# REVIEW ARTICLE

# Should coronavirus disease 2019 concern rheumatologists?

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**ABSTRACT**

Coronavirus disease 2019 (COVID-19) is an infectious disease that became a global health emergency. This review focuses on the aspects of COVID-19 pertaining to rheumatology, including signs and symptoms akin to those observed in rheumatic disorders, risk of infection or severe course of the disease in patients with a pre-existing rheumatic disease and those receiving antirheumatic or immunosuppressive medication, as well as potential use of antirheumatic or anticytokine therapeutic strategies that are already applied in rheumatology (among others, chloroquine, hydroxychloroquine, tocilizumab, and baricitinib) in patients with COVID-19.

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**Introduction** Coronavirus disease 2019 (COVID-19) is caused by the newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel RNA virus was previously provisionally named 2019 novel coronavirus (2019-nCoV). In a short time, the emergence of COVID-19 that began in December 2019 in China escalated to a pandemic and became a major public health issue with a significant sequela of a number of fatal cases all over the world.[1-3]

Coronaviruses are a group of pathogens which took their name from the crown-like spikes on their surface. The viruses infect vertebrates including humans. Since the mid-1960s, a few human coronaviruses have been identified as causative agents of respiratory infections, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). These 2 are responsible for a large number of fatal cases (SARS-CoV caused at least 774 deaths in 2003 and MERS-CoV at least 850 in 2012).[4] The zoonotic origin of SARS-CoV-2 is suggested to be similar to that of the previously reported coronaviruses. Despite the probable role of an intermediate host (pangolin), all current infections are a result of human-to-human viral transmission.[5] Possibly, at the time of publication of this review, the number of infected patients in the whole world exceeded 2 million cases.

This short review focuses on potential converging views on COVID-19 and rheumatology.

Despite a relatively large number of papers on coronaviruses and COVID-19 that have been published in recent months, the problems common to rheumatology and infectiology regarding COVID-19 are discussed in a few papers only.[6-9]

**Musculoskeletal involvement in coronavirus disease 2019** Severe acute respiratory syndrome coronavirus 2 exploits membrane-bound angiotensin-converting enzyme 2 (ACE2) to enter its target cells. This mechanism seems to be common to all coronaviruses including SARS-CoV and MERS-CoV. The ACE2 receptor is expressed in the epithelial cells of the mouth and tongue, type 1 and 2 alveolar epithelial cells of the lungs, as well as in the cells of the heart, kidneys, and parts of the gastrointestinal tract. From the epidemiological point of view, the most pathological phenomenon is the virus binding to the ACE2 receptor in the respiratory tract. It is possible that other locations of ACE2 are also involved in the clinical course of the disease, but their role in this process remains unknown.[10] The infection starts with the binding of the spike glycoprotein of the viral envelope to the ACE2 receptor.[11,12] The next step is endocytosis of the complex. Inside the cell, the virus uses transcriptional pathways to replicate itself.[13] It results in spreading the virus throughout the lungs. Infection of the alveolar and bronchial cells causes loss of the cellular function, including loss of ability of ciliated cells to eliminate fluids, mucin, and cellular debris from the lungs.

This is believed to be the main causative mechanism of severe acute respiratory syndrome. Binding of the spike glycoprotein to the ACE2 receptor is hypothetically a mechanism for the development of potential antiviral agents.[14]

Clinical manifestations of COVID-19 vary from mild to severe.[1] The most common symptoms are fever, cough, fatigue, and signs of pneumonia. Some patients present with headache, diarrhea, vomiting, runny nose, and hemoptysis. The heterogeneous clinical presentation of COVID-19 also includes manifestations that can mimic rheumatic diseases. They include myalgias and arthralgias. Myalgias are considered to be more common and occur in about one-fourth of all infected symptomatic patients.[15] Arthralgias are found in about 15% of the patients with COVID-19.[9] Other features of COVID-19 are also nonspecific and some of them are similar to those observed in rheumatic patients.[16] They include fatigue, which commonly precedes the development of systemic autoimmune disorders, and leukopenia, predominantly lymphopenia and thrombocytopenia, which are seen in patients with systemic lupus erythematosus.[9]

Our knowledge of the clinical course of COVID-19 is still limited. More attention has been paid to the risk factors of a severe or fatal course of the disease. Coronaviruses seem to be characterized by significant tropism to the respiratory system. Published analyses of signs and symptoms do not indicate symptomatology akin to rheumatic disorders. The clinical manifestations of COVID-19 are also different from those typical for viral arthritis.[17,18] Joob and Wiwanitkit[19] reported arthralgia as an initial presentation of COVID-19 that occurred in 1 woman among 40 patients monitored in Thailand. It is possible that some mild cases may be seen by rheumatologists as the first doctors contacted and future analyses of symptomatology in a large population of patients with COVID-19 might reveal possible disease manifestations resembling acute arthritis or other systemic rheumatic disorders.

