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COVID-19 infection and rheumatoid arthritis: faraway, so close!

Ennio Giulio Favalli[1], Francesca Ingegnoli[1,2], Orazio De Lucia[1], Gilberto Cincinelli[2], Rolando Cimaz[2,3], Roberto Caporali[1,2]

[1] Division of Clinical Rheumatology, ASST Gaetano Pini-CTO Institute, Milan, Italy

[2] Department of Clinical Sciences and Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milano, Italy

[3] Division of Pediatric Rheumatology, ASST Gaetano Pini-CTO Institute, Milan, Italy

Corresponding author:

Ennio Giulio Favalli, MD

Division of Clinical Rheumatology, ASST Gaetano Pini-CTO Institute, Milan

Via Gaetano Pini, 9

20122 Milan - Italy

email address: enniofavalli@me.com

Phone: +39 0258296421

Mobile: +39 3289659778

FAX: +39 0258296315

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ABSTRACT

The outbreak of the new coronavirus infections COVID-19 in December 2019 in China has quickly become a global health emergency. Given the lack of specific anti-viral therapies, the current management of severe acute respiratory syndrome coronaviruses (SARS-CoV-2) is mainly supportive, even though several compounds are now under investigation for the treatment of this life-threatening disease. COVID-19 pandemic is certainly conditioning the treatment strategy of a complex disorder as rheumatoid arthritis (RA), whose infectious risk is increased compared to the general population because of an overall impairment of immune system typical of autoimmune diseases combined with the iatrogenic effect generated by corticosteroids and immunosuppressive drugs. However, the increasing knowledge about the pathophysiology of SARS-CoV-2 infection is leading to consider some anti-rheumatic drugs as potential treatment options for the management of COVID-19. In this review we will critically analyse the evidences on either positive or negative effect of drugs commonly used to treat RA in this particular scenario, in order to optimize the current approach to RA patients.

1. INTRODUCTION

In December 2019 a new type of pneumonia supported by a novel member of the coronoviridae family named SARS-CoV-2 (severe acute respiratory coronavirus 2 syndrome) developed from Wuhan Province in China [1]. Phylogenetic analysis demonstrated that this is a different virus with ~80% nucleotide identity with SARS-CoV-1 [2]. The disease caused by SARS-CoV-2 is characterized by dry cough, fever, dyspnea and fatigue, accompanied by lymphopenia [3–6]. In more severe cases (apparently up to 15-20% of infected patients) the picture may become more complicated by the onset of interstitial pneumonia with alveolar damage, which clinically can lead to severe Acute Respiratory Distress Syndrome (ARDS) and even death [7]. Since the initial outbreak, the

epidemic has had a rapid global spread worldwide which led the World Health Organization (WHO) to declare the disease now called COVID-19 a Public Health Emergency of International Concern on 30th January 2020 and a pandemic on 11th March 2020. The epidemiological picture is constantly evolving, and data updated as of March 17th count 159 countries involved with more than 185,000 cases and 7,500 confirmed deaths [8].

In this context of growing health emergency, clarifying the relationship between COVID-19 and the population of fragile patients suffering from immune-rheumatological diseases is absolutely crucial. On the one hand, the rapid and uncontrolled spread of the epidemic can clearly generate even more concerns in rheumatic patients, which are intrinsically characterized by an increased infectious risk due to the disease itself and to the iatrogenic effect of immunosuppressive agents such as corticosteroids and synthetic or biological disease-modifying drugs [9]. On the other hand, the growing knowledge about the pathogenesis of SARS-CoV-2 infection is leading to the introduction of drugs commonly used for the treatment of rheumatoid arthritis (RA) even for the management of more complex cases of COVID-19. Chloroquine and hydroxychloroquine have now been permanently included, alongside antiviral drugs, in protocols for the treatment of COVID-19 pneumonia [10]. In addition, the use of interleukin 6 (IL-6) blockers seems to be very promising for the management of the massive cytokine storm associated to the development of the typical lung damage and the consequent ARDS occurring in the most aggressive patterns of SARS-CoV infection [11].

Therefore, waiting for observational data on the incidence of COVID-19 in rheumatological patients, the best strategy to manage immune-rheumatological diseases during this emergency period is still far to be clear. The purpose of this review is to provide an overview on viral infectious risk in RA patients, with a particular focus on the knowledge about the current new pandemic and the use of anti-rheumatic drugs in this context of health emergency.

