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Anti-Rheumatic Therapy for Patients with Systemic Autoimmune Diseases Due to Covid-19

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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 (RDs) are a large group of inflammatory and degenerative-metabolic diseases of different origin, affecting all structures that include connective tissue: joints, cartilage, bones, periarticular tissues, as well as blood vessels, internal organs, often skin and mucous membranes, and are usually systemic, less often local.

Rheumatic diseases occupy a significant place in the structure of the general morbidity of the population in all countries of the world, including Uzbekistan.

Every year, the number of new cases of inflammatory and degenerative joint diseases, including systemic connective tissue diseases (CVTD), 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 diseases such as rheumatoid arthritis, spondyloarthritis, CFST, gout and osteoarthritis [3].

It is known that pathology of the musculoskeletal system is one of the main causes of temporary disability, ranking 2nd–3rd 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 RH in the structure of general disability is about 10% [19]. Despite the high prevalence of RH, the etiology of these diseases is still poorly understood. The role of triggering factors in the development of RH 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 studied to date. For thousands of years, epidemics have changed the history of mankind. The plague, smallpox, and 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 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 declared a global health emergency [19].

Coronaviruses are positive, single-stranded, large enveloped RNA-containing viruses that were first described in 1966. Tyrell and Bynoe as causative agents of acute respiratory infections [44]. There are four subfamilies of coronaviruses: alpha, beta, gamma, and delta coronaviruses. SARS-CoV-2 is a beta coronavirus. COVID-19 is an infectious disease accompanied by severe acute respiratory syndrome. SARS-CoV-2 predominantly affects the lungs and, under certain circumstances, leads to excessive immune activation and 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 an immune nature. Cytokines do not function as separate molecules, but as a system of interconnected neurotransmitters. The effects of cytokines are not unique, they overlap. The versatility of the cytokine network lies in the fact that most cell types of both innate (macrophages, monocytes) and adaptive (T-helper) immunity are able to produce 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 exposure 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 increased pain sensitivity threshold. TNF-α in high concentrations causes the development of septic

shock and initiates the collapse and development of disseminated intravascular coagulation, activates catabolism processes, induces the synthesis of acute phase proteins by liver cells, inhibits 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 of glucocorticoid hormones from the cells of the adrenal cortex into the blood, which ultimately leads to the inhibition of the expression of interleukin genes in cells. Corticosteroids can also lead to a change in the balance between the 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 activation and 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 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 inflammatory 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 excessive cytokine reaction observed in SARS-CoV-2-infected patients is 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 severe forms of COVID-19 is a decrease in the production of IL-10 [34].

The "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. A correlation has been found between high serum levels of IL-6 and the risk of lethal outcome of the disease [33]. The development of SARS-CoV-2 infection is accompanied by excessive activation of cellular immunity, which is There is 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 a decrease in CD4+ T cell counts is a characteristic feature of COVID-19 [19,26]. The level of cytotoxic CD38+HLA+DR+CD8+ T cells increases from day 7 and decreases only after 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 days 7–9 of the disease contributes to sanogenesis in COVID-19 [14].

Patients with COVID-19 have a high content of inflammatory Th17 cells. The overactivation of Th17 cells and the extremely high level of cytotoxicity of CD8+ T cells underlie the severity of immune tissue damage. In patients with COVID-19, there

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

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

Purpose of the review: assess the possible adverse impact of the novel coronavirus infection on the course of RH.

Patients and Methods:

Literature search in the electronic databases PubMed, Scopus and Web of Science was carried out until October 1, 2020. Use of the terms "COVID-19", "rheumatic diseases", "glucocorticoids", disease-modifying antirheumatic drugs" or "corticosteroids" in order to identify relevant publications. The articles were first selected by their title and annotation, and then the full text was searched for relevant relevant content. From Studies were excluded from articles without access to the full text, articles in other languages, as well as articles that did not correspond to the objectives of the analysis.

