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Recommendations for coronavirus infection in rheumatic diseases treated with biologic therapy

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ABSTRACT

The Coronavirus-associated disease, that was first identified in 2019 in China (CoViD-19), is a pandemic caused by a bat-derived beta-coronavirus, named SARS-CoV2. It shares homology with SARS and MERS-CoV, responsible for past outbreaks in China and in Middle East. SARS-CoV2 spread from China where the first infections were described in December 2019 and is responsible for the respiratory symptoms that can lead to acute respiratory distress syndrome. A cytokine storm has been shown in patients who develop fatal complications, as observed in past coronavirus infections. The management includes ventilatory support and broad-spectrum antiviral drugs, empirically utilized, as a targeted therapy and vaccines have not been developed. Based upon our limited knowledge on the pathogenesis of CoViD-19, a potential role of some anti-rheumatic drugs may be hypothesized, acting as direct antivirals or targeting host immune response. Antimalarial drugs, commonly used in rheumatology, may alter the lysosomal proteases that mediates the viral entry into the cell and have demonstrated efficacy in improving the infection. Anti-IL-1 and anti-IL-6 may interfere with the cytokine storm in severe cases and use of tocilizumab has shown good outcomes in a small cohort. Baricitinib has both antiviral and anti-inflammatory properties. Checkpoints inhibitors such as anti-CD200 and anti-PD1 could have a role in the treatment of CoViD-19. Rheumatic disease patients taking immunosuppressive drugs should be recommended to maintain the chronic therapy, prevent infection by avoiding social contacts and pausing immunosuppressants in case of infection. National and international registries are being created to collect data on rheumatic patients with CoViD-19.

1. SARS-CoV2 and the acute respiratory distress syndrome

Coronavirus Disease-2019 (CoViD-19) has emerged over the past months as a clinical syndrome caused by a novel beta-Coronavirus, named Severe Acute Respiratory Syndrome (SARS)-CoV2. It was first reported in late December 2019 in Wuhan, China and the disease was officially named CoViD-19 by the World Health Organization (WHO) on February 11th, 2020 following an outbreak of acute respiratory illness in the Hubei province. Since these earliest reports, this infection has spread in many countries worldwide with a significant rate of infection in Italy that currently accounts for more than 110,000 infected cases associated with 13,155 fatalities. The WHO declared CoViD-19 a pandemic on March 11th. The CoViD-19 pandemic has important implications for patients with rheumatic diseases, particularly those undergoing a variety of immunosuppressive therapies. As it seems obvious that immunosuppressive therapy increases their risk of severe disease if infected with CoViD-19, many patients have the tendency to stop their immunosuppressive treatments, especially in highly impacted areas such as the Italian Lombardy region. However, it is important to note that many commonly used immunosuppressive drugs such as JAK kinase inhibitors and tocilizumab have been proposed and/or used for the treatment of select patients who develop a frequently fatal clinical sequalae known as Cytokine Release Syndrome (CRS) (also referred to as “cytokine storm”) following CoViD-19 infection. While data are

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changing rapidly and the disease trajectories can only be hypothesized, the issue whether to continue treating rheumatic disease patients needs to be addressed by the field of Rheumatology and other medical subspecialties, since some of these agents may be beneficial for specific phases or complications of the disease. SARS-CoV2 is a positive single strand 30,000 nucleotide RNA virus that includes 14 open reading frames that encode 27 proteins and belongs to the *Coronaviridae* family. Its phylogenetic data are consistent with the presence of a bat reservoir and subsequent spill over into the human population. Sequencing data shows that SARS-CoV2 shares a high degree of sequence homology with a betacoronavirus isolated from bats termed Bat-CoV-RaTG13, suggesting that the Chinese chrysanthemum bat is the likely origin of SARS-CoV2. Nonetheless, an unknown animal sold at the seafood market in Wuhan has been hypothesized to act as the intermediate host, as the first cases had common contacts in a market where no bats were present (bats hibernate in December). In addition, SARS-CoV2 shares 79% and 50% gene homologies with the SARS Coronavirus (SARS-CoV) that was responsible for an outbreak in 2002 and with the Middle East Respiratory Syndrome (MERS)-CoV responsible for infections in Saudi Arabia in 2012, respectively. Both these viruses had intermediate hosts that included the civet and camel, respectively, with humans serving as terminal hosts [1]."