2. THE PATHOPHYSIOLOGY OF COVID-19 INFECTION

Coronaviruses are the largest viruses with a positive-sense single-stranded-RNA genome. The host immune response is by one side essential for the resolution of COVID-19 infection, but it can also be crucial for the pathogenesis of major clinical manifestations of the disease. The angiotensin-converting enzyme 2 (ACE2) has been identified as the host cell-surface receptor for SARS-CoV2 envelope spike glycoprotein [12]. ACE2 is a type I membrane protein expressed on cells in the kidney, heart, gastrointestinal tract, blood vessels, and, importantly, lung AT2 alveolar epithelial cells, which are particularly prone to viral infection [13]. SARS-CoV-2 infection leads to the downregulation of ACE2 expression, thus resulting in excessive production of angiotensin II by the related enzyme ACE. It has been suggested that the stimulation of type 1a angiotensin II receptor (AGTR1A) increases pulmonary vascular permeability, thus potentially explaining the increased lung damage when the expression of ACE2 is decreased [14]. Due to this mechanism of action, it has been postulated that subjects with diabetes mellitus or hypertension using ACE-inhibitors or angiotensin receptor blockers may have an increase of both the risk of infection and the severity of COVID-19 [15]. As only scarce evidence supports this hypothesis, the European Society of Cardiology recently published a position statement that strongly recommends continuing these treatments despite the current epidemic [16]. An additional point to be clarified is also the role of the genetic predisposition for an increased risk of SARS-CoV-2 infection due to ACE2 polymorphisms that have been linked to hypertension, diabetes mellitus, and cerebral stroke, especially in Asian populations [15].

The viral RNA genome is released into the cytoplasm, and the RNA is uncoated to allow translation of the two polyproteins, transcription of the sub-genomic RNAs and replication of the viral genome [17]. Progression to ARDS is associated with the upregulation of pro-inflammatory

cytokines and chemokines, known as Cytokines Release Syndrome (CRS), with a pattern very similar to that of secondary haemophagocytic lymphohistiocytosis (sHLH). In adults, sHLH is an under-recognized, hyperinflammatory syndrome characterized by a massive and fatal hypercytokinaemia with multiorgan failure, most commonly triggered by viral infections [18,19]. Main clinical features of sHLH include unremitting fever, hyperferritinaemia and cytopenias, and pulmonary involvement (including ARDS) occurring in approximately 50% of patients [20]. A cytokine profile resembling sHLH has been reported in most severe COVID-19 infections, characterized by increased levels of a number of cytokines (interleukin-1β [IL-1β], IL-2, IL-6, IL-7, IL-8, tumor necrosis factor-α [TNF]) and chemokines (CXC chemokine ligand 10 [CXCL10] and CC-chemokine ligand 2 [CCL2]) [21,22]. The management of this cytokine storm is one of the major unmet needs regarding COVID-19 infection.

3. IS THE RISK OF VIRAL INFECTION INCREASED IN RA PATIENTS?

The relationship between RA and infectious diseases is very complex and can be interpreted in two different directions. On the one hand, in fact, the potential role of external microorganisms in producing acute and chronic arthritis in the form of either the direct colonization of the joints by the pathogen or the aberrant autoimmune reaction produced by the host response to the infection is well known [23,24]. Few studies have investigated a potential link between respiratory viral infections and the development of RA [25] and in particular a Korean study reported parainfluenza and coronavirus to be associated with the number of incident RA [26]. In addition, in patients with overt inflammatory arthritis, infections are a major concern as they can contribute to disease flares [27–29]. On the other hand, RA patients carry a documented increased risk of infection compared with the general population. A population-based study by Doran and colleagues compared two matched groups of 609 patients with or without RA showing that RA

patients had a significantly higher risk of serious (RR 1.53, 95 % CI 1.41-1.65) and hospitalized (RR 1.88, 95 % CI 1.71-2.07) infections [30]. Similarly, a prospective cohort study conducted on 2108 patients with inflammatory polyarthritis reported a 2- to 4-fold increased risk of hospitalized infection compared to healthy population [31]. This trend is primarily the result of a general impairment of the immune system typical of all autoimmune disorders and strictly dependent on the degree of disease activity. In fact, it has been demonstrated by an analysis conducted in 16242 RA patients from the US CORRONA registry that each 0.6 unit increase in Disease Activity Score 28 (DAS28) corresponded to a 25% increased rate of infections requiring hospitalization (Incident rate ratio [IRR] 1.25, p=0.03) and a 4% increased rate of outpatient infections (IRR 1.04, p=0.01) [32]. In addition, a subsequent report from the same registry showed that the risk of serious infections increased progressively from patients achieving clinical remission to those achieving low (adjusted IRR 1.69, 95% CI 1.32–2.15) or moderate (adjusted IRR 1.30, 95% CI 1.09–1.56) disease activity, demonstrating the importance of maintaining a good disease control in order to reduce infectious complications [33].

Another important determinant of infectious risk is the presence of comorbidities, which very often complicate the course of RA [34]. Diabetes mellitus, cardiovascular diseases, renal failure, interstitial lung disease, and chronic obstructive pulmonary disease (COPD) are all concomitant disorders associated with an increased incidence of infections in RA [27,35].

Finally, RA can also be complicated by infections caused by the iatrogenic effect of immunosuppressive therapies, which will be discussed in detail in the next section.

