REVIEWS

COVID-19: the new challenge for rheumatologists

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Currently, the infection caused by the new coronavirus COVID-19 is considered by the global community as an emergency of international concern. Rheumatologists are particularly concerned about this problem, since patients with immune-mediated inflammatory rheumatic diseases (IMIRDs) are at higher risk for infectious diseases and receive immunosuppressive treatment. The use of disease-modifying antirheumatic drugs and biological agents increases the incidence of serious infections, but insufficient/no monitoring of IMIRD activity is an even greater risk factor for infectious complications. In addition, the role of vaccination mainly against influenza and pneumococcal infection is substantially increasing in modern conditions, since the risk of death from respiratory tract infections is quite high in patients with IMIRDs, which is very important in the context of the current COVID-19 pandemic.
The paper presents an update on the incidence of viral infections in patients with IMIRDs and also discusses whether antirheumatic drugs can be used to treat COVID-19.

Keywords: *COVID-19; immune-mediated inflammatory rheumatic diseases; nonsteroidal anti-inflammatory drugs; hydroxychloroquine; tocilizumab; baricitinib.*
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In December 2019 an outbreak of a new coronavirus infection, called 2019-CoV, was registered in Wuhan (Hubei province, China). On February 11, 2020 the WHO proposed an official name to this infection caused by a new coronavirus – COVID-19 (Coronavirus disease-19). At the same time the international Committee on virus taxonomy assigned an official name to the infectious agent SARS-Cov-2 (Severe acute respiratory syndrome coronavirus-2). Since its first outbreak, the infection spread rapidly around the world, until finally on January 30 2020 the WHO declared that its propagation was an international health emergency and on February 11, 2020 called it a pandemic. The epidemiological picture is constantly changing: as of the second half of April 2020, there were 200 countries in the world where more than 2,200 thousand cases of the disease were registered, including more than 150,000 verified deaths.

In the context of this situation, it is extremely important to determine the significance of COVID-19 for patients suffering from immunoinflammatory rheumatic diseases (IRD). On the one hand, the rapid and uncontrolled spread of the COVID-19 epidemic may pose a particular danger for this category of patients, since the frequency of infectious diseases in them is increased due to the negative impact on the immune system of both the IRD themselves and many anti-rheumatic drugs that have an immunosuppressive effect. On the other hand, the data obtained in the study of the pathogenesis of COVID-19 became the reason to apply the drugs widely used in rheumatology to treat this new disease.

A number of questions arise about the optimal strategy for IRD therapy during the COVID-19 period due to the lack of complete information about the frequency of COVID-19 in rheumatological patients. Therefore, in our opinion, it would be appropriate to present the risk of viral infections in patients with IRD with a special focus on data obtained during this pandemic, as well as to identify the potential advantages and/or disadvantages of the main anti-rheumatic drugs that are currently being used or are planned for use in patients with COVID-19.

COVID-19 infection

The SARS-CoV-2 coronavirus is single-stranded RNA-containing virus that belongs to the *Coronaviridae* family. Like some representatives of this family (severe acute respiratory syndrome coronavirus-SARS-CoV and Middle East respiratory syndrome coronavirus-MERS-CoV), this pathogen fall in the second group of pathogenicity. The genetic sequence of SARS-CoV-2 is at least 79% similar to that of SARS-CoV [1]. Structural modeling performed using the decoded virus genome demonstrated that the receptor-binding S-protein of the virus has a sufficiently high affinity for angiotensin-converting enzyme-2 (ACE-2) and can use it as an «entrance gate» to enter the cell [2]. At the same time, this affinity of the SARS-CoV-2 virus is 10–20 times higher than that of SARS-CoV, which explains the higher contagiousness of the former. APF-2 is a type I membrane protein that is widely represented on cells of the kidneys, heart, gastrointestinal tract and, most importantly, on epithelial alveolar cells of the lungs, whose extensive damage causes the severity of the disease [3]. In this case, the binding of SARS-CoV-2 to ACE-2 leads to excessive accumulation of angiotensin type II, which is considered an important element of the pathogenesis of acute respiratory distress syndrome and myocarditis.

