risk and outcome of COVID-19 in patients with systemic autoimmune diseases are summarized in the overview of the article. Currently there are no wide range of randomized trials studying the use of antirheumatic medication in patients with RD associated with a new coronavirus infection. Besides, there is no convincing evidence that any disease-modifying anti-rheumatic medication (usually synthetic, biological or targeted synthetic) can prevent the progress of severe course of COVID-19. At the same time, the relevance of accompanying pathology (arterial hypertension, obesity, cardiovascular diseases, diabetes mellitus) and risk factors (smoking) are shown in the progress of a severe course of a new coronavirus infection in patients with RD. The article presents possible options for initiation and continue therapy with antirheumatic medication in patients with RD, depending on the stage of the infectious process.

**Keywords:** COVID-19, rheumatic diseases, disease-modifying anti-rheumatic medication, interleukin, tumor necrosis factor, glucocorticosteroids.

## PREAMBLE.

Rheumatic diseases (RD) are a large group of inflammatory and degenerative-metabolic diseases of various descent, affecting all structures including connective tissue: joints, cartilage, bones, periarticular tissues, as well as vessels, internal organs, often skin and mucous membranes, and carrying, as a rule, systemic feature, less often — local nature.

Rheumatic diseases take a significant place in the structure of the general morbidity of the population in all countries of the world, including Uzbekistan. The number of new cases of inflammatory and degenerative joint diseases, including systemic connective tissue diseases (SDCT), is growing every year [1].

Rheumatic diseases include more than 80 diseases and syndromes, but the medical, social and economic burden on society is primarily associated with diseases such as rheumatoid arthritis, spondyloarthritis, SDCT, gout and osteoarthritis [2].

It is known that the pathology of the musculoskeletal system is among the main causes of temporary disability, taking the 2nd-3rd place in terms of duration and number of cases of disability among all classes of diseases registered by official statistics, and the share of disability due to RD in the structure of general disability is about 10% [3]. Despite the high prevalence of RD, the etiology of these diseases is still poorly understood. The role of trigger factors in the progress of RD is attributed to various infectious agents. At the same time, the use of immunosuppressive medication is associated with a high risk of infectious complications.

However, despite the long-standing close relationship between rheumatic and infectious diseases, the issue of this interaction remains understudied today. Over the millennia, epidemics have changed the history of mankind. The plague, smallpox, and the Spanish flu covered the world centuries ago, claimed hundreds of millions of lives. In the XXI century, humanity faced a pandemic of viral infection, which had its global impact not only on the world economy, but also changed the course and prognosis of many diseases, including rheumatic ones.

The COVID-19 coronavirus infection pandemic (coronavirus disease 2019, formerly known as 2019—nCoV) caused by the SARS-CoV-2 virus began in December 2019 in Hubei Province of the People's Republic of China, and on January 30, 2020, the WHO Emergency Committee declared a global health emergency [4].

Coronaviruses are positive single—stranded large enveloped RNA-containing viruses that were first described in 1966 by Tyrell and Bynoe as pathogens of acute respiratory infections [5]. There are four subfamilies of coronaviruses: alpha-, beta-, gamma- and delta-coronaviruses. SARS-CoV-2 refers to beta-coronaviruses. COVID-19 is an infectious disease accompanied by severe acute respiratory syndrome. SARS-CoV-2 mainly affects the lungs and under certain circumstances leads to excessive immune activation and

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cytokine response mainly in the alveolar structures of the lungs [6].

