Pathophysiological Mechanisms of Rheumatic Diseases Due to Covid-19 Infection

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ABSTRACT

The article describes the main pathophysiological mechanisms underlying the potential use of antirheumatic therapy in the new COVID-19 in patients with rheumatic diseases. Also, it summarizes current data on the risk and outcome of COVID-19 in patients with systemic autoimmune diseases. To date, there are no large randomized studies on the use of antirheumatic drugs in patients with rheumatic diseases in the setting of COVID-19. Besides, there is no convincing evidence that any disease-modifying antirheumatic drug (conventional synthetic, biological, or targeted synthetic) can prevent the development of a severe COVID-19 course. At the same time, the importance of concomitant pathology (hypertension, obesity, cardiovascular diseases, diabetes mellitus) and risk factors (smoking) in the development of a severe COVID-19 course in patients with rheumatic diseases is shown. The article presents possible options for initiating and continuing treatment with antirheumatic drugs in pa tients with rheumatic diseases, depending on the stage of the infectious disease process.

Keywords: COVID-19, rheumatic diseases, disease-modifying antirheumatic drug, interleukin, tumor necrosis factor, glucocorticosteroids.

Introduction. Rheumatic diseases (RD) are a large group of inflammatory and degenerative-metabolic diseases of various origins that affect all structures, including connective tissue: joints, cartilage, bones, periarticular tissues, as well as blood vessels, internal organs, often skin and mucous membranes. , and wearing, as a rule, systemic, less often - local in nature.

Rheumatic diseases occupy a significant place in the structure of the general morbidity of the population in all countries of the world, including in Uzbekistan. Every year, the number of new cases of inflammatory and degenerative diseases of the joints, including systemic connective tissue diseases (CCTD) is growing [1, 2].

Rheumatic diseases include more than 80 diseases and syndromes, but the medical, social and economic burden on society is primarily associated with such diseases as rheumatoid arthritis, spondyloarthritis, CTD, gout and osteoarthritis [3].

It is known that the pathology of the musculoskeletal system is among the main causes of temporary disability, ranking 2-3rd in terms of duration and number of cases of disability among all classes of diseases registered by official statistics, and the proportion of disability due to RD in the structure of general disability is about 10% [19].

Despite the high prevalence of RD, the issue of the etiology of these diseases is still poorly understood. The role of trigger factors in the development of RD is attributed to various infectious agents. At the same time, the use of immunosuppressive drugs 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 poorly understood today. For millennia, epidemics have changed human history. Plague, smallpox, flu "Spanish flu" that swept the world centuries ago, claimed hundreds of millions of

lives. In the 21st century humanity is faced with a pandemic of a viral infection, which has had its global impact not only on the world economy, but also changed the course and prognosis of many diseases, including rheumatic diseases.

The COVID-19 pandemic (coronavirus disease 2019, formerly 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 announced global health emergency [19].

Coronaviruses are positive single-stranded large enveloped RNA viruses that were first described in 1966 by Tyrell and Bynoe as the causative agents of acute respiratory infections [44]. There are four subfamilies of coronaviruses: alpha, beta, gamma and delta coronaviruses. SARS-CoV-2 belongs to the betacoronaviruses. COVID-19 is an infectious disease associated with severe acute respiratory syndrome. SARS-CoV-2 predominantly affects the lungs and, under certain circumstances, leads to excessive immune activation and a cytokine response predominantly in the alveolar structures of the lungs [14].

The key role of the new coronavirus infection in the development of severe consequences is associated with the uncontrolled hyperproduction of cytokines, which are peptide mediators of the immune nature. Cytokines do not function as separate molecules, but as a system of interrelated mediators. The effects of cytokines are not unique, they overlap. The universality of the cytokine network lies in the fact that most cell types of both innate (macrophages, monocytes) and adaptive (T-helper) immunity are capable of producing cytokines, and all body cells have specific receptors. Each cytokine has its own receptor. Some of them have high-affinity and low-affinity receptors. In infectious diseases, each pathogen has pathogenicity patterns that, interacting with the corresponding receptor formations (Toll-like receptors) on immunocompetent cells, activate the expression of cytokine genes, after which the process of production of these mediators by the cells immediately begins. Thus, IL-6, IL-1β and TNF-α have the most pronounced systemic effects. Systemic exposure of the body to elevated concentrations of TNF-α, IL-1 (the synthesis of which is induced by TNF-α) and IL-6 is manifested by symptoms such as fever, drowsiness, and an increase in pain sensitivity threshold. TNF-α in high concentrations causes the development of septic shock and initiates collapse and the development of disseminated intravascular coagulation, activates catabolism processes, induces the synthesis of acute phase proteins by liver cells, suppresses the division of hematopoietic stem cells, and leads to the development of lymphopenia. IL-1β 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, which in turn initiates the release from the cells of the adrenal cortex into the blood l glucocorticoid hormones, which ultimately leads to inhibition of the expression of interleukin genes in cells. Also, corticosteroids can lead to a change in the balance between Th1 and Th2 subpopulations towards the predominance of Th2 cells, which contributes to a more pronounced humoral response [32].