Results:

A total of 233 references were obtained during the search in PubMed, Scopus and Web of Science, of which 73 full-text articles were selected, which analyzed the experience of treating patients with RH against the background of COVID-19 and the impact of this treatment on the course of RH. For example, the largest study to date, initiated by the Global Rheumatology Alliance, included 600 patients with RH 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%). Medicines included synthetic disease-modifying antirheumatic drugs (csDMARDs) (48%), biologic disease-modifying antirheumatic drugs (bDMARDs) (29%), targeted disease-modifying antirheumatic drugs (tsDMARDs) (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]. The authors of many other studies have also emphasized the importance of comorbidities, in particular arterial hypertension, obesity, cardiovascular diseases, diabetes mellitus and risk factors (smoking), in the development of a severe course of new coronavirus infection in patients with RH. Most of the articles studied demonstrate a greater incidence of hospitalization and adverse outcomes (mechanical ventilation, death) in patients taking corticosteroids greater than 10 mg/day (based on prednisolone) compared with those receiving basic antirheumatic therapy without corticosteroids. E.G. Favalli et al. [24], having examined 955 patients (531 patients with rheumatoid arthritis, 203 patients with psoriatic arthritis, 181 patients with spondyloarthritis, and

40 patients with CVCT and vasculitis), concluded that the incidence of confirmed cases of COVID-19 in this category of patients was consistent with 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 the 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 parameters, and vital statuses, and represents more than 52 million people from 35 medical organizations) [21]. In the study, the authors showed that congestive heart failure as a complication of coronavirus infection occurs in 6.8% of patients with RH versus 2.2% of cases in the control group, but at the same time, mortality rates, although they were numerically higher among patients with RH, did not reach statistical significance in comparison with the control group.

Thus, the presence of cardiovascular diseases is an unfavorable prognostic factor for a 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 related to the chronic inflammatory process involving the main cytokines: IL-6, IL-1β and TNF-α. Overproduction 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 the new coronavirus infection is obesity, which is associated with an imbalance of adipokines. Adiponectin has a number of antiatherosclerotic and anti-inflammatory properties, and also has a protective effect on the vascular endothelium [14]. Leptin has the opposite properties to adiponectin. Some studies have shown that visceral obesity is specifically associated with low serum adiponectin levels, and have suggested that this association is actually due to the production of higher amounts of TNF-α and IL-6 and smaller amounts of adiponectin [7]. In addition, an inverse correlation between circulating levels of TNF-α and adiponectin in obese and diabetic patients has previously been reported [23], suggesting that TNF-α and probably IL-6 among other cytokines have a suppressive effect on adiponectin production by adipocytes [27].

Thus, the inhibition of these cytokines in the treatment of RH prevents the development of atherosclerotic plaque instability, suppresses the excess production of TNF-α and IL-6 in obesity and, accordingly, contributes to a more favorable outcome of the new coronavirus infection. Immune mechanisms likely play an important role in the pathogenesis of COVID-19. SARS-CoV-2 infection has the potential to provoke the development of autoimmune processes in susceptible patients as a result of cross-reactivity of the virus with autoantigens [13,36].

Recent small studies have shown the presence of antibodies against nuclear antigens in severe COVID-19 in high titer, which have been found in most intensive care unit

patients in countries such as Germany and China [8,10]. Coagulopathy observed in patients with COVID-19 raises concerns that the 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], but 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, but there are no data on the presence of autoantibodies in the post-COVID period after the elimination of the virus from the body in the literature. 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 present due to the constant increase in the incidence of the disease, which may be associated with an increase in life expectancy, an increase in the impact of adverse environmental factors, smoking, exposure to viruses, including, possibly, SARS-CoV-2. To date, recommendations for the treatment of patients with RH are well known, but there are no conclusive data on the treatment of such patients against the background of COVID-19.

Thus, the similarity of the pathogenesis of the new coronavirus infection and RH, which consists in the presence of a syndrome of hyperproduction of inflammatory cytokines, makes the use of genetically engineered biological drugs (GEBPs) to suppress the "cytokine storm" developing in this category of patients justified. The syndrome of cytokine overproduction observed in the new coronavirus infection contributes to the development of serious complications, such as pneumonia with respiratory failure, acute respiratory distress syndrome, infectious and toxic shock. The use of GIBT in patients with and without RH should be aimed at preventing the development of cytokine overproduction syndrome that occurs both as a result of the underlying disease and against the background of COVID-19.