The key role of the new coronavirus infection in the development of severe consequences is associated with uncontrolled hyperproduction of cytokines, which are peptide mediators of an immune nature. Cytokines do not function as individual molecules, but as a system of interconnected mediators. The effects of cytokines are not unique, they interact. The universality of the cytokine network consists in the fact that most cell types of both innate (macrophages, monocytes) and adaptive (T-helper) immunity are capable of producing cytokines, and all cells of the body have specific receptors. Each cytokine has its own receptor. For some of them, there are high-affinity and low-affinity receptors. In infectious diseases, each pathogen has pathogenicity patterns, which, interacting with the corresponding receptor formations (Toll-like receptors) on immunocompetent cells, activate the expression of cytokine genes, after which the process of cell production of these mediators immediately begins. Thus, IL-6, IL-1β and TNF-α have the most pronounced systemic effects. Systemic effects on the body of elevated concentrations of TNF-α, IL-1 (the synthesis of which is induced by TNF-α) and IL-6 are manifested by symptoms such as fever, sleepiness, and an increase in the threshold of pain sensitivity. TNF-α in high concentrations is the cause of septic shock and initiates the collapse and development of disseminated intravascular coagulation, activates catabolism processes, induces synthesis of acute phase proteins by liver cells, suppresses the division of hematopoietic stem cells, leads to the development of lymphopenia. IL-1ß stimulates the secretion of corticotropin-releasing factor in the paraventricular nucleus of the hypothalamus, which increases the production of adrenocorticotropic hormone by the pituitary gland, and that in turn initiates the release of glucocorticoid hormones from the cells of the adrenal cortex into the blood, which ultimately leads to inhibition of the expression of interleukin genes in cells. Corticosteroids can also lead to a change in the balance between Th1 and Th2 subpopulations towards the predominance of Th2 cells, which contributes to a more demonstrable humoral response [7].

Currently, the response of the innate immune system in SARS-CoV-2-infected patients has not been sufficiently studied. One of the important manifestations of activation of innate immunity in COVID-19 is an increase in the number of neutrophils, an increase in the concentration of IL-6 and C-reactive protein in blood serum [8]. Lymphocytopenia is a specific quality of the severe form of COVID-19 [9]. COVID-19 is characterized by a high level of production of proinflammatory cytokines: IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, GM–CSF, etc., as well as chemokines. Such an excess cytokine reaction observed in SARS-CoV-2-infected patients has been called a "cytokine storm". These cytokines and chemokines recruit effector immune cells, which leads to the development of an inflammatory response. A very important feature of the severe forms of COVID-19 is the reduction of IL-10 production [10].

"Cytokine storm" causes the development of acute respiratory distress syndrome and multiple organ failure in severe SARS-CoV-2 infection, which leads to a fatal outcome [10-12]. In severe COVID-19, there is hyperproduction of cytokines such as IL-1β, IL-6, TNF-α.The relationship between the high level of IL-6 in serum and the risk of fatal outcome of the disease was revealed [13]. The development of SARS-CoV-2 infection is accompanied by excessive activation of cellular immunity, as indicated by an increase in the representation of cells expressing HLA-DR and CD38 [14], against the background of a reliable decrease in the population of CD4+ T cells and NK cells in the peripheral blood of patients. It is suggested that particularly the decrease in CD4+ T-cell content is a characteristic feature of COVID-19 [15, 16]. The level of cytotoxic CD38+HLA-DR+CD8+ T cells increases starting from day 7 and decreases only 3 weeks after the onset of the disease. Cytotoxic CD8+ T cells in COVID-19 produce a large amount (34-54% more than in healthy people) of granzymes A and B and perforin. It is believed that a fairly rapid increase in the population of cytotoxic CD38+HLA-DR+CD8+ T cells by the 7th-9th day of the disease contributes to sanogenesis in COVID-19 [17].

Patients with COVID-19 have a high content of pro-inflammatory Th17 cells. Excessive Th17 cell activation and extremely high levels of CD8+ T cell cytotoxicity underlie the severity of immune tissue damage. In patients with COVID-19, the Tcup cell pool is depleted, which leads to the development of excessive activation of inflammatory processes and slowing down process of recovery [18].

Thus, the structure of proinflammatory cytokines induced in COVID-19 is similar to those cytokines that form the basis of the pathological process in RD

**PURPOSE:** To assess the possible adverse effect of a new coronavirus infection on the course of RD.

**MATERIAL AND METHODS:** The literature search in the electronic databases PubMed, Scopus and Web of Science was conducted up to October 1, 2020. The terms "COVID-19", "rheumatic diseases", disease-modifying anti-rheumatic drugs", "glucocorticoids" or "corticosteroids" were used in order to identify relevant publications. The articles were initially selected by their title and annotation, and then the full text was searched for the relevant relevant content. Articles without access

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to the full text, articles in other languages, as well as articles that do not meet the objectives of the analysis were excluded from the study.