**Coronavirus disease 2019 and patients with rheumatic diseases** The relationship between infection and rheumatic disorders is complex. Altered immunity, including autoimmune phenomena, is a common mechanism of a number of rheumatic diseases. Many currently applied therapeutic strategies are based on immunosuppressive drugs or medications that are believed to modulate patient immunity. Two main aspects of the problem should be highlighted. The first is the role of viral infection in the development of certain rheumatic disorders, and the second is susceptibility of rheumatic patients to viral infections, resulting from altered immunity. Aberrant immunity is caused by the disease and administered medication as well.

**Viral infections and rheumatic disorders** Viral infections are considered to be a trigger of some immune-mediated rheumatic diseases. Altered immunity, including autoimmunity, is a common mechanism of a number of rheumatic diseases and it has been suggested that viruses play a role in the development of autoimmunity.[20-23] The mechanism behind the induction of autoimmunity by viral infections in susceptible individuals remains unclear. The oldest hypothesis is based on antigen mimicry. According to that hypothesis, viruses carry antigens that are structurally akin to self-antigens and autoimmunity results from immune cross-reactivity. Another hypothesis is related to local inflammation caused by viral infection. Localized inflammatory environment is responsible for the release of self-antigens from the damaged tissue and the development of autoimmune phenomena. A modified version of this view is a simple hypothesis that infecting viruses directly damage the cells, which triggers the release of self-antigens. This process may be associated with impaired immune tolerance and generation of autoreactive cellular lines.[24]

Several studies linked viral infections of the respiratory tract to autoimmunity. A few reports suggested an association of respiratory viral infections with the development of rheumatic diseases.[25,26] Studies investigating the incidence and course of autoimmune disorders in individuals who recovered from COVID-19 would be of value. Immunity alterations that may be caused by viral infections are unknown, but it is possible that they could intensify autoimmune phenomena. At least a few years of observations are needed to evaluate this issue.

**The risk of coronavirus disease 2019 in patients with rheumatic disorders** The risk of infections in patients with rheumatic disorders is a subject of numerous studies. It is believed that most of immune-mediated inflammatory rheumatic diseases are associated with decreased immunity. Reduced immunity also results from the management of rheumatic disorders, because almost all treatment options involve agents with immunosuppressive properties. It is impossible to distinguish between the role of disease mechanisms and medication activity while assessing the patient's immunity. There are almost no data available on immunity of treatment-naive patients. On the other hand, the relationship between disease activity and decreased immunity remains unclear. It has been observed that patients with active disease are prone to infections due to impaired immunity, and administration of a drug that is also immunosuppressive results in a decreased disease activity. Thus, despite immunosuppressive properties of the agent, the overall resistance to infection improves in these patients.

There is a large body of evidence indicating that patients with inflammatory diseases are prone to infections. Detailed numbers describing the risk provided in various studies or meta-analyses differ because of multifactorial nature of susceptibility of an individual to infection. All those data indirectly support an increased risk of COVID-19 in

rheumatic patients.[27] Up to now, there have been no systematic studies of that cohort. Favalli et al[7] are the first investigators who addressed the risk of viral infection in patients with rheumatoid arthritis. Monti et al[28] reported 4 confirmed cases of COVID-19 in a group of 320 patients from Lombardy. The patients had rheumatoid arthritis or spondyloarthritis and were treated with biological or targeted, synthetic, disease-modifying antirheumatic drugs. However, the small group of infected patients does not allow us to draw any conclusions on the incidence rate of COVID-19 in patients with rheumatic diseases or the overall outcome of the infection. Mihai et al[29] reported a case of a woman with systemic sclerosis treated with tocilizumab who developed COVID-19. The course of the disease was mild and the patient was declared to have recovered from infection. Sawalha et al[30] suggested a potential mechanism of enhanced susceptibility of patients with systemic lupus erythematosus to SARS-CoV-2 infection. In patients with lupus, hypomethylation and overexpression of ACE2 was proven. Oxidative stress induced by viral infection additionally impaired defective DNA methylation and enhanced viremia. It has been also suggested that demethylation of other genes that code immune active proteins (eg, interferon-regulated proteins, nuclear factor κB, and cytokines) may facilitate development of cytokine storm. Epigenetic dysregulation, although only hypothetically, indicates that patients with lupus are more prone to the development, and severe course, of COVID-19 as compared with the general population.