4. THE IMPACT OF DRUGS FOR RHEUMATIC DISEASES ON VIRAL INFECTIONS: what do we know?

Corticosteroids and NSAIDs

It has now been more than 70 years that corticosteroids (CS) are pivotal for RA management and their role as remission inducer and bridging therapy for the management of disease flare has recently been renewed by the latest update of EULAR recommendations for RA treatment [36]. Even though CS efficacy in rapidly suppressing inflammation during RA initial course or flares is well recognized [37], their downside is the broad spectrum of adverse events, including severe infections and the high risk of developing comorbidities further increasing the risk of infection [27,38]. Although RCTs conducted in the past with CS showed no higher risk of infections in RA patients [39–41], cohort and case-control studies reported increased rates of overall infections in RA patients treated with CS, according to a dose-dependent fashion [42]. The majority of these infectious events are of bacterial etiology, but RA patients receiving CS exhibit a greater risk of developing even viral infections. As an example, a 2012 retrospective cohort-study demonstrated an increased risk of Herpes Zoster infections with an incidence rate of 8.54 cases per 1000 patient-years in CS treated population [29].

Thus, CS on the one hand inhibit the immune response and delay the clearance of the pathogen, while on the other hand they suppress the host inflammatory response, which in the case of viral infections of the respiratory tract is the major responsible for lung damage and occurrence of ARDS [43]. The latter represented the rational for the widely use of CS for the management of Middle East respiratory syndrome (MERS)-CoV [44] and SARS-CoV [45] outbreaks, both histologically characterized by lung inflammation and diffuse alveolar damage [46]. However, evidence from the literature points to a predominantly negative effect of CS in the management of this type of infection. A 2019 systematic review and meta-analysis including ten observational studies (n=6548) conducted in influenza reported increased mortality (risk ratio [RR] 1.75, 95% CI 1.3–2.4; p=0.0002),

increased rate of secondary bacterial or fungal infection (RR 2·0, 95% CI 1·0–3·8; p=0.04), and longer stay in an intensive care unit (mean difference 2.1, 95% CI 1.2–3.1; p<0.0001) in patients receiving CS [47]. Moreover, a review exploring treatments for ARDS, including six studies with a total of 574 patients, concluded that insufficient evidence exists to recommend CS treatment [48]. Overall, no clear reason exists to expect that patients with COVID-19 infection will benefit from CS, and they might be more likely to be harmed with such therapy [49]. In fact, current interim guidance from WHO on clinical management of COVID-19 infection advises against the use of CS unless indicated for another reason [10].

The role of NSAIDs in the course of viral infections is still controversial. Ibuprofen has been demonstrated to induce an overexpression of ACE2 when used in diabetic rats [50] and this effect might theoretically increase the susceptibility and worsen the clinical course of COVID-19 infection in treated patients [15]. In addition, the use of both NSAIDs and acetaminophen could be associated with a masking of the fever rise during COVID-19, resulting in a delay in diagnosis and proper management of the infection.

csDMARDs

The most comprehensive analysis of infectious risk in patients treated with csDMARDs is a retrospective, longitudinal study of a population-based RA cohort using an administrative database including a total of 27,710 individuals with RA and providing 162,710 person-years of follow-up [51]. Use of csDMARDs without corticosteroids was associated with a small decrease in mild infection risk (adjusted rate ratio [RR] 0.90, 95% confidence interval [95% CI] 0.88–0.93) and was not associated with increased serious infection risk (adjusted RR 0.92, 95% CI 0.85–1.0). Similarly, another retrospective analysis conducted on 1,993 patients from a claim database demonstrated a slightly reduced risk of hospitalized infection for methotrexate (adjusted RR 0.81, 95% CI 0.70-0.93) and hydroxychloroquine (adjusted RR 0.74, 95% CI 0.62-0.89) [52]. A recent

systematic review and meta-analysis of the literature confirmed the lack of an increased risk of infection in patients receiving MTX (RR: 1.14; 95% CI, 0.98–1.34) [53]. However, all these reports provided no data on the risk of stratified infection by pathogen.

bDMARDs

The risk of infection observed in RA patients treated with bDMARDs is generally considered slightly higher (from 1.5- up to 2-fold) compared with csDMARDs [27,54]. This evidence recurred in most RCTs [55] and observational registry studies [56–58] and was confirmed by a recent meta-analysis which showed that this risk is progressively increasing in relation to the use of bDMARDs at higher than recommended dosages [59]. Following the results of comparative metanalyses and real-life studies, abatacept is accepted as the safest bDMARD in terms of infectious risk [60,61].

Data focused on viral respiratory infections in bDMARD cohort are still very limited. The incidence of influenza-like infections observed in a cohort of 159 Italian patients treated with bDMARDs during the influenza season 2009-2010 was higher than the value reported in a wide sample of Italian population in the same period, even though no important complications or hospitalizations have been reported [62]. Overall, post-marketing experience is relatively reassuring that anti-TNF treated patients may not be at any specifically increased risk of influenza and that severe adverse outcomes, including death, do not appear to be exceedingly frequent [63].