**RESULTS:** During the search in PubMed, Scopus and Web of Science systems, a total of 233 links were obtained, 73 full-text articles were selected from them, in which the experience of treating patients with RD associated with COVID-19 and the effect of this treatment on the course of RD were analyzed. Thus, the largest study to date initiated by the Global Rheumatology Alliance (Global Rheumatology Alliance) included 600 patients with RD from 40 countries of the world. The most common diseases were rheumatoid arthritis (38%), spondyloarthritis (20%), systemic lupus erythematosus (14%) and other diseases, including vasculitis and Sjogren's syndrome (33%). The medications included synthetic disease—modifying antirheumatic drugs (csDMARDs) — 48%, biological disease-modifying antirheumatic drugs (bDMARDs) - 29%, targeted disease-modifying antirheumatic drugs (tsDMARDs) - 4% and glucocorticosteroids (GCS) - 27%. Concomitant diseases included hypertension — in 33% of patients, lung diseases — in 21%, diabetes — in 12%, cardiovascular diseases - in 11% and chronic renal failure — in 7% of patients [19].

The authors of many other studies also emphasized the significance of accompanying pathology, in particular hypertension, obesity, cardiovascular diseases, diabetes mellitus and risk factors (smoking), in the development of a severe course of a new coronavirus infection in patients with RS. Most of the articles studied demonstrate a high frequency of hospitalizations and adverse outcomes (artificial ventilation, death) in patients taking GCS more than 10 mg/day (in terms of prednisone), compared with those receiving basic antirheumatic therapy without GCS. E.G. Favalli et al. [20], having examined 955 patients (531 patients with rheumatoid arthritis, 203 with psoriatic arthritis, 181 with spondyloarthritis and 40 patients with CST and vasculitis), concluded that the frequency of confirmed cases of COVID—19 in this category of patients corresponded to that in the general population (0.62% vs. 0.66%, p=0.92).

K.M. D'Silva et al. [21] conducted a cohort study of patients included in the TriNetX research Network (a large Federal healthcare Research Network that updates electronic medical records data in real time, including demographics, diagnoses, procedures, medications, laboratory indicators and vital statuses, and represents more than 52 million people from 35 medical organizations) [21]. In the study, the authors showed that in patients with RD, congestive heart failure as a complication of coronavirus infection occurs in 6.8% of cases versus 2.2% of cases in the control group, but at the same time, mortality rates, although numerically higher among patients with RD, did not reach statistical value in comparison with the control group.

Thus, the presence of cardiovascular diseases is an unfavorable prognostic factor for the severe course of a new coronavirus infection. This may be due to systemic atherosclerosis, which is the basis of coronary heart disease, hypertension, heart failure. Atherosclerosis, like immuno-inflammatory diseases, is closely associated with a chronic inflammatory process involving the main cytokines: IL-6, IL-1ß and TNF-α.Hyperproduction of these cytokines in a new coronavirus infection most likely leads to destabilization of the atherosclerotic plaque and the development of complications of atherosclerosis (myocardial infarction, decompensation of heart failure), which ultimately leads to a severe course of this infection.

Another independent factor in the severe course of the new coronavirus infection is obesity, which is associated with an imbalance of adipokines. Adiponectin has a number of anti-atherosclerotic and anti-inflammatory properties, and also has a protective effect on the vascular endothelium [17]. Leptin has properties opposite to adiponectin. Some studies have shown that visceral obesity is specifically associated with low serum adiponectin levels, and suggested that this association is actually due to the production of more TNF-α and IL-6 and less adiponectin [22]. In addition, an inverse correlation was previously reported between circulating levels of TNF-α and adiponectin in obese and diabetic patients [23], assuming that TNF-α and, probably, IL-6 among other cytokines have a suppressive effect on adipocyte production of adiponectin [24].