Children are generally considered less prone to develop severe symptoms of COVID-19 and mortality is relatively low in this population. The mechanism of this phenomenon remains unclear. It is suggested that coinfections (and coclearance) with other viruses may help children to overcome SARS-CoV-2 infection. Considering the cohort of children with rheumatic diseases, it has been suggested that pre-existing anti-inflammatory treatment might not increase the risk significantly, but this statement is based on limited experience only.[8,31]

A potentially increased risk of infection, a severe course of the disease, and death among the patients with rheumatic diseases who are immunocompromised is the main concern among rheumatologists.[32,33] Summing up, there are no direct data on susceptibility of patients with inflammatory rheumatic diseases who receive immunosuppressive medication to SARS-CoV-2 infection. All indirect data strongly support the view that these patients are prone to COVID-19. Other factors affecting host resistance to infection should be considered. Of note, clinical manifestations of COVID-19 may also differ from these present in other viral disorders, and the disease may have an altered course in rheumatic patients. Further studies on the topic are urgently needed. For clinical practice, we have to adopt indirect suggestions and manage patients on a case-by-case basis, taking into account the risk of infection and disease activity associated with the need for therapy continuation. The only reasonable recommendation as of today is the application of enhanced general protective measures against infection in rheumatic patients.

**Can antirheumatic therapies be a potential tool to treat coronavirus disease 2019?** Application of medication used for the management of rheumatic disorders in patients with COVID-19 is based on selected findings on the mechanism of cytokine dysregulation in patients with COVID-19. In some aspects, they are similar to those revealed in patients with rheumatic diseases and can be controlled with antirheumatic therapy. The role of hydroxychloroquine and chloroquine in the potential management of COVID-19 is relatively well explored. Another issue is the hypothetical application of anticytokine therapy in patients with COVID-19. A few suggestions regarding possible use of other therapeutic agents (Janus kinase inhibitors) have also been put forward.

The use of antirheumatic drugs in patients with COVID-19 is still based on low-evidence observations. Some authors added a word of caution, especially addressing long-term outcomes.[34] There is also an ethical dilemma related to the availability of the drugs, including chloroquine and hydroxychloroquine, which are still needed by patients with rheumatic diseases, but in some parts of the world they are available only for patients with COVID-19.[35]

**Phases of coronavirus disease 2019 and the potential use of antirheumatic drugs** From the rheumatologist's perspective, the following phases of COVID-19 can be distinguished: 1) early phase, that is, penetration of the virus to the cells; 2) viremic phase; and 3) cytokine storm phase.[9] As described above, SARS-CoV-2 utilizes the ACE2 receptor for cellular entry. Modifications in the structure and expression of the receptor may be a genetic or environmental factor affecting susceptibility to infection or determining the course and severity of the disease. The rheumatological perspective is focused on the potential use of chloroquine or hydroxychloroquine to prevent the virus from entering the target cells. More details on this approach and its possible clinical application are described later in this review.

Of note, there is an anecdotal report suggesting that ibuprofen, a commonly used nonsteroidal anti-inflammatory drug, increases the expression of ACE2 receptors and in this way enhances viral penetration to the cells.[36] It also remains unclear if this suggestion is limited to ibuprofen only, may be a class feature of all nonsteroidal anti-inflammatory drugs, or is a property of only a few drugs from this group. Despite lack of evidence, it has been suggested to avoid using ibuprofen during the COVID-19 pandemic.[9] Additionally, cardiologists advised either initiation or discontinuation of management with

angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists in patients with COVID-19 or those at high risk of infection.[37]

The viremic phase of COVID-19 is associated with manifestations of musculoskeletal symptoms and cytopenia. In this phase, upregulation of inflammatory phenomena takes place. It is possible that chloroquine or hydroxychloroquine interfering with Toll-like receptor stimulation may be useful in the management of the infected patients. Some authors suggested that the drugs limit replication of the virus as well.[13,38]

The last and most severe phase of COVID-19 is known as cytokine storm and is characterized by a mechanism and clinical manifestation very similar to a severe complication of some rheumatic diseases. Possibly, therapeutic measures applied in rheumatology are potentially effective also in patients with COVID-19.