tsDMARDs

The overall risk of serious and opportunistic infections observed with Janus Kinase (JAK) inhibitors in RA patients is roughly comparable with bDMARDs [64,65], although these early years of tofacitinib and baricitinib use have raised the issue of an increased risk of Herpes Zoster virus (HZV) infections [66]. Data from tofacitinib pooled population enrolled in RCTs showed an HZV incidence rate of 4.0 per 100 patient-years (with greater incidence in geographic area with high HZV endemicity), doubling the rates of RA patients not receiving JAKis [67]. A similar picture has

also been observed in the overall development program of baricitinib, with an incidence rate of 3.2 cases per patient-years [68]. The subsequent real-life experience from US claim databases revealed that the risk of HZV was higher in patients receiving tofacitinib compared to those treated with abatacept (aHR 2.01 (95% CI 1.40; 2.88) [69], and the risk of serious hospitalized HZV infection is 2-fold higher versus all bDMARDs [70]. Older age, female sex, prednisone >7.5 mg/day, prior infection, and greater number of hospitalizations were associated with increased HZV risk, whereas vaccination was associated with a lower risk [71]. More recent reports from RCTs conducted with novel JAK-1 selective inhibitors upadacitinib and filgotinib have basically confirmed the same trend, suggesting that the increase in HZV infections can be considered as a class effect of JAKis [72,73]. Although the exact mechanism by which HZV reactivation occurs in the context of JAK inhibition is unclear, the downregulation of both cell-mediated immunity and innate antiviral signaling through type I and II interferons (IFN) is likely to be involved [74].

Currently, no data are available on the risk of respiratory virus infections carried by JAK inhibitors.

5. THE MANAGEMENT OF COVID-19: A ROOM FOR ANTI-RHEUMATIC DRUGS?

Currently, vaccines and approved targeted therapeutics for the treatment of the new SARS-CoV-2 infection are still lacking and the management of COVID-19 is only supportive, even though a multitude of compounds are now under investigation for the treatment of this emerging disease [75]. The need to urgently identify an effective approach to manage COVID-19 led to the strategy of testing the efficacy of the existing antiviral drugs commonly used for other viral infections. In particular, considering the similarity between SARS-CoV-2 and other Betacoronavirus associated with previous epidemics as SARS-CoV and MERS-Cov, the same drugs used with controversial results for these conditions (interferon, ribavirin, and lopinavir-ritonavir) have been considered even for COVID-19 [76]. Anecdotal cases have demonstrated the ability of lopinavir-ritonavir to

significantly reduce viral load and improve disease outcome [77]. In addition, remdesivir, an adenosine analogue currently under development for the management of Ebola virus infection [78], has been recently recognized as a promising antiviral therapy against a wide spectrum of RNA viruses [79] and showed good preliminary *in vitro* results in the control of SARS-CoV-2 infection [80]. Consequently, lopinavir-ritonavir and remdesevir are currently the only anti-viral drugs included in the more severe case management protocols of COVID-19 [10]. Recent reports described the potential role of human monoclonal antibodies that bind the coronavirus spike receptor binding domain, leading to the neutralization of SARS-CoV2 capability to interact with human target cells [81,82]. However, at the moment these can only be considered as potential treatment options for the future, but they are obviously not available for the management of the current pandemic.

Beyond the use of specific anti-viral products, many drugs commonly used in the treatment of RA have been proposed as possible therapies for COVID-19 as a consequence of the increased knowledge about the pathophysiology of the infection (Table 1).

Chloroquine/hydroxychloroquine

Chloroquine and hydroxychloroquine are widely used anti-malarial drugs with well-known immunomodulatory properties that have extended their use to several immuno-rheumatological diseases including RA [83]. The ability of chloroquine to produce an anti-viral effect has been known since the late 1960s [84]. Several mechanisms by which the drug is able to interfere with the growth and spread of different viruses (including SARS coronavirus) have been demonstrated in *in vitro* studies [85], even though the subsequent *in vivo* experience was controversial [86,87].

At clinically admissible concentrations chloroquine is able to increase the endosomal pH required for virus/cell fusion, to inhibit the toll-like receptor activity, and to interfere with terminal

glycosylation of the cellular receptor ACE 2 [88–90]. All these functions may negatively influence the virus-receptor binding, resulting in a potential effect of the drug on both entry and post-entry stages of the SARS CoV infection. As a consequence, chloroquine has recently been included in at least 10 randomized controlled trials currently ongoing in China, where it is tested for the treatment of COVID-19 under various combination protocols with the anti-viral drugs mentioned above [91]. Interim results from more than 100 patients have demonstrated that chloroquine is superior to the control treatment in improving lung imaging findings, inhibiting the exacerbation of pneumonia, promoting a virus negative conversion, and shortening the disease course at different levels of severity [92]. More recently, hydroxychloroquine was demonstrated to be more 3-times more potent than chloroquine in an *in vitro* study based on pharmacokinetic models (PBPK). An oral loading dose of 400 mg twice daily, followed by a maintenance dose of 200 mg given twice daily for 4 days seems to be the best option for the management of SARS-CoV-2 infection [93].

IL-6 and IL-1 blockers

As already described, ARDS occurring in most severe case of COVID-19 infection is mainly produced by the massive release of pro-inflammatory mediators (CRS) associated with viral replication and lung injury, leading to multiorgan failure [22]. Moreover, the high levels of these cytokines have been reported to be inversely related to the absolute lymphocytes count, with surviving T-cells functionally exhausted [94]. Since an effective immune response against viral infections depends on the activation of cytotoxic T cells, CRS might be associated with a decreased viral clearance, contributing to COVID-19 worsening. IL-6 and IL-1 play a pivotal role in this hyperinflammatory condition, suggesting the potential use of their blockers as treatment option for SARS-CoV2 related interstitial pneumonia. Data from a phase 3 RCT of IL-1 blockade (anakinra)

in sepsis showed significant survival benefit in patients with hyperinflammation, without increased adverse events [95]. A small retrospective study on 21 patients affected by severe COVID-19 demonstrated that tocilizumab improved CT scan abnormalities and oxygen saturation, and normalized CRP levels and lymphocytes count in most of the patients [96]. A multicentre RCT of tocilizumab (IL-6 receptor blocker licensed for both RA and cytokine release syndrome) has been approved in China and is currently ongoing in patients with COVID-19 pneumonia and elevated IL-6 levels (ChiCTR2000029765) and a phase II study has been approved by the Italian Regulatory Drug Agency (AIFA) and will enrol 330 patients with pneumonia and early respiratory failure, with 1-month mortality reduction as primary outcome (TOCIVID-19). Moreover, the company that produces the second marketed IL-6 inhibitor sarilumab recently announced its intention to undertake a study with a similar design [97].

The identification of a unique definition of CRS during COVID-19 infection is crucial to better customize the management of critical patients. The presence of a large area of lung injury (≥50%) with decreased levels of CD4 and CD8 T-lymphocytes (lower than 50% of minimum normal range), and increased levels of IL-6 in peripheral blood have been recognized as the greatest risk factors of CRS in a retrospective analysis of 11 critically pneumonia Chinese patients infected with COVID-19 [98]. Increasing ferritin level and erythrocyte sedimentation rate or decreasing platelet counts would be additional parameters potentially useful to discriminate patients requiring immunosuppressive treatment [22].

TNF inhibitors

As previously described, SARS-CoV infection is associated with a downregulation of ACE2 expression coupled with an increased activity of the renin-angiotensin system responsible for lung injury [14].

Moreover, the viral spike protein is able to induce a TNF-α-converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain, crucial for the penetration of the virus into the cell [99]. Since this process seems to be strictly coupled to TNFα production, it has been postulated that the use of TNF inhibitors may be effective in reducing both SARS-CoV2 infection and the consequent organ damage [100]. As a result, a study evaluating adalimumab in COVID-19 infection has recently been registered in the Chinese Clinical Trial Registry (ChiCTR2000030089).

Janus Kinase inhibitors

As previously described in detail, SARS-CoV-2 enters targeted cells through receptor-mediated endocytosis [12]. Some of the identified regulators of clathrin-mediated endocytosis are members of the numb-associated kinase (NAK) family, such as AP2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK) [101]. Inhibition of AAK1 may stop the access of the virus into lung cells and also the intracellular assembly of virus particles [102]. Of 47 AAK1 blockers approved for medical use, 6 inhibit AAK1 with high affinity. These include oncologic agents such as erlotinib, sunitinib, ruxolitinib, and fedratinib, which have all been demonstrated to inhibit infection of cells by Dengue virus, Ebola virus, and respiratory syncytial virus [103]. Unfortunately, all these compounds are able to produce adequate NAK inhibition only at doses significantly higher than those normally used in clinical practice and therefore potentially toxic for the patient [104,105]. Conversely, the JAK inhibitor baricitinib is able to effectively inhibit AAK1 and GAK at the plasma concentration obtained with the approved dosage for the treatment of RA (2 to 4 mg daily) [106]. Moreover, as a selective inhibitor of JAK 1 and 2, baricitinib is also able to produce an important dampening of host inflammatory response due to CRS (including IL-6 and interferon gamma) responsible for the more severe forms of interstitial pneumonia during COVID-19 [107,108]. Finally, the minimal interaction of baricitinib with the relevant CYP drug-metabolising enzymes

makes the drug a possible candidate for inclusion in combination protocols with antiviral drugs such as lopinavir/ritonavir and remdesivir [109]. Interestingly, tofacitinib shows no detectable inhibition of AAK1 [104], whereas currently no data are available on the possible effect of other JAK inhibitors approved or tested for RA (such as upadacitinib or filgotinib) in relation to coronavirus infection. Unexpectedly, the only clinical trial evaluating the potential role of clathrin-mediated endocytosis blockade in the management of COVID-19 is currently ongoing with ruxolitinib (ChiCTR2000029580).

On the other side, IFN is one of the most potent innate immune responses to prevent viral replication during the early phases of infection [110]. The activation of transcription through JAK/STAT signaling pathway by IFNs leads to the up-regulation of several interferon stimulated genes which have the ability to rapidly kill viruses within infected cells [111]. Almost all viruses have developed strategies to combat the effects of type 1 and type 3 IFNs by blocking the IFN signaling pathway [112] and viral encoded factors able to antagonize the JAK/STAT pathway are crucial determinants of virulence [113]. In particular, Influenza A viruses disrupt JAK/STAT signaling by reducing the expression of the IFN receptor and by directly inhibiting IFN signaling [114]. As a consequence, JAK/STAT blockade generated by baricitinib certainly produces an impairment of IFN-mediated anti-viral response, with a potential facilitating effect on the progression of SARS-CoV2 infection at the moment not yet better quantified.