The new coronavirus infection has a certain clinical stage of the infectious process and in the first stages is characterized by a direct viral impact without the development of a "cytokine storm", so the effect of GIBT during this period on the course of the disease has not been properly studied. An analysis of the literature showed that the intake of basic antirheumatic drugs does not affect the body's susceptibility to a new coronavirus infection, a possible exception to this is drugs from the group of JAK kinase inhibitors (probably due to blocking the receptor-mediated endocytosis of the virus in the alveolar epithelial cells of the lungs) [11,39]. The phase of the inflammatory response (in the case of a new coronavirus infection) starts 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 with and without RH after the period of direct viral exposure.

Currently, information on 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 proven to be ineffective, since the experience of treating patients with a new coronavirus infection is measured in only a few months. Moreover, the epidemiological process today remains incomplete, since herd immunity has not been formed and the issues of intensity and persistence of immunity have not been studied. Thus, issues related to the development and course of COVID-19 in people with RH remain poorly understood due to the paucity of studies.

Conclusions:

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

-The possibilities of COVID-19 will induce the development of RH;

- Effects of COVID-19 on the course of RH in patients receiving GIBT;

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

REFERENCES:

1. Балабанова Р.М., Эрдес Ш.Ф. Ревматические заболевания у взрослого населения в федералных округах России. Научно-практическая ревматология. 2014; 52(1):5–7. DOI: 10.14412/1995-4484-2014-5-7. [Balabanova R.M., Erdes S.F. Rheumatic diseases in the adult population in federal districts of Russia. Rheumatology Science and Practice. 2014; 52(1):5–7 (in Russ.)]. DOI: 10.14412/1995-4484-2014-5-7.
2. Gordeev A.V., Galushko E.A., Nasonov E.L. The Concept of Multimorbidity in Rheumatological Practice. Scientific and Practical Rheumatology. 2014; 52(4):362–365. DOI: 10.14412/1995-4484-2014-362-365. [Gordeev A.V., Galushko E.A., Nasonov E.L. The concept of multimorbidity in rheumatologic practice. Rheumatology Science and Practice. 2014; 52(4):362–365 (in Russ.)]. DOI: 10.14412/1995-4484-2014-362-365.
3. Kozlov V.K. Cytokine Therapy: Pathogenetic Orientation and Clinical Effectiveness in Infectious Diseases: A Guide for Doctors. St. Petersburg: AlterEgo; 2010. [Kozlov V.K. Cytokine therapy: pathogenetic focus and clinical efficacy in infectious diseases: a guide for physicians. SPb.: AlterEgo; 2010 (in Russ.)].
4. Nasonova V.A., Folomeeva O.M., Erdes Sh.F. Rheumatic diseases in Russia at the beginning of the XXI century. Scientific and Practical Rheumatology. 2003; 1:6–10. DOI: 10.14412/1995-4484-2003-1124. [Nassonova V.A., Folomeyeva O.M., Erdesz S.F. Rheumatic diseases in Russia at the beginning of XXI century.

Rheumatology Science and Practice. 2003; 41(1):6–10 (in Russ.)]. DOI: 10.14412/1995-4484-2003-1124.