**Chloroquine and hydroxychloroquine in the treatment of coronavirus disease 2019** Chloroquine and hydroxychloroquine are aminoquinolines primarily applied as antimalarial drugs and have been used as disease-modifying antirheumatic drugs for more than half a century. Currently, hydroxychloroquine and chloroquine are recommended for the management of patients with systemic lupus erythematosus,[39,40] rheumatoid arthritis,[41] primary Sjögren syndrome,[42] antiphospholipid syndrome,[43,44] and some other immune-mediated rheumatic disorders. The use of hydroxychloroquine and chloroquine in rheumatology is based on empirical findings confirmed by clinical trials, although the drugs' mechanism of action is not fully understood.[45] The are 4-aminoquinolines, which are weak bases due to presence of a basic side chain. The chain is suggested to be responsible for drug accumulation in lysosomes and interaction with nucleic acids. Chloroquine is used as a phosphate, and hydroxychloroquine as a sulfate. Hydroxychloroquine has an N-hydroxy-ethyl side chain in place of the N-diethyl group of chloroquine and it is generally considered less toxic.

Several mechanisms of action of the drugs have been postulated. The main suggested mechanisms are: affecting lysosomal activity, inhibition of the Toll-like receptor signaling pathway, binding to DNA, affecting immune phenomena (due to influence upon antigen-presenting cells, T and B cell activity), and inhibition of proinflammatory cytokines. A detailed description of the potential mechanisms of action of chloroquine and hydroxychloroquine in patients with rheumatic disorders can be found elsewhere.[38] Here, the mechanisms that can be involved in the control of COVID-19 are reviewed briefly.

Chloroquine and hydroxychloroquine increase pH of endosomes and in this way inhibit internalization of the SARS-CoV-2 and ACE2 complex. The drugs have the ability to accumulate in lysosomes and inflamed tissue. Moreover, the drugs are protonated inside the cells, which enhances their activity. Interference with the endocytic

pathway is considered as the main antiviral mechanism of action of the drugs in an early phase of infection. It is also possible that other anti-inflammatory mechanisms of action of hydroxychloroquine or chloroquine are also efficient in the management of patients with COVID-19. The drugs have been reported to indirectly reduce secretion of proinflammatory cytokines by various cell types. In vitro, an inhibited secretion of interleukin 1, interleukin 6, tumor necrosis factor α, and interferon γ by mononuclear cells exposed to hydroxychloroquine or chloroquine was reported.[45]

A systematic review of 8 papers and 23 clinical trials by Cortegiani et al[13] revealed that there is a sufficient preclinical rationale and evidence regarding the effectiveness of chloroquine or hydroxychloroquine in the treatment of patients with COVID-19, although further results based on high-quality, controlled clinical trials coming from various locations worldwide are needed to obtain evidence in order to include these drugs in the therapeutic strategy. Some national guidelines included hydroxychloroquine or chloroquine in the armamentarium against COVID-19. Similar conclusions can be found in other recently published papers on the use of hydroxychloroquine or chloroquine in patients with COVID-19.[46-48] Importantly, there are no data recommending the use of these drugs as prophylaxis against SARS-CoV-2 infection and we should wait for the results of clinical trials.[49]

**Anticytokine drugs in the management of coronavirus disease 2019** Severe forms of COVID-19 are associated with cytokine oversecretion and dysregulation known as cytokine release syndrome, or cytokine storm. Mehta et al[50] suggested that the pathogenesis of acute respiratory distress syndrome is similar to that of secondary hemophagocytic lymphohistiocytosis leading to fulminant hypercytokinemia with multiple organ failure. This clinical condition is seen in rheumatology and is known as macrophage activation syndrome. The pathophysiology of the syndrome is understood only partially, but it is believed that defective lysis of activated antigen-presenting cells results in amplification of a proinflammatory cascade. Oversecretion of proinflammatory cytokines leads to activation of macrophages, causing hemophagocytosis and organ damage.[51-53] Clinically, macrophage activation syndrome is a severe, life-threatening complication of some systemic autoimmune disorders characterized by high fever, disseminated intravascular coagulation, hypofibrinogenemia, hyperferritinemia, hypertriglyceridemia, pancytopenia, hepatosplenomegaly, lymphadenopathy, and hepatic dysfunction. The syndrome may be triggered by viral infection. Treatment includes glucocorticoids and biological agents against interleukin 1 (anakinra)[51] and interleukin 6 (tocilizumab). The management of macrophage activation syndrome includes administration of glucocorticoids and anticytokine

biological medication. Some reports suggested a beneficial effect of interleukin-1 blockade.[54,55] More attention has been paid to tocilizumab, a monoclonal antibody against the interleukin-6 receptor.[56] Similar measures are suggested for patients with COVID-19. A small retrospective study of critically ill patients with COVID-19 demonstrated some improvement after tocilizumab administration. Further investigations are in progress.[55,56]