Thus, inhibition of these cytokines in the treatment of RH prevents the development of instability of atherosclerotic plaque, suppresses excess production of TNF-α and IL-6 in obesity and, accordingly, contributes to a more favorable outcome of a new coronavirus infection. Immune mechanisms probably play an important role in the pathogenesis of COVID-19. MERS-CoV-2 infection can potentially cause the development of autoimmune processes in susceptible patients as a result of cross-reactivity of the virus with autoantigens [25, 26].

Data from recent small studies indicate the presence of antibodies against nuclear antigens in severe COVID-19 in a high titer, which were found in most patients of the intensive care unit in countries such as Germany and China [27, 28]. Coagulopathy observed in patients with COVID-19 raises concerns that antiphospholipid antibodies produced in this pathology may play a role in initiation of the autoimmune reactions in the body [29]. The production of antinuclear antibodies is characteristic of a number of autoimmune diseases [30], however, these antibodies can also be

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produced in acute diseases of various etiologies, including infectious ones [31, 32].

In most published sources, there are reports of the autoantibodies existance in the acute period of coronavirus infection, however, in the literature there are no data on the presence of autoantibodies in the postcovid period after the elimination of the virus from the body. This circumstance requires further study of the reactivity of the macroorganism after a new coronavirus infection [33].

**DISCUSSION:** The concern of RD is highly relevant at the present time due to the constant increase in morbidity, which may be associated with an increase in life expectancy, an increase in the influence of adverse environmental factors, smoking, exposure to viruses, including, possibly, SARS-CoV-2. Nowadays, the recommendations for the treatment of patients with RD are well known, but there is no conclusive data on the therapy of such patients on the background of COVID-19.

Thus, the similarity of the pathogenesis of a new coronavirus infection and RD, consisting in the presence of a syndrome of hyperproduction of proinflammatory cytokines, makes it reasonable to use genetically engineered biological drugs (GIBP) to suppress the "cytokine storm" developing in this category of patients. The cytokine hyperproduction syndrome observed in a new coronavirus infection contributes to the development of serious complications, such as pneumonia with respiratory insufficiency, acute respiratory distress syndrome, infectious and toxic shock. The use of traffic police in patients with and without RD should be aimed at preventing the development of cytokine hyperproduction syndrome, which occurs both as a result of the underlying disease and on the background of COVID-19.

The new coronavirus infection has a certain clinical stage of the infectious process and at the first stages is characterized by direct viral exposure without the development of a "cytokine storm", therefore, the effect of GEBT during this period on the course of the disease has not been adequately studied. The analysis of the literature has shown that taking basic antirheumatic drugs does not affect the body's susceptibility to a new coronavirus infection, a possible exception to this are drugs from the group of JAK kinase inhibitors (probably due to blocking receptor-mediated endocytosis of the virus into alveolar epithelial cells of the lungs) [34, 35]. The phase of the inflammatory response (with a new coronavirus infection) is started only by the end of the 1st week of the disease, followed by the development of a hyperinflammatory reaction by the end of the 2nd week. Most likely, it is advisable to use GEBP in patients with COVID-19 on the background of acute respiratory infections and without RD at the end of the period of direct viral impact.

At present, information about the epidemiology, clinical features, prevention and treatment of COVID-19 in patients with rheumatic pathology is limited. The traditional method of obtaining the necessary information by using data from previously performed scientific studies has proved ineffective, since the experience of treating patients with a new coronavirus infection is measured in just a few months. Moreover, the epidemiological process remains incomplete today, since collective immunity has not been formed and the issues of tension and resistance of immunity have not been studied. Thus, questions concerning the peculiarities of the development and course of COVID-19 in people with RD, due to the small number of studies, remain poorly studied.

**SUMMARY:** In order to better understand the interdependence of RD and COVID-19 coronavirus infections it is necessary to conduct further researches on:

-The ability of COVID-19 to induce the development of RD;

--The impact of COVID-19 on the course of MS in patients receiving GEBT;

-The possibility of continuing therapy with GEBP in patients with mixed CTD affected by the COVID-19 and in the post-covid period.

1.

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