5. Azadaeva K. E., Karimov M. Sh., Tukhtaeva N. Kh. Dyslipidemia in combination with dysbiosis of the gastroduodenal zone in patients with reactive arthritis / repository.tma.uz / 2022.
6. Caso F., Costa L., Ruscitti P. et al. Could Sars-coronavirus-2 trigger autoimmune and/or autoinflammatory mechanisms in genetically predisposed subjects? Autoimmun Rev. 2020;19:102524. DOI: 10.1016/j.autrev.2020.102524.
7. Cossarizza A., De Biasi S., Guaraldi G. et al. Modena Covid-19 Working Group (MoCo19). SARSCoV-2, the Virus that Causes COVID-19: Cytometry and the New Challenge for Global Health. Cytometry A. 2020; 97(4):340–343. DOI: 10.1002/cyto.a.24002.
8. D'Silva K.M., Serling-Boyd N., Wallwork R. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US "hot spot". Ann Rheum Dis. 2020; 79:1156–1162. DOI: 10.1136/annrheumdis-2020-217888.
9. Fasshauer M., Kralisch S., Klier M. et al. Interleukin-6 is a positive regulator of tumor necrosis factor alpha-induced adipose-related protein in 3T3-L1 adipocytes. FEBS Lett. 2004; 560:153–157. DOI: 10.1016/S0014-5793 (04) 00096-1.
10. Favalli E.G., Monti S., Ingegnoli F. et al. Incidence of COVID-19 in patients with rheumatic diseases treated with targeted immunosuppressive drugs: what can we learn from observational data? Arthritis Rheumatol. 2020; 72:1600–1606. DOI: 10.1002/art.41388.
11. Gagiannis D., Steinestel J., Hackenbroch C. et al. COVID-19-induced acute respiratory failure: an exacerbation of organ-specific autoimmunity? medRxiv. 2020. DOI: 10.1101/2020.04.27.20077180.
12. Gavrila A., Chan J.L., Yiannakouris N. et al. Serum adiponectin levels are inversely associated with overall and central fat distribution but are not directly regulated by acute fasting or leptin administration in humans: cross-sectional and interventional studies. J Clin Endocrinol Metab. 2003; 88:4823–4831. DOI: 10.1210/jc.2003-030214.
13. Gianfrancesco M., Hyrich K.L., Al-Adely S. et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020; 79(7):859–866. DOI: 10.1136/annrheumdis-2020-217871.
14. He F., Deng Y., Li W. Coronavirus disease 2019: What we know? J Med Virol. 2020; 10.1002/jmv.25766. DOI: 10.1002/ jmv.25766.
15. Im J.H., Chung M.H., Park Y.K. et al. Antinuclear antibodies in infectious diseases. Inf Disp. 2020; 52:177–185. DOI: 10.1080/23744235.2019.1690676.

16. Kern P.A., Di Gregorio G.B., Lu T. et al. Adiponectin expression from human adipose tissue: relation to obesity, insulin resistance, and tumor necrosis factor-alpha expression. Diabetes. 2003; 52:1779–1785.
17. Khasanova G.Kh. Best Practices in the Dietotherapy of Hypertension. Scientific Electronic Journal "Academic Journalism", No 12-2/2022 / https://aeterna-ufa.ru/sbornik/AP-2022-12-2.pdf.
18. Khasanova G.Kh., Tukhtayeva N.Kh.. Effect of Diet Therapy and Nutriceutic Support in Metabolic Syndrome in Women of Fertile Age. Galaxy International Interdisciplinary Research Journal. Feb 7, 2023, 11(2) / https://giirj.com/index.php/giirj/article/view/4763.
19. Li X., Geng M., Peng Y. et al. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm. 2020; 10(2):102–108. DOI: 10.1016/j.jpha.2020.03.001.
20. Litwin C.M., Binder S.R. ANA testing in the presence of acute and chronic infections. J Immunoassay Immunochem. 2016; 37(5):439–452. DOI: 10.1080/15321819.2016.1174136.
21. Liu J., Zheng X., Tong Q. et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol. 2020; 92(5):491–494. DOI: 10.1002/jmv.25709.
22. Liu Y., Yang Y., Zhang C. et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020; 63(3):364–374. DOI: 10.1007/ s11427-020-1643-8.
23. Qin C., Zhou L., Hu Z. et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis. 2020; 71(15):762–768. DOI: 10.1093/cid/ciaa248.
24. Ruan Q., Yang K., Wang W. et al. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020; 46(5):846–848. DOI: 10.1007/s00134-020-05991-x.
25. Schett G., Manger B., Simon D., Caporali R. COVID-19 revisiting inflammatory pathways of arthritis. Nat Rev Rheumatol. 2020; 16(8):465–470. DOI: 10.1038/s41584-020-0451-z.
26. Shi Y., Wang Y., Shao C. et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 2020; 27(5):1451–1454. DOI: 10.1038/s41418-020-0530-3.
27. Skilton M.R., Celermajer D.S. The effects of obesity-related peptides on the vasculature. Curr Vasc Pharmacol. 2006; 4(1):79–85. DOI: 10.2174/157016106775203135.
28. Tan E.M. Antinuclear antibodies: diagnostic markers for autoimmune diseases and probes for cell biology. Adv Immunol. 1989; 44:93–151.