Increased levels of tumor necrosis factor α were observed in patients with COVID-19 and their correlation with disease severity indicated a possible role of this cytokine in the development of inflammation.[57,58] A potential role of adalimumab is under investigation and the study results have not been available yet.

**Janus kinase inhibitors** Baricitinib and tofacitinib are Janus kinase inhibitors that affect signal transduction from the external cell surface receptor to the cell nucleus. Baricitinib is registered for the management of rheumatoid arthritis, and tofacitinib is used in patients with ankylosing spondylitis, psoriatic arthritis, ulcerative colitis, and rheumatoid arthritis. Baricitinib has been suggested to be useful in blocking viral entry into the target cells and in the prevention of excessive inflammatory response and cytokine dysregulation.[59] These suggestions need further evaluation.

**Intravenous immunoglobulins** The potential role of intravenous immunoglobulins in the management of patients with COVID-19 has been also suggested.[6] This is not supported by evidence from research data. Moreover, immunoglobulin infusion does not contain specific antibodies against SARS-CoV-2 and has no specific antiviral activity. Such properties are attributed only to plasma from individuals who recovered from the disease. In rheumatic disorders, intravenous infusions of immunoglobulins are used to modulate immunity. There are no data showing that application of immunoglobulins is beneficial to the patients. In the author's opinion, this medication will not be recommended for patients with COVID-19, particularly because of the fact that immunoglobulin infusion may exert some immunosuppressive effect on the body. It is unclear whether the administration of immunoglobulins will diminish cytokine storm, but this effect seems to be lower as compared with anticytokine medication. On the contrary, plasma from convalescents seems to be a very valuable tool for the management of severe forms of COVID-19.

**Global rheumatology and coronavirus disease 2019** On April 6, 2020, *The Lancet* published a letter by Lewandowski and Hsieh[60] describing the launch of a global registry of patients with rheumatic and musculoskeletal diseases and COVID-19. The project is addressed to physicians worldwide and intended to report such cases and establish a database. The COVID-19 Global Rheumatology Alliance engaged rheumatologists all over the world and received support from nonprofit organizations and major rheumatological journals. The paper includes a list of scientific and clinical challenges faced by the rheumatologist community and the COVID-19 Global Rheumatology Alliance may facilitate obtaining answers to those questions. Initial data from the COVID-19 Global Rheumatology Alliance provider registries have been recently published[61] and some clinical characteristics of patients with rheumatic disease in the United States during the early days of the COVID-19 pandemic are currently available.[62]

**Conclusions** Five months of the COVID-19 pandemic and its severe worldwide succession—the unusually progressive increase in the number of fatal cases in particular—are associated with an increased number of published studies. Despite this, there are currently no cumulative analyses based on large groups of patients; however, they will certainly be published in the future. This explains the particular style of this review, addressing the questions rather than summarizing the cumulative answers.

There are a few points of confluence between COVID-19 and rheumatology. The key role of the rheumatologist in coping with the pandemic seems to be offering expertise in the use of drugs affecting immune processes, which might be useful in the management of patients with COVID-19. These drugs have already been successfully applied in rheumatology for 1 or 2 decades.

The risk of SARS-CoV-2 infection in patients with rheumatic disorders or developing a severe form of COVID-19 constitute a significant problem in the practice of rheumatologists. It is associated with a question of continuation or modification of already administered antirheumatic medication. These questions, in order to be answered, need further investigation and evidence from well-controlled studies. Currently, they can be answered based on expert opinions only. It seems highly probable that analyses of large populations of patients with COVID-19 will reveal more details on "rheumatic" manifestations or involvement of the musculoskeletal system in some patients.[63]

In the author's opinion, despite lack of answers and need for further research, rheumatologists all over the world have already joined the medical community in the difficult battle with COVID-19. We all understand that the implementation of infection control measures should be accompanied by our joint effort to understand the complex manifestations of COVID-19, also those within the musculoskeletal system. Once we learn more, we can respond better.

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