Person-to-person transmission has already been established for SARS-CoV2 infection and reasoned to be mediated by respiratory droplets. The current data also suggests that the elderly and patients with a compromised immune system are at a significantly higher risk and higher mortality.

The CoViD-19 infection is suspected when patients develop fever, cough, myalgia and fatigue, with bilateral interstitial pneumonia diagnosed in most patients (up to 76% in the earliest series) by ground glass opacity and patchy infiltrates in the chest as visualized by computerized tomography. Around 20% of cases rapidly worsen into respiratory failure or acute respiratory distress syndrome (ARDS), requiring admission to the intensive care unit (ICU) with a mortality rate of approximately 2–3%, being highest in older age patients particularly those with chronic diseases and who are currently hospitalized in ICUs (up to 38%) [2–4]. Currently there are no specific drugs and/or vaccines for SARS-CoV2 infection, prompting the use of several broad-spectrum antiviral molecules. In addition, an animal model to study the disease and test potential vaccines is at present missing [5].

2. Anti-rheumatic drugs as possible therapies: antimalarials, anti-IL6, anti-IL1 and baricitinib

Some drugs usually used in rheumatologic field and targeting the host and its immune response seem to have the potential to interfere with CoViD-19 infection and their potential benefit is being studied in patients (Fig. 1). The pathogenesis of CoViD-19 remains unclear, but modelling assays revealed a high degree of homology in the receptor binding domains between SARS-CoV2 and SARS-CoV. All coronaviruses express a surface glycoprotein termed a “spike” which bind to the host receptor for viral entry that has been identified as angiotensin-converting enzyme 2 receptors (ACE2r) [1], expressed by mature lung epithelial cells, enterocytes, kidney proximal tubular cells and endothelial cells [6]. After receptor binding, lysosomal proteases cleave the spike protein releasing the signal peptide that facilitates viral entry into the cell [7]. These mechanisms may be targeted and interrupted by therapies such as chloroquine, an antimalarial drug, and preliminary data demonstrate that it may have clinical benefit in the management of CoViD-19 infected patients as determined by improved imaging and shortening of the diseases course [8]. We should note that hydroxychloroquine, which shares the same mechanism of action as chloroquine but has a better safety profile and is frequently used particularly in connective tissue disease, has a more potent anti-viral effect than chloroquine in vitro. From the results of physiologically-based pharmacokinetic models, a loading dose of 800 mg orally followed by

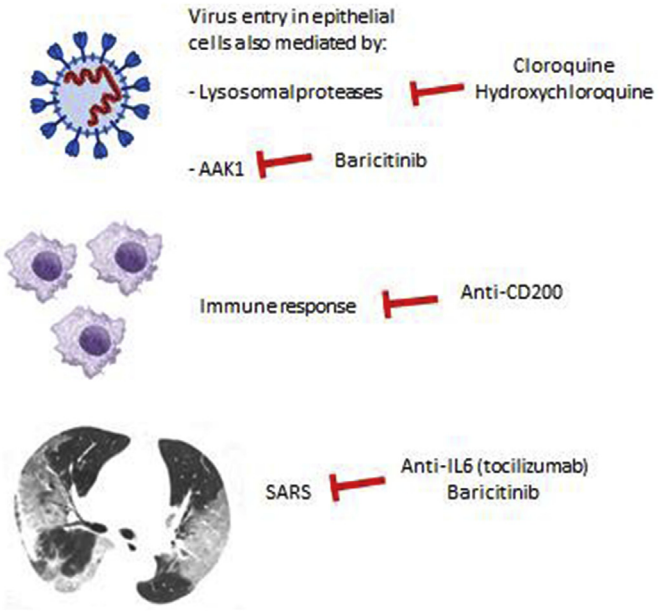

Fig. 1. Representation of possible mechanisms of action of anti-rheumatic drugs in coronavirus infection. AAK1 = AP2-associated protein kinase 1; SARS = severe acute respiratory syndrome.

400 mg daily for four days reaches three times the potency of chloroquine and is therefore a promising drug for both the prevention and the treatment of CoViD-19, with low risk of toxicity [9]. These findings have led to several clinical trials that are ongoing to study the efficacy of chloroquine or hydroxychloroquine in CoViD-19 patients. Hydroxychloroquine is thus being used in Italy for the treatment of CoViD-19 patients despite the absence of efficacy data in the clinical setting. In light of these data, the recommendation for rheumatic patients chronically taking antimalarial drugs is to not discontinue them, considering the antiviral efficacy and the immunomodulatory rather than immunosuppressive effect.

The pulmonary complications in human CoViD-19 patients are due to an exuberant local inflammatory response with diffuse alveolar damage. Patients dying because of SARS have lung consolidation, edema and mucopurulent material in the bronchial tree. At microscopic examination, alterations such as diffuse alveolar damage, hyaline membrane and fibrin formation, neutrophils and macrophages infiltrates were detected in the interstitium and alveoli. Similar features were noted in the only human autopsy report available of MERS infection. Cytokines and chemokines play a key role in the immune response against viral infections, and their altered production has been demonstrated in both SARS and MERS coronavirus infections. Such altered levels have been shown to be likely due to the low synthesis of antiviral cytokines such as interferons (IFN)α or β and in concert increased levels of other pro-inflammatory cytokines/chemokines that have pathogenic consequences. Among them, interleukin (IL)-1, IL-6 and other pro-inflammatory cytokines were shown to be significantly more elevated in patients with severe compared to uncomplicated SARS or MERS infection [10,11]. Recent preliminary data from China reported high plasma levels of cytokines including IL-6, related to the severity and the prognosis of the disease with a clear implication for the occurrence of “cytokine storm” and CRS. Tocilizumab, an anti-IL-6 receptor antibody that has been used clinically to treat rheumatoid arthritis and other autoimmune diseases, has been used and approved for treatment of a variety of clinical conditions that include CRS. These have included clinical conditions such as those associated with chimeric antigen receptor T-cell (CAR-T) therapy that appears to induce severe or life-threatening cytokine release syndrome [12]. A single dose of tocilizumab was used in 21 patients in China suffering from severe

respiratory syndrome during CoViD-19 infection, at the dosage of 400 mg intravenously, in addition to routine therapy. In a few days, 90% of patients recovered and lung opacities disappeared [13], suggesting that anti-IL-6 might be a powerful potential rescue therapy in respiratory distress syndrome of CoViD-19.

A potential role for anti-IL1 biologics could be hypothesized from data showing an activation of the NLRP3 inflammasome by SARS-CoV, with secretion of IL-1β. Studies have demonstrated that inflammasome activation also occurs in SARS-CoV2 infection, especially within lymphoid cells and patients have increased serum IL-1β [14]. Another potential treatment under evaluation for SARS-CoV2 related acute respiratory disease is baricitinib, an oral drug used to treat rheumatoid arthritis patients that functions as a blocker of Janus Kinases (JAK) 1 and 2, enzymes associated with intracellular signaling, including Type I and type II IFN signaling. One rationale for its use is based on the fact that viruses such as SARS-CoV2 utilize a protein expressed on its spike to bind to the ACE2 receptor and enter cells through a mechanism of receptor-mediated endocytosis. One of the known regulators of receptor mediated endocytosis is a kinase termed the AP2-associated protein kinase 1 (AAK1). Baricitinib has high affinity for AAK1. Inhibition of AAK1 is reasoned to not only inhibit receptor mediated endocytosis (blocking intracellular entry of the virus) but it may also function in the intracellular assembly of virus particles [15]. The plasma concentration of baricitinib at its current therapeutic dosage (2 or 4 mg orally once daily) is sufficient to inhibit AAK1, thus it may be able to reduce both the viral entry and the inflammation characteristic of CoViD-19 patients.

Another important aspect in CoViD-19 is that patients are not able to initiate a valid and rapid type I IFN response [10], but the mechanisms underlying this defective response are not completely clear. In SARS, macrophages and dendritic cells are only abortively infected and natural killer cells are not activated by the virus, thus suggesting a defective innate immune response with an altered virus clearance [6]. In a mouse model using the related coronavirus, delayed type-I IFN responses (with IFN levels peaking later in the immune response and remaining elevated) were associated with mortality from severe lung disease, due to recruitment of highly inflammatory macrophages into the lung [16,17]. Studies of human SARS-CoV infections also strongly suggest that dysregulated and persistently elevated type-I IFN responses are associated with severe human lung disease [18]. In the mouse model, absence of Type-I IFN signaling (achieved by knockout of the IFN-receptor) abolished lung mediated lethality. These data also suggest a second possible explanation for a therapeutic effect of JAK inhibitors such as baricitinib, since they block the downstream signaling of alpha and beta IFN receptors. The situation is complicated by the finding that very early administration of IFN-β in the mouse model also decreased lung disease, suggesting that timing and duration of type-I IFN responses is critical to whether the outcome is helpful or deleterious [16]. What does this imply for patients on JAK inhibition therapy? They may have a decreased IFN response to the virus, which would cause excess virus replication, but they also might have less risk of severe lung disease due to downregulation of the IFN signaling pathway. This illustrates the difficult balance between an adequate immune response to prevent viral replication and an over-exuberant immune response that causes severe lung pathology [17]. The role of type I IFN in SARS-CoV2 and the role of blocking IFN-I pathways therefore requires more detailed studies.

3. The role of the checkpoints inhibitors

The evasion of the immune system checkpoints are often used by both malignant cancer cells and pathogens to escape immune surveillance. One of the most interesting checkpoint inhibitors is the CD200-CD200R1 system (Fig. 1). This checkpoint negatively regulates the immune response with the aim to prevent an excessive inflammatory response to different triggers [19]. Thus, it has been shown to down-modulate TLR7 (single strand RNA virus sensor) in plasmacytoid dendritic cells of a mouse model of coronavirus infection [20] and to down-modulate macrophage activation [21]. Interestingly, the inhibition of CD200-CD200R1 has positive effects on coronavirus infection [19,20,22], restoring IFN production and increasing virus clearance. Checkpoint inhibitors are currently and effectively used as therapeutic agents for a variety of cancers, but have only minimally been studied in human infectious diseases, although their function was clearly defined using the murine model of LCMV infection. A CD200-Fc fusion protein has been successfully used in experimental settings [21] and trials on inhibitory antibody targeting of CD200 has been tested for the treatment of human cancer [19], thus suggesting the intriguing possibility to use currently available checkpoint inhibitors for the treatment of CoViD-19. A trial with another checkpoint inhibitor, anti-PD1, is also ongoing in CoViD-19 patients.

4. Management of rheumatic patients during the CoViD-19 pandemic

The scientific research on SARS-CoV2 and its possible therapies are based on the knowledge of previous coronaviruses and on data recently made available by the Chinese scientific society. Likewise, social and health policy, information and containment measures are based on what has been learned from previous epidemics, in order to optimize the current measures. From the epidemiology of SARS-CoV and SARS-CoV2 in China we have learned how fundamental are measures such as early recognition of the problem, strict infection control and identification of infected patients, isolation measures, inclusion and formation of new medical and sanitary staff in the health system, designation of new hospital wards with appropriate equipment and information through the mass and social media [14]. As part of these measures, recently, the Italian Society of Rheumatology has proposed a set of practical recommendations to improve the management of CoViD-19 patients and to decrease the risk of acquiring this infection in particular in rheumatic patients undergoing immunosuppressive therapies (Table 1). In general, the interruption of therapies used in rheumatic patients is not advised, as it may be responsible for the onset of clinical flares of the rheumatic disease with subsequent use of other immunosuppressants such as oral glucocorticoids that may be equally unsafe for patients in case of acquired CoViD-19. Although the data are at present unavailable, it appears important to maintain chronic therapies and to have a strict control of each patient in order to evaluate specific clinical needs. In fact, the infection risk in rheumatic diseases such as rheumatoid arthritis is also related to disease activity and a flare due to therapy discontinuation would confer a higher risk of infection [23].

For the same reason, rheumatic patients on long term oral glucocorticoid treatment should not only never stop these abruptly but in addition it should be kept in mind that ending of such therapy may also lead to adrenal crisis. Prevention measures suggested by the Italian

Table 1
Recommendations proposed for rheumatic diseases during CoViD-19 pandemic.

1- Do not discontinue immunosuppressive treatment
2- Follow the recommendations for infection prevention suggested by the Italian Ministry of Health, in particular avoid contact with crowded places. Smart working is encouraged.
3- Chloroquine and hydroxychloroquine seem to have some efficacy on SARS-CoV2 infection.
4- Chronic immunomodulatory therapies, including biologic drugs, must be guaranteed for rheumatic patients. This includes tocilizumab and baricitinib availability for patients chronically taking these compounds, as they may start to be used to treat CoViD-19 severe pneumonia cases.
5- Outpatients clinics, albeit with limited activity, should be guaranteed for biologic therapies, as the National Health System has authorized people to move for very specific reasons such as health issues. For all patients, consulting should be made available using media that exclude a person-to-person relationship.

Ministry of Health must be applied to everyone, in particular by rheumatic patients undergoing immunosuppressive therapies. Patients are therefore strongly encouraged to avoid social contact and maintain isolation. Chronic therapies will be guaranteed for rheumatic patients also in these weeks of CoViD-19 outbreak in which the routine outpatient clinics are closed, as the National Health System has authorized people to move for very specific reasons such as health issues and the need for biologic therapies which are available only in some hospitals. As tocilizumab and baricitinib may start to be used to treat CoViD-19 severe pneumonia cases, their availability must be guaranteed for the treatment of rheumatic patients who are using these compounds. If a rheumatic patient develops symptoms of any infection, it is important to follow the guidelines suggested by the rheumatology community and immunosuppressive therapy should be paused for the duration of the infection. The one exception is hydroxychloroquine, which may have therapeutic potential for CoViD-19 infection and should therefore not be stopped in patients who have been taking it for a rheumatic disease. As mentioned above, it is possible that IL-6 blockade and the use of JAK inhibitors could have beneficial effects on severe lung disease, but we don't yet know enough to recommend continuing these agents, since they could adversely affect viral clearance. Much more study of the kinetics of SARS-CoV2 in the lung, and the relation of the immune response to the onset of CRS, is therefore needed to clarify recommendations for patients on these agents.

The epidemiological scenario is rapidly changing daily and we still have no knowledge about the infection rate and course of CoViD-19 in rheumatologic conditions. Therefore, a national or international registry is strongly encouraged to understand the impact of the infection on specific rheumatic diseases or treatments and the risk factors for poor outcomes. The Italian Society of Rheumatology has established such a registry in March 2020 and data are being collected. Although our observations have no epidemiological grounds, we are quite surprised by the limited number of rheumatic patients contacting us because of a CoViD-19 infection. Furthermore, an international registry supported by America College of Rheumatology, European League Against Rheumatism and other rheumatologic societies worldwide is being launched.

In the meantime, it is important that patients are reassured and consultations made available using media that exclude a person-to-person relationship to minimize the risk of infection.

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