Currently, the response of the innate immune system in SARS-CoV-2-infected patients is not well understood. One of the important manifestations of innate immunity activation in COVID-19 is an increase in the number of neutrophils, an increase in the concentration of IL-6 and C-reactive protein in the blood serum [30]. Lymphocytopenia is a characteristic feature of severe COVID-19 [31]. COVID-19 is characterized by a high level of production of pro-inflammatory cytokines: IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, GM–CSF, etc., and also chemokines. This excessive cytokine response, seen in SARS-CoV-2-infected patients, has been termed 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 severe forms of COVID-19 is the decrease in IL-10 production [34].

"Cytokine storm" causes the development of acute respiratory distress syndrome and multiple organ failure in severe SARS-CoV-2

infection, which leads to death [25,33,34]. In severe COVID-19, there is an overproduction of cytokines such as IL-1β, IL-6, TNF-α. An association between a high level of IL-6 in serum and the risk of a lethal outcome of the disease was revealed [33]. The development of SARS-CoV-2 infection is accompanied by excessive activation of cellular immunity, as evidenced by an increase in the representation of cells expressing HLA-DR and CD38 [17], against the background of a significant decrease in the population of CD4+ T cells and NK cells in the peripheral blood of patients. It has been suggested that it is the decrease in the content of CD4+ T cells that is a characteristic feature of COVID-19 [19,26]. The level of cytotoxic CD38+HLA-DR+CD8+ T cells increases starting from the 7th day and decreases only after 3 weeks. after the onset of the disease. Cytotoxic CD8+ T cells in COVID-19 produce large amounts (34–54% more than in healthy individuals) 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 [14].

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 pool of Treg cells is depleted, which leads to the development of excessive activation of inflammation processes and a slowdown in the resolution of the inflammatory process [19].

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

The purpose of the review: to assess the possible adverse impact of a new coronavirus infection on the course of RD.

Material and Methods: Literature searches were conducted through PubMed, Scopus, and Web of Science electronic databases until October 1, 2020. Use of the terms “COVID-19”, “rheumatic diseases”, “glucocorticoids”, disease-modifying antirheumatic drugs” or “corticosteroids” to identify relevant publications. Articles were initially selected by their title and abstract, and then the full text was searched for relevant relevant content. Articles without access to the full text, articles in other languages, and articles that did not meet the goals of the analysis were excluded from the study.

Results: During the search in PubMed, Scopus and Web of Science systems, a total of 233 references were obtained, of which 73 full-text articles were selected, which analyzed the experience of treating patients with RD on the background of COVID-19 and the impact of this treatment on the course of RD. Thus, the largest study to date, initiated by the Global Rheumatology Alliance, included 600 patients with RD from 40 countries. The most common diseases were rheumatoid arthritis (38%), spondyloarthritis (20%), systemic lupus erythematosus (14%) and other diseases, including vasculitis and Sjögren's syndrome (33%). 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%. Comorbidities included hypertension in 33% of patients, lung disease in 21%, diabetes in 12%, cardiovascular disease in 11%, and chronic renal failure in 7% of patients [36].

Many other studies have also emphasized the importance of accompanying pathology, in particular arterial 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 RD. Most of the articles studied demonstrate a higher incidence of hospitalizations and adverse outcomes (artificial lung ventilation, death) in patients taking corticosteroids more than 10 mg / day (in terms of prednisolone), compared with people receiving basic antirheumatic therapy without corticosteroids. E.G. Favalli et al. [24], examining 955 patients (531 patients with rheumatoid arthritis, 203 with psoriatic arthritis, 181 with spondyloarthritis, and 40 patients with CTD 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).