In the development of COVID-19-associated internal organ damage, central importance is given to uncontrolled cytokine hyperproduction, called «cytokine storm». The essence of this potentially life-threatening reaction of the immune system is an uncontrolled and non-protective hyperproduction of a wide range of pro-inflammatory cytokines: interleukins (IL) 1, 6, 7, 8, 17, granulocyte colony-stimulating factor, tumor necrosis factor α (TNFα), etc., as well as chemokines (CCL1, 3, 5, etc.) that develop in response to viral infection. This leads to systemic activation of the inflammatory response cells (macrophages, neutrophils, lymphocytes), which, in turn, synthesize an increasing number of cytokines and this process turns into a vicious circle. Such hyperproduction of cytokines was registered in the most severe forms of COVID-19 [4]. At the same time, the clinical picture of cytokine storm caused by viral infection was similar to that of secondary adult lymphohistiocytic syndrome, macrophage activation syndrome (found in rheumatology as a complication in patients with juvenile idiopathic arthritis, adult Still's disease, systemic lupus erythematosus, etc.) and cytokine release syndrome in CAR-T-cell therapy in oncology. The main clinical and laboratory manifestations of these conditions are intermittent fever, lung damage (including SARS) observed in 50% of patients, cytopenia and hyperferritinemia [5]. Chinese scientists found out that the increase in IL6, ferritin, and D-dimer concentrations, which are biomarkers of cytokine storm, had a direct correlation with the severity of COVID-19 infection and the likehood of a fatal outcome [6,7]. Thus, the cytokine storm phenomenon is an important component in the pathogenesis of COVID-19 and one of the «targets» at which therapeutic measures should be aimed in these patients.

Risk of respiratory infection in patients with IRD

As it was mentioned above, patients with IRD have an increased risk of infection compared to the general population. This trend is primarily a reflection of immunopathological disorders inherent in all IRD, and has a clear association with the degree of activity of the disease. The analysis, which included 16,242 patients from the CORRONA registry, showed that an increase in the DAS28 index by 0.6 led to higher frequency of outpatient infections by 4% (p=0.01) and serious infections requiring hospitalization by 25% (p=0.03) [8]. Later, data from this registry showed that in comparison with patients who reached clinical remission (CDAI ⩽2.8), the risk of serious infections significantly increased in patients with low and moderate disease activity. Thus, the incidence of infections in patients with remission was 1.03 (95% confidence interval, CI 0.85–1.26), in patients with low activity – 1.92 (95% CI 1.68–2.19), with moderate activity – 2.51 (95% CI 2.23–2.82) per 100 patients/years [9]. In a study conducted at the Nasonova Research Institute of Rheumatology, it was shown that patients with rheumatoid arthritis (RA) had high inflammatory activity (odds ratio, OR 15.5; p<0.001) and no intake of synthetic disease-modifying antirheumatic drugs – sDMARDs (OR 5.6; p<0.001) as risk factors for developing pneumonia. When both factors were combined, the risk of developing pneumonia increased to 19.3 [10]. These data highlight the important role of achieving and maintaining control over IRD activity to reduce the incidence of comorbid infections.

Vaccines are the most effective and economical means prevention and control of infectious diseases. Currently, more than 40 pharmaceutical companies and academic institutions around the world have begun work on creating a vaccine against COVID-19 [11]. However, after the development of a vaccine, it is necessary to conduct clinical studies to assess its safety, immunogenicity and effectiveness, which requires a long time. Today, in the context of the ongoing COVID-19 pandemic, experts from the European League Against Rheumatism (EULAR) strongly recommend vaccination, primarily against influenza and pneumococcal infection, to the absolute majority of patients with IRD [12]. This is associated with a high risk of death from respiratory tract infections among rheumatological patients, especially given the high incidence of respiratory tract infections in COVID-19. The immunogenicity and safety of these vaccines has been demonstrated in numerous studies in various IRD [13].