29. Tukhtaeva N. Kh., Karimov M. Sh., Sibirkina M. V., Khabibullo T. Features of Helicobacter Pylori Genes in Nsaid Gastropathy in Patients with Rheumatoid Arthritis. Hunan University 48 (10). 2021.
30. Tukhtaeva N.Kh., Karimov M.Sh., Khasanova G.Kh. Changes in the Pharmacokinetics of Diclofenac in Rheumatological Patients Taking Complex Treatment. World Journal of Pharmaceutical and Medical Research. 2022, 12(7), 05.
31. Tukhtaeva N.Kh., Karimov M.Sh., Sibirkina M.V. Genotypical Features of Helicobacter Pylori in the Formation of Nsaid Gastropathies in Patients with Rheumatoid Arthritis. Eurasian Medical Research Periodical 8. 2022, 94-97.
32. Tukhtayeva N.Kh., Karimov M.Sh., Khasanova G.Kh. The degree of damage to the gastroduodenal zone in patients with rheumatoid arthritis on the background of basic and anti-inflammatory therapy. ScienceAsia 49 (2023). 2 Feb 2023 / doi:10.2307/scienceasia155-158.2023.SA156 / https://www.scopus.com/sourceid/4000151817.
33. Tyrrell D.A., Bynoe M.L. Cultivation of viruses from a high proportion of patients with colds. Lancet. 1966; 1(7428):76–77. DOI: 10.1016/s0140-6736 (66) 92364-6.
34. Velavan T.P., Meyer C.G. The COVID-19 epidemic. Trop Med Int Health. 2020; 25(3):278–280. DOI: 10.1111/tmi.13383.
35. Vojdani A., Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol. 2020;217:108480. DOI: 10.1016/j.clim.2020.108480.
36. Xu Z., Shi L., Wang Y. et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020; 8(4):420–422. DOI: 10.1016/S2213-2600 (20) 30076-X.
37. Zhang X., Zhang Y., Qiao W. et al. Baricitinib, a drug with potential effect to prevent SARS-COV-2 from entering target cells and control cytokine storm induced by COVID-19. Int Immunopharmacol. 2020; 86:106749. DOI: 10.1016/j.intimp.2020.
38. Zhang Y., Xiao M., Zhang S. et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med. 2020; 382:e38. DOI: 10.1056/NEJMc2007575.
39. Zhou Y., Han T., Chen J. et al. Clinical and autoimmune characteristics of severe and critical cases of COVID-19. Clin Trans Sci. 2020; 13(6):1077–1086. DOI: 10.1111/cts.12805.
40. Tukhtaeva N.Kh., Karimov M.Sh., Kurbanov A.K. (2021). Assessment of the gastrointestinal tract in patients with rheumatoid arthritis. European Journal of Pharmaceutical and Medical Research, 2(5), 34-37.
41. Mavlyanov, I. R., Mustafin, R. I., Tukhtaeva, N. Kh. (2012). Characteristics of luminal and parietal gastric microflora in patients with rheumatoid and reactive arthritis. Bulletin of New Medical Technologies, 19(2), 319-322.

42. Tukhtaeva, N.Kh., Mavlyanov, I.R., Mavlyanov, S.I. (2019). Types of the nervous system and its relationship with patients' compliance with the therapy. In Safe Sport 2019 (pp. 74-76).
43. Tukhtaeva, N. K. (2023). The degree of damage to the gastroduodenal zone in patients with rheumatoid arthritis against the background of basic and anti-inflammatory therapy. Texas Journal of Medical Science, 25, 58-62.
44. Xudayberganova, N.X., Rahmatullayeva, G. K. (2023). To assess the incidence of iron deficiency anemia and Helicobacter pylori infection among school-age children with chronic gastroduodenal pathology. European Scientific and Methodological Journal 1(8), 10-18.
45. Khudaiberganova, N. Kh., Akhmedova, I. M. (2023). Clinical and biochemical features of extragastric manifestations of helicobacter pylori associated gastroduodenal pathology in children.
46. Khudaiberganova, N. Kh., Akhmedova, I. M. (2023). The course of chronic gastroduodenal pathology in children and helicobacter pylor infection. Academic research in educational sciences, (1), 196-205.
47. Akhmedova, I. M., Khudaiberganova, N. Kh. (2022). Extragastric manifestations of chronic gastroduodenitis in children.
48. Khudaiberganova N. Kh., (May 2022). Clinical characteristics of Helicobacter pylori associated gastroduodenal pathology in children. Journal of new centure innovations. Volume -4.