D'Silva K.M. et al. [21] conducted a cohort study of patients enrolled in the TriNetX research network (a large Federated Health Research Network that updates electronic health record data in real time, including demographics, diagnoses, procedures, medications, laboratory values, and vital statuses, and presents more 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 against 2.2% of cases in the control group, but at the same time, mortality rates, although they were numerically higher among patients with RD, did not reach statistical significance 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 underlies coronary heart disease, hypertension, and heart failure. Atherosclerosis, like immunoinflammatory diseases, is closely associated with a chronic inflammatory process involving major cytokines: IL-6, IL-1β, and TNF-α. Hyperproduction of these cytokines in a new coronavirus infection most likely leads to destabilization of 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 a 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 [14]. Leptin has opposite properties 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 [7]. In addition, an inverse correlation between circulating levels of TNF-α and adiponectin has been previously reported in obese and diabetic patients [23], suggesting that TNF-α and probably IL-6 among other cytokines have a suppressive effect on adipocyte production of adiponectin [27].

Thus, inhibition of these cytokines in the treatment of RD prevents the development of atherosclerotic plaque instability, suppresses the excessive production of TNF-α and IL-6 in obesity, and, accordingly, contributes to a more favorable outcome of a new coronavirus infection. Immune mechanisms likely play an important role in the pathogenesis of COVID-19. SARS-CoV-2 infection can potentially provoke the development of autoimmune processes in susceptible patients as a result of cross-reactivity of the virus with self-antigens [13,36]. Data from recent small studies suggest the presence of high titer antibodies against nuclear antigens in severe COVID-19, which have been found in most intensive care unit patients in countries such as Germany and China [8,10]. The coagulopathy observed in patients with COVID-19 raises concerns that antiphospholipid antibodies produced in this pathology may play a role in triggering autoimmune reactions in the body [12]. The production of antinuclear antibodies is characteristic of a number of autoimmune diseases [16], however, these antibodies can also be produced in acute diseases of various etiologies, including infectious ones [6,9].

In most published sources, there are reports of the presence of autoantibodies in the acute period of coronavirus infection, however, there are no data in the literature on the presence of autoantibodies in the post-COVID period after elimination of the virus from the body. This circumstance requires further study of the autoreactivity of the macroorganism after a new coronavirus infection [35].

Discussion: The problem of RH is very relevant at the present time time due to the constant increase in the incidence, 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. To date, recommendations for the treatment of

patients with RD are well known, but there are no convincing data on the treatment of such patients against the background of COVID-19.

Thus, the similarity of the pathogenesis of a new coronavirus infection and RD, which consists in the presence of a syndrome of hyperproduction of pro-inflammatory cytokines, makes it reasonable to use genetically engineered biological drugs (GEBDs) to suppress the "cytokine storm" that develops 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 failure, acute respiratory distress syndrome, and infectious toxic shock. The use of GIBT 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 against the background of COVID-19.

A new coronavirus infection has a certain clinical staging of the infectious process and in the first stages is characterized by direct viral exposure without the development of a "cytokine storm", therefore, the effect of GIBT during this period on the course of the disease has not been adequately studied. The analysis of the literature showed that the use of 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 the receptor-mediated endocytosis of the virus into the alveolar epithelial cells of the lungs) [11.39]. The inflammatory response phase (with a new coronavirus infection) starts only by the end of the 1st week of the disease, followed by the development of a hyperinflammatory response by the end of the 2nd week. It is most likely that it is advisable to use GIBP in patients with COVID-19 on the background of RD and without RD after the end of the period of direct viral exposure.

Data on the epidemiology, clinical features, prevention, and treatment of COVID-19 in patients with rheumatic disease are currently limited. The traditional way of obtaining the necessary information by drawing on data from previous scientific studies has proven to be 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 the intensity and stability of immunity have not been studied. Thus, issues related to the features of the development and course of COVID-19 in people with RD, due to the scarcity of studies, remain poorly understood.

Conclusions: Further research is required to better understand the relationship between RH and COVID-19:

-Possibility of COVID-19 to induce the development of RD;

- Influence of COVID-19 on the course of RD in patients receiving GIBT;

- Possibilities of continuing therapy with GEBA in patients with CTD against the background of COVID-19 and in the post-COVID period.

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