In the context of the COVID-19 pandemic, a number of questions arise which are related to the use of anti-rheumatic therapy in IRD. Theoretically, nonsteroidal anti-inflammatory drugs (NSAIDs) can have a prohypertensive effect, they can increase the expression of ACE-2, and thus raise the chance to get COVID-19 [14]. However, there is no clear clinical data on the negative effect of these drugs on the development of COVID-19 infection [15]. It should be noted that NSAIDs are widely used to relieve symptoms associated with acute respiratory viral infection (ARVI), such as fever, headache, joint and muscle pain [16]. It is quite safe to take these drugs in low («over-the-counter») doses for a short time in SARS.

At the same time, we have contradictory information about the effect of NSAIDs on the course of bacterial pneumonia and sepsis. A number of observational studies show that there is an increase in complicated forms of lung infections and adverse outcomes in patients who received NSAIDs as an antipyretic agent [18, 19]. Among the reasons to explain this phenomenon, we suppose the negative impact of NSAIDs on the functioning of macrophages and neutrophils that provide non-specific immune protection, as well as late diagnosis and late initiation of antibacterial therapy, which can be a result of the absence of clinical symptoms, first of all, absence of febrile syndrome. It is important to note that a meta-analysis of 4 randomized controlled trials (RCTs), which evaluated the effectiveness of the antipyretic action of NSAIDs in resuscitation patients, did not show an increase in mortality when using these drugs [20].

When prescribing NSAIDs to patients with IRD, it is necessary to keep in mind the possible development of complications from the gastrointestinal tract, cardiovascular system and kidneys, especially in the elderly patients with multiple comorbid conditions. It is also necessary to remember the ability of NSAIDs and paracetamol to mask one of the main symptoms of COVID-19 – fever, which can lead to late diagnosis of complicated forms of this disease [15].

Glucocorticoids (GC) have played a key role in the IRD treatment for more than 70 years. It is known that GC have a wide range of adverse reactions (AP), including an increased risk of severe infections and serious comorbid diseases (in particular, diabetes mellitus), which further increase the likelihood of infection [21]. The use of GC in viral respiratory tract infections can lead, on the one hand, to an inhibition of the immune

response and a decrease in the clearance of the pathogen, on the other hand – to the suppression of the inflammatory response of the macroorganism, which is the main cause of lung damage and SARS development. The 2019 meta-analysis, which included 10 observational studies performed during influenza epidemics, showed increased mortality (relative risk, RR 1.75; p=0.0002), an increase in the frequency of secondary bacterial or fungal infection (RR 2.0; p=0.04), as well as a longer stay in the intensive care unit (RR 2.1; p=0.0001) in patients treated with GC [22]. The WHO interim guidelines for the management of patients with COVID-19 note that the use of GC is not indicated in the absence of good reasons [23]. Nevertheless, it is recommended that patients with IRD who receive GC during the COVID-19 pandemic should not interrupt treatment, but reduce the dose of these drugs as much as possible [24].

Many studies have demonstrated that the frequency of upper and lower respiratory tract infections increases when patients with IRD take sDMARDs and especially biological agents. In particular, according to one Dutch study, the administration of TNFα inhibitors made the likelihood of influenza development in RA patients twice as high [25]. In another study of similar structure, the incidence of influenza in patients with RA, psoriatic arthritis and spondyloarthritis who were treated with biologics was 17%, which was 1.75 times higher than average in the population data [26]. However, based on information recently published on new (SARS-CoV-2) and previous (SARS-CoV, MERS) outbreaks caused by coronaviruses, there is no conclusive evidence that patients with IRD are at an increased risk of developing these infections compared to those suffering from other illnesses.

Italian researchers provided information about 320 patients (RA – 57%, spondyloarthritis – 43%) who live in the province of Lombardy – the region in Northern Italy with the highest incidence of COVID-19[27]. Therapy with TNFα inhibitors was received by 52% of patients, with other biologics – by 40%, and with targeted disease-modifying antirheumatic drugs (tDMARDs) – by 8%. 4 cases of COVID-19 and 4 cases with clinical symptoms similar to COVID-19 were verified in this group. Five patients contacted with COVID-19 patients, but all of them remained asymptomatic during the 2-week follow-up period. Patients with COVID-19 symptoms temporarily stopped taking biologics or tDMARDs and received at least one course of antibiotic treatment. There were no severe respiratory complications, recurrent IRD, or fatalities in any of the observations. In addition, among the 700 patients admitted to the regional medical center with severe COVID-19, no one took tDMARDs or biologics. According to the authors, patients with chronic arthritis who are being treated with tDMARDs or biologics do not appear to be at an increased risk of respiratory or other life-threatening complications of COVID-19 compared to the general population. Therefore, despite the need for constant monitoring of patients receiving the specified therapy, doctors should avoid its unjustified "preventive" cancellation, which can increase the risk of basic IRD relapse.