In conclusion, evidence of the possible use of baricitinib in the treatment of COVID-19 infection remains highly controversial and further studies are warranted to better clarify its potential role in the treatment of more serious cases of viral pneumonia.

5. CONCLUSIONS

The COVID-19 epidemic represents a health emergency that is inevitably affecting the management of a complex disease such as RA [115,116]. As a chronic autoimmune inflammatory disorder, RA carries a higher infectious risk than the general population. The use of synthetic and biologic disease-modifying drugs is associated with a potential further increase in the incidence of serious infections, but the poor control of RA disease activity is an even greater infectious risk factor. Thus, RA patients should be encouraged to continue their treatment even during COVID-19 outbreak. In our opinion, this strategy is reasonable as it aims to prevent disease flares that can contributes to increase patient burden, disability, poor quality of life, and healthcare use [117]. In addition, the discontinuation of ongoing treatments could lead to the need to introduce CS as bridging therapy, which may further increase the risk of viral infection, as well as being inappropriate for the management of SARS-CoV2 interstitial pneumonia.

Chloroquine and hydroxychloroquine are currently included in the treatment protocol for the management of COVID-19 infections and might be useful to prevent or mitigate the course of infection in patients with RA taking them as csDMARDs. The use of IL-6 inhibitors as tocilizumab or sarilumab seems to be promising for the management of most critical cases of interstitial pneumonia complicated by CRS, but the identification of definite criteria to discriminate patients to be treated with these compounds is still under debate. Finally, although baricitinib has the potential to affect SARS-CoV2 penetration into pulmonary epithelial cells, major concerns remain about the inhibition of IFNs activity which could be detrimental in the course of viral infection.

REFERENCES

[1] Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3. doi:10.1038/s41586-020-2012-7.

[2] Tang X, Wu C, Li X, Song Y, Yao X, Wu X, et al. On the origin and continuing evolution of SARS-CoV-2. Natl Sci Rev 2020. doi:10.1093/nsr/nwaa036.

[3] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. Jama 2020;323. doi:10.1001/jama.2020.2648.

[4] Zhang J-J, Dong X, Cao Y-Y, Yuan Y-D, Yang Y-B, Yan Y-Q, et al. Clinical characteristics of 140 patients infected by SARS-CoV-2 in Wuhan, China. Allergy 2020. doi:10.1111/all.14238.

[5] Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New Engl J Medicine 2020. doi:10.1056/nejmoa2002032.

[6] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet Lond Engl 2020;395:497–506. doi:10.1016/s0140-6736(20)30183-5.

[7] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Medicine 2020. doi:10.1016/s2213-2600(20)30079-5.

[8] https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd. Accessed 17th March 2020

[9] Favalli EG, Biggioggero M, Meroni PL. Methotrexate for the treatment of rheumatoid arthritis in the biologic era: Still an "anchor" drug? Autoimmun Rev 2014;13:1102–8. doi:10.1016/j.autrev.2014.08.026.

[10] World Health Organization. Clinical management of severe acute respiratory infection when Novel coronavirus (2019-nCoV) infection is suspected: Interim Guidance. 2020.

[11] Tisoncik JR, Korth MJ, Simmons CP, Farrar J, Martin TR, Katze MG. Into the eye of the cytokine storm. Microbiol Mol Biology Rev Mmbr 2012;76:16–32. doi:10.1128/mmbr.05015-11.

[12] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020. doi:10.1016/j.cell.2020.02.052.

[13] Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. Biorxiv 2020:2020.01.26.919985. doi:10.1101/2020.01.26.919985.

[14] Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, et al. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. Nat Commun 2014;5:3594. doi:10.1038/ncomms4594.

[15] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Medicine 2020. doi:10.1016/s2213-2600(20)30116-8.

[16] G DS, Cardiology ES o. Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers n.d.

[17] Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Analysis 2020. doi:10.1016/j.jpha.2020.03.001.

[18] Yildiz H, Neste EVD, Defour JP, Danse E, Yombi JC. Adult haemophagocytic lymphohistiocytosis: a Review. Qjm Mon J Assoc Physicians 2020. doi:10.1093/qjmed/hcaa011.

[19] Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. Lancet 2013;383:1503–16. doi:10.1016/s0140-6736(13)61048-x.

[20] Seguin A, Galicier L, Boutboul D, Lemiale V, Azoulay E. Pulmonary Involvement in Patients With Hemophagocytic Lymphohistiocytosis. Chest 2016;149:1294–301. doi:10.1016/j.chest.2015.11.004.

[21] Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, et al. Characteristics of lymphocyte subsets and cytokines in peripheral blood of 123 hospitalized patients with 2019 novel coronavirus pneumonia (NCP). Medrxiv 2020:2020.02.10.20021832. doi:10.1101/2020.02.10.20021832.

[22] Mehta, P, McAuley DF, Brown M, Sanchez E, Tattersall, RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020. doi:doi.org/10.1016/S0140-6736(20)30628-0.

[23] Mathew AJ, Ravindran V. Infections and arthritis. Best Pract Res Clin Rheumatology 2014;28:935–59. doi:10.1016/j.berh.2015.04.009.

[24] Bogdanos DP, Smyk DS, Invernizzi P, Rigopoulou EI, Blank M, Pouria S, et al. Infectome: a platform to trace infectious triggers of autoimmunity. Autoimmun Rev 2012;12:726–40. doi:10.1016/j.autrev.2012.12.005.

[25] Arleevskaya MI, Shafigullina AZ, Filina YV, Lemerle J, Renaudineau Y. Associations between Viral Infection History Symptoms, Granulocyte Reactive Oxygen Species Activity, and Active Rheumatoid Arthritis Disease in Untreated Women at Onset: Results from a Longitudinal Cohort Study of Tatarstan Women. Front Immunol 2017;8:1725. doi:10.3389/fimmu.2017.01725.

[26] Joo YB, Lim Y-H, Kim K-J, Park K-S, Park Y-J. Respiratory viral infections and the risk of rheumatoid arthritis. Arthritis Res Ther 2019;21:199. doi:10.1186/s13075-019-1977-9.

[27] Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology Oxf Engl 2012;52:53–61. doi:10.1093/rheumatology/kes305.

[28] Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology Oxf Engl 2010;50:124–31. doi:10.1093/rheumatology/keq242.

[29] Widdifield J, Bernatsky S, Paterson JM, Gunraj N, Thorne JC, Pope J, et al. Serious infections in a population-based cohort of 86,039 seniors with rheumatoid arthritis. Arthritis Care Res 2013;65:353–61. doi:10.1002/acr.21812.

[30] Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: A population-based study. Arthritis and Rheumatism 2002;46:2287–93. doi:10.1002/art.10524.

[31] Franklin J, Lunt M, Bunn D, Symmons DPM, Silman AJ. Risk and predictors of infection leading to hospitalisation in a large primary-care-derived cohort of patients with inflammatory polyarthritis. Annals of the Rheumatic Diseases 2007;66:308–12. doi:10.1136/ard.2006.057265.

[32] Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:785–91. doi:10.1136/ard.2010.128637.

[33] Accortt NA, Lesperance T, Liu M, Rebello S, Trivedi M, Li Y, et al. Impact of Sustained Remission on the Risk of Serious Infection in Patients With Rheumatoid Arthritis. Arthrit Care Res 2018;70:679–84. doi:10.1002/acr.23426.

[34] Dougados M, Soubrier M, Antunez A, Balint P, Balsa A, Buch MH, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). Ann Rheum Dis 2013;73:62–8. doi:10.1136/annrheumdis-2013-204223.

[35] Ranganath VK, Maranian P, Flaschoff DA, Woodworth T, Khanna D, Hahn T, et al. Comorbidities are associated with poorer outcomes in community patients with rheumatoid arthritis. Rheumatology 2013;52:1209–17. doi:10.1093/rheumatology/ket224.

[36] Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020:annrheumdis-2019-216655. doi:10.1136/annrheumdis-2019-216655.

[37] Strehl C, Ehlers L, Gaber T, Buttgereit F. Glucocorticoids-All-Rounders Tackling the Versatile Players of the Immune System. Front Immunol 2019;10:1744. doi:10.3389/fimmu.2019.01744.

[38] Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Practice & Research Clinical Rheumatology 2007;21:885–906. doi:10.1016/j.berh.2007.06.002.

[39] Boers M, Verhoeven AC, Markusse HM, Laar MA van de, Westhovens R, Denderen JC van, et al. Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. Lancet 1997;350:309–18. doi:10.1016/s0140-6736(97)01300-7.

[40] Everdingen AA van, Jacobs JWG, Reesema DRS van, Bijlsma JWJ. Low-Dose Prednisone Therapy for Patients with Early Active Rheumatoid Arthritis: Clinical Efficacy, Disease-Modifying Properties, and Side Effects: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Ann Intern Med 2002;136:1. doi:10.7326/0003-4819-136-1-200201010-00006.

[41] Bakker MF, Jacobs JWG, Welsing PMJ, Verstappen SMM, Tekstra J, Ton E, et al. Low-Dose Prednisone Inclusion in a Methotrexate-Based, Tight Control Strategy for Early Rheumatoid Arthritis. Ann Intern Med 2012;156:329. doi:10.7326/0003-4819-156-5-201203060-00004.

[42] Dixon WG, Suissa S, Hudson M. The association between systemic glucocorticoid therapy and the risk of infection in patients with rheumatoid arthritis: systematic review and meta-analyses. Arthritis Res Ther 2011;13:R139. doi:10.1186/ar3453.

[43] Tang NL-S, Chan PK-S, Wong C-K, To KF, Wu AK-L, Sung Y-M, et al. Early Enhanced Expression of Interferon-Inducible Protein-10 (CXCL10) and Other Chemokines Predicts Adverse Outcome in Severe Acute Respiratory Syndrome. Clin Chem 2005;51:2333–40. doi:10.1373/clinchem.2005.054462.

[44] Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, et al. Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. Am J Resp Crit Care 2018;197:757–67. doi:10.1164/rccm.201706-1172oc.

[45] Stockman LJ, Bellamy R, Garner P. SARS: Systematic Review of Treatment Effects. Plos Med 2006;3:e343. doi:10.1371/journal.pmed.0030343.

[46] Memish ZA, Perlman S, Kerkhove MDV, Zumla A. Middle East respiratory syndrome. Lancet Lond Engl 2020. doi:10.1016/s0140-6736(19)33221-0.

[47] Ni Y-N, Chen G, Sun J, Liang B-M, Liang Z-A. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. Crit Care 2019;23:99. doi:10.1186/s13054-019-2395-8.

[48] Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. Cochrane Database Syst Rev 2019;7:CD004477. doi:10.1002/14651858.cd004477.pub3.

[49] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet Lond Engl 2020;395:473–5. doi:10.1016/s0140-6736(20)30317-2.

[50] Qiao W, Wang C, Chen B, Zhang F, Liu Y, Lu Q, et al. Ibuprofen Attenuates Cardiac Fibrosis in Streptozotocin-Induced Diabetic Rats. Cardiology 2015;131:97–106. doi:10.1159/000375362.

[51] Lacaille D, Guh DP, Abrahamowicz M, Anis AH, Esdaile JM. Use of nonbiologic disease-modifying antirheumatic drugs and risk of infection in patients with rheumatoid arthritis. Arthritis Rheumatism 2008;59:1074–81. doi:10.1002/art.23813.

[52] Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatology 2008;35:387–93.

[53] Ibrahim A, Ahmed M, Conway R, Carey JJ. Risk of Infection with Methotrexate Therapy in Inflammatory Diseases: A Systematic Review and Meta-Analysis. J Clin Medicine 2018;8:15. doi:10.3390/jcm8010015.

[54] Tudesq J-J, Cartron G, Rivière S, Morquin D, Iordache L, Mahr A, et al. Clinical and microbiological characteristics of the infections in patients treated with rituximab for autoimmune and/or malignant hematological disorders. Autoimmun Rev 2018;17:115–24. doi:10.1016/j.autrev.2017.11.015.

[55] Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, Heijde D van der, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2017;76:1101–36. doi:10.1136/annrheumdis-2016-210708.

[56] Favalli EG, Desiati F, Atzeni F, Sarzi-Puttini P, Caporali R, Pallavicini FB, et al. Serious infections during anti-TNFα treatment in rheumatoid arthritis patients. Autoimmun Rev 2009;8:266–73. doi:10.1016/j.autrev.2008.11.002.

[57] Atzeni F, Sarzi-Puttini P, Botsios C, Carletto A, Cipriani P, Favalli EG, et al. Long-term anti-TNF therapy and the risk of serious infections in a cohort of patients with rheumatoid arthritis: Comparison of adalimumab, etanercept and infliximab in the GISEA registry. Autoimmun Rev 2012;12:225–9. doi:10.1016/j.autrev.2012.06.008.

[58] Rutherford AI, Subesinghe S, Hyrich KL, Galloway JB. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Ann Rheum Dis 2018;77:905–10. doi:10.1136/annrheumdis-2017-212825.

[59] Singh JA, Cameron C, Noorbaloochi S, Cullis T, Tucker M, Christensen R, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 2015;386:258–65. doi:10.1016/s0140-6736(14)61704-9.

[60] Singh JA, Wells GA, Christensen R, Ghogomu ET, Maxwell LJ, MacDonald JK, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Db Syst Rev 2011:CD008794. doi:10.1002/14651858.cd008794.pub2.

[61] Atzeni F, Sarzi-Puttini P, Marotti A, Bugatti S, Cavagna L, Caporali R. Long-term safety of abatacept in patients with rheumatoid arthritis. Autoimmun Rev 2013;12:1115–7. doi:10.1016/j.autrev.2013.06.011.

[62] Bello SL, Serafino L, Bonali C, Terlizzi N, Fanizza C, Anecchino C, et al. Incidence of influenza-like illness into a cohort of patients affected by chronic inflammatory rheumatism and treated with biological agents. Reumatismo 2012;64:299–306. doi:10.4081/reumatismo.2012.299.

[63] Shale M, Czub M, Kaplan GG, Panaccione R, Ghosh S. Anti-tumor necrosis factor therapy and influenza: keeping it in perspective. Ther Adv Gastroenter 2010;3:173–7. doi:10.1177/1756283x10366368.

[64] Sepriano A, Kerschbaumer A, Smolen JS, Heijde D van der, Dougados M, Vollenhoven R van, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2020:annrheumdis-2019-216653. doi:10.1136/annrheumdis-2019-216653.

[65] Favalli EG, Matucci-Cerinic M, Szekanecz Z. The Giants (biologicals) against the Pigmies (small molecules), pros and cons of two different approaches to the disease modifying treatment in rheumatoid arthritis. Autoimmun Rev 2019;19:102421. doi:10.1016/j.autrev.2019.102421.

[66] Favalli EG. Tofacitinib's infectious profile: concerns for clinical practice. Lancet Rheumatology 2020;2:e65–7. doi:10.1016/ S2665-9913(20)30001-1.

[67] Winthrop KL, Yamanaka H, Valdez H, Mortensen E, Chew R, Krishnaswami S, et al. Herpes Zoster and Tofacitinib Therapy in Patients With Rheumatoid Arthritis. Arthritis Rheumