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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. The paper reviews aspects of COVID-19 that pertain to rheumatology, including symptoms and signs 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 applications of antirheumatic or anticytokine therapeutic strategies that are already applied in rheumatology (including chloroquine, hydroxychloroquine, tocilizumab, baricitinib, and others) for patients with COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by a newly discovered severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The novel RNA virus was previously provisionally named 2019 novel coronavirus (2019-nCoV). The emergence of COVID-19 that began on the last day of 2019 in China, in a short time resulted in a pandemic, and became a major public health issue with a significant sequela of a number of fatal causes 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 deaths in 2012) [4]. The zoonotic origin of SARS-CoV-2 is suggested similarly as in the previously reported coronaviruses. Despite the probable role of an intermediate host (pangolin), all current infections are a result of human-to-human viral transfer [5]. It is possible that at the time of publication of this review, the number of infected patients in the whole world exceeded 2 million cases.

The presented 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 infectious medicine with focus on COVID-19 are discussed in few papers only [6-9].

Musculoskeletal involvements of coronavirus disease 2019

SARS-CoV-2 exploits membrane-bound angiotensin-converting enzyme 2 (ACE2) to enter its target cells. This mechanism seems to be common for all coronaviruses including SARS-CoV and MERS-CoV. The ACE2 receptor is expressed in the epithelial cells of the mouth and tongue, type I and II alveolar epithelial cells of the lungs as well as cells in the heart, kidney, and parts of the gastrointestinaltract. From the epidemiological point of view, the most important virus is the one 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 the transcriptional pathways to replicate itself [13]. It results in spreading of the virus thought 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 lung. It is believed that this is 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 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 heterogenous clinical presentation of COVID-19 also includes manifestations which 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 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 that commonly precedes the development of systemic autoimmune disorders, and leukopenia, predominantly lymphopenia as well as thrombocytopenia which are seen in patients with systemic lupus erythematosus [9].

Our knowledge on clinical course of COVID-19 is still limited. More attention was paid to risk factors of severe or fatal course of the disease. Coronaviruses seem to be characterized by significant tropism to the respiratory system. Published analyses of symptoms and signs do not indicate symptomatology akin to rheumatic disorders. 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 from 40 observed patients in Thailand. It is possible that some mild cases may be seen by rheumatologists as the first doctor, 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, and 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 are to 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 results from the disease as well as administered medication.

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 have 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 akin structurally to self-antigens and autoimmunity results from immune cross-reactivity. The other 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 suggest 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. An evaluation of this subject needs at least a few years of observations.

The risk of coronavirus disease 2019 in patients with rheumatic disorders

The risk of infections in patients with rheumatic disorders is a subject of a number of 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 patients who are not receiving medication. On the other hand, the relationship between disease activity and reduced immunity remains unclear. It has been observed that patients with active disease are prone to infections due to impaired immunity, and administration of medicine that also is 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 due to multifactorial nature of susceptibility of an individual to infection. All those data indirectly support an enhanced risk of COVOD-19 in rheumatic patients [27]. Up to now, there are no systematic studies with regard to that cohort. Favalli et al[7] are the first investigators who addressed the question of 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 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 be 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

evidenced. Oxidative stress induced by the viral infection additionally impaired defective DNA methylation and enhanced viremia. It has been also suggested that demethylation of other genes which 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 as less prone to develop severe symptoms of COVID-19, and their mortality is relatively low. The mechanism of this phenomenon remains unclear. It is suggested that coinfections (and coclearance) with other viruses may help children to overcome SARS-CoV2 infection. Considering the cohort of children with rheumatic diseases, it has been suggested that pre-existing anti-inflammatory treatment may not increase the risk significantly, but this statement is based on limited experience only[8,31].

Potentially increased risk of infection and severe course 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. All other factors that affect the host resistance to infection should be taken into consideration. We have to also remember that clinical manifestations of COVID-19 may also differ from 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 individually consider each patient, taking into account risk of infection and disease activity associated with the need for the continuation of therapy. The only rational recommendation as of today is 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 of mechanism of cytokine dysregulation in patients with COVID-19, which in some aspects are similar to those revealed in patients with rheumatic diseases, and can be controlled by antirheumatic therapy. The role of

hydroxychloroquine and chloroquine in the potential management of COVID-19 is relatively well explored. Another aspect is the hypothetical application of anticytokine therapy in patients with COVID-19. A few suggestions on possible application of other therapeutic agents (Janus kinase inhibitors) have been also published.

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

Phases of coronavirus disease 2019 and the potential application of antirheumatic drugs

From the rheumatologist's perspective, the following phases of the 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]. SARS-CoV-2 utilizes the ACE2 receptor for cellular entry, as described earlier. Modifications in the structure and expression of the receptor may be a genetic or environmental factor affecting susceptibility to infection or determining course and severity of the disease. Rheumatological perspective is focused on the potential application 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 paper.

It should be also mentioned that there is an anecdotal report suggesting that ibuprofen, the commonly used nonsteroidal anti-inflammatory drug, increases the expression of ACE2 receptors, and in this way enhances viral penetration to the cells [36]. It remains also unclear if this suggestion is limited to ibuprofen only, or may be a class feature of all nonsteroidal anti-inflammatory drugs, or is a property of only a few drugs from this group. Despite the lack of evidence, it has been suggested to avoid using ibuprofen during SARS-CoV-2 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].

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 suggestion 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 mechanism and clinical manifestation very similar to severe complication of some rheumatic diseases. It is possible that therapeutic measures applied in rheumatology are potentially effective in patients with COVID-19 as well.

Chloroquine and hydroxychloroquine in the treatment of coronavirus disease 2019

Chloroquine and hydroxychloroquine are aminiquinolines primary 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], and antiphospholipid syndrome[43,44] as well as some other immune-mediated rheumatic disorders. The use of hydroxychloquine and chloroquine in rheumatology is based on empirical findings confirmed by clinical trials, although the drugs' mechanism of action is understood only partially [45]. The are 4-aminoquinolines and are weak bases due to the presence of a basic side chain. The chain is suggested to be responsible for the drug accumulation in lysosomes and the drug interaction with nucleic acids. Chloroquine is used as a phosphate, and hydroxychloquine is applied as a sulfate. Hydroxychloroquine has an N-hydroxy-ethyl side chain in place of the N-diethyl group of chloroquine, and hydroxychloroquine is generally considered to be 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 cells activity), and inhibition of proinflammatory cytokines. Detailed description of potential mechanisms of action of chloroquine and hydroxychloquine in patients with rheumatic disorders can be found elsewhere[38]. Here, the mechanisms which can be involved in control of COVID-19 are reviewed briefly.

Chloroquine and hydroxychloquine increase pH of endosomes and in this way inhibit internalization of the SARS-CoV-2 and ACE2 complex. The drugs exert ability to concentrate

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, inhibited secretion of interleukin 1, interleukin 6, tumor necrosis factor-α, and interferon-γ by mononuclear cells exposed to hydroxychloroquine or chloroquine was described [45].

A systemic review of 8 papers and 23 clinical trials by Cortegiani et al[13] revealed that there is sufficient preclinical rationale and evidence regarding the effectiveness of chloroquine or hydroxychloroquine for the treatment of patients with COVID-19, although further results based on high-quality, coordinated, clinical trials coming from different locations worldwide are needed to obtain evidence to include these drugs in therapeutic strategy. Some national guidelines included hydroxychloquine or chloroquine in armamentarium against COVID-19. Similar conclusions can be found in other recently published papers on application of hydroxychloroquine or chloroquine in patients with COVID-19 [46-48]. Additionally, it is important that there are no data to recommend the application 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 hemophagocyte lymphohistiocytosis leading to fulminant hypercytokinemia with multiple organ failure. This clinical state 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 lyse of activated antigen presenting cells results in the amplification of a proinflammatory cascade. The state of oversecretion of proinflammatory cytokines leads to activation of macrophages, causing hemophagocytosis and organ damage [51-53]. Clinically, macrophage activation syndrome is a severe life-threating 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 beneficial effect of interleukin 1 blockade [54,55]. More attention has been paid to tocilizumab, monoclonal antibody against the interleukin 6 receptor [56]. Similar measures are suggested for patients with COVID-19. A small retrospective study in critically ill patients with COVID-19 revealed some improvement after the administration of tocilizumab. Further investigations are in progress [55,56].

Increased levels of tumor necrosis factor α were observed in patients with COVID-19, and the correlation of the level with severity of the disease suggested the role of this cytokine in the development of inflammation [57,58]. Potential role of adalimumab is under investigation, and results are not yet available.

Janus kinase inhibitors

Baricitinib and tofacitinib are Janus kinase inhibitors that affect signal transduction from the external cell surface receptor to the cellular nucleus. Baricitinib is registered for the management of rheumatoid arthritis, and tofacitinib is used in the management of patients with ankylosing spondylitis, psoriatic arthritis, and 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 immunoglobulin

The potential role of intravenous immunoglobulin in the management of patients with COVID-19 have been suggested [6]. This suggestion is not supported by evidence from research data, moreover immunoglobulin infusion does not contain specific antibodies against SARC-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 is no data that application of immunoglobulins is beneficial to the patients, and in the author’s opinion this

medication will not be recommended for patients with COVID-19, especially that the immunoglobulin infusion may exert some immunosuppressive effect. 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 with COVID-19. The project is addressed to physicians worldwide and is 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 as well as 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. The first initial data from the COVID-19 Global Rheumatology Alliance provider registries recently were published [61] as well as a few clinical data on patients with rheumatic disease in the US during the early days of COVID-19 pandemic are currently available [62].

Conclusions

Five months of the COVID-19 pandemic and its severe world-wide succession, especially the unusually progressive increase in number of fatal cases, is associated with an increase in the 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 different style of this review, addressing the questions rather than summarizing the cumulative answers.

There is a few confluence points of COVID-19 and rheumatology. The most important role of the rheumatologist in coping with the pandemic seems to be offering expertise in the application of drugs affecting immune processes that 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 development of 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 investigations and evidence from well-controlled studies. Currently, they can be answered based on expert opinion 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 of the patients [63].

Despite the lack of answers and need for further research, in the author's opinion 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 complex manifestations of COVID-19, also those within the musculoskeletal system, and once we learn more, we can respond better.

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