Anti-rheumatic drugs in COVID-19 therapy

The need to urgently develop new approaches to treat patients with COVID-19 is now a powerful incentive to study the effectiveness of drugs used for other viral infections. As knowledge of the pathogenesis of COVID-19 was accumulated, a number of drugs widely used in rheumatology have been proposed as possible therapies for this infection.

Chloroquine and hydroxychloroquine

The use of synthetic quinine derivatives – chloroquine (CQ) and hydroxychloroquine (HCQ) in COVID-19 therapy is widely discussed in medical literature. These drugs, which came into practice for malaria treatment, are now actively used in rheumatology because of their immunomodulatory properties. The antiviral effect of CHL has been known since the late 1960s. *In vitro* studies demonstrated several mechanisms by which the drug can inhibit the growth and reproduction of various viruses (including SARS-CoV-2), although further *in vivo* studies showed mixed results [28–30].

According to available data, when used in clinically acceptable concentrations, CQ is able to increase the pH of endosomes (which prevents the virus from leaving them inside the cell), to inhibit the activity of toll-like receptors, and limit the glycosylation of the cell receptor ACE-2 [31–33]. These mechanisms presumably determine the antiviral effect of the drug at the initial and subsequent stages of COVID-19, which was the reason to include CQ in a number of studies that have already been performed and are currently being performed in China under various protocols, including studies which combine CQ with antiviral drugs. Preliminary results indicate a positive effect of CQ on the clinical and radiological symptoms of pneumonia, which led to a reduction in the length of hospital stay [34, 35]. *In vitro* studies on pharmacokinetic models showed a more than 3-fold superiority of HCQ over CQ. These studies suggested HCQ at a starting loading dose of 400 mg 2 times a day, then 200 mg 2 times a day for 4 days as a treatment option for COVID-19 [36]. At the same time, Italian and British authors give a number of well-grounded objections to this treatment, urging higher-quality and larger-scale RCTs [37, 38].

In connection with the above, scientists have come up with the idea of using HCQ as a means of prevention of COVID-19 and now it is widely discussed, given its relatively low cost and good tolerance for long-term use, in particular for IRD. However, according to S. Shah et al. [39], although the results of preclinical studies are promising, there is currently no evidence to support the preventive efficacy of CQ or HCQ in COVID-19. Given the potential safety concerns and the likelihood of a false sense of security, the effectiveness of COVID-19 prevention with CQ or HCQ should be carefully evaluated in both observational studies and high-quality RCTs.

IL1 and IL6 inhibitors

As mentioned above, SARS-Cov-2, which develops in the most severe course of COVID-19, is the result of a massive release of pro-inflammatory cytokines caused by the immune system's response to viral replication, with further lung damage and the development of multiple organ failure. IL1 and IL6 play a key role in the formation of the «hyperinflammatory status», which suggests the feasibility of using these cytokine inhibitors for SARS-Cov-2 pharmacotherapy. Thus, the use of a recombinant soluble IL1 – anakinra receptor antagonist during phase III RCT in severe sepsis showed a significant improvement in the survival of patients with the signs of macrophage activation syndrome in the absence of any severe HP [40].

In a small retrospective study involving 21 patients with severe SARS-CoV-2, after applying a humanized monoclonal antibody to the IL6 – tocilizumab receptor in a single dose of 400 mg, there was a normalization of body temperature, the level of CRP, the number of lymphocytes, positive dynamics according to computed tomography of the chest organs, and a decrease in the need for oxygen therapy [41]. Currently, several RCTS (China, Italy, USA, etc.) have been announced to study the effectiveness of tocilizumab in patients with pneumonia, accompanied by early respiratory failure and increased IL6 levels against the background of COVID-19 [42–44]. In addition, a study of the effectiveness and safety of the IL6 – sarilumab inhibitor in patients with COVID-19 was announced [45].

The latest version of the temporary guidelines of the Ministry of health of Russian Federation [46] emphasizes that patients with COVID-19 and those with suspected development of severe life-threatening cytokine release syndrome (increase or retention of fever >38.5 °C, development of leucopenia or lymphopenia on day 8, increasing D-dimer content >1500 ng/ml, IL6 >40 PG/ml, CRP >75 mg/l, as well as the ineffectiveness of antibiotic therapy) should be prescribed tocilizumab in a dose 4–8 mg/kg, if necessary, the same dose should be administered in 12 hours.

It should be noted that on April 3, 2020, the Ministry of health approved clinical trials of the effectiveness and safety of olokizumab (IL6 inhibitor) and RPH-104 (IL1 inhibitor) for the treatment of patients with severe COVID-19 [47].

Baricitinib

M. Hoffmann et al. showed in their study [48] that SARS-CoV-2 penetrates target cells by receptor-mediated endocytosis. Numb-associated kinases – AP-2-associated protein kinase (AAK1) and cyclin-G-associated kinase (GAK) are directly involved in the regulation of this process [48]. Inhibition of AAK1 can interrupt both the penetration of the virus into the cell and the intracellular assembly of viral particles [49]. 6 out of 378 AAK1 have high affinity, which include erlotinib, sunitinib, ruxolitinib and fedratinib which are used in oncology. It was previously shown that these drugs adequately suppress cell infection with Dengue, Ebola, and respiratory syncytial viruses [50], but positive results can be achieved only if these drugs are used in doses that are toxic to the macroorganism. At the same time, a Janus kinase inhibitor of type 1 and type 2 baricitinib (BARI) effectively blocks the activity of AAK1 and GAK in serum concentrations reached when the drug is prescribed in therapeutic doses (in particular, for RA patients), i.e. 2–4 mg/day [51]. In addition, BARI blocks the intracellular transmission of signals from a number of biologically active molecules, including IL6 and interferon γ. Minimal interaction of BARI with P450 enzymes makes it possible to use BARI in combination with antiviral drugs such as lopinavir/ritonavir and remdesivir [52]. At the same time, blocking the JAK/STAT signal path leads to inhibition of interferon-mediated antiviral response, which can potentially contribute to the development of SARS-CoV-2 infection. Moreover, it is believed that this mechanism is associated with an increased risk of herpes virus infections, the frequency of which in intensive care units reaches 10% in community-acquired pneumonia and 5% in ventilator-associated pneumonia [53]. The frequency of the latter is expected to increase in patients with impaired immunity when they are treated with Janus kinase inhibitors. Therefore, the arguments in favor of using BARI for COVID-19 are not very convincing yet. Further research is needed to assess the potential role of this drug in the treatment of severe pneumonia in COVID-19 [54].

Conclusion

The COVID-19 pandemic is not only a global health emergency, but also a major factor in global historical processes that will undoubtedly change the attitude of many people to reality. This problem is extremely relevant for patients with IRD, given their higher susceptibility to the infectious process. The use of s/tDMARDs and biologics increases the frequency of serious infections, but insufficient control of IRD activity (or lack thereof) is an even greater risk factor for infectious complications. Therefore, it is necessary to explain to patients with IRD the need to continue pathogenetic therapy even during COVID-19 outbreaks. This strategy is fully justified, because it is mainly aimed at preventing relapses of background IRD, which will decrease the number of requests for medical care, reduce disability cases and improve the quality of life of patients. In addition, in modern conditions, the role of vaccination is significantly increasing, primarily against influenza and pneumococcal infection, since the risk of death from respiratory tract infections is quite high in patients with IRD, which is very important in the current COVID-19 pandemic. It is also extremely important to emphasize the need for careful compliance with the anti-epidemic regime and the requirements of non-specific prevention at both the individual and collective levels. All this requires balanced, reasonable and coordinated actions of doctors of all specialties as well as society as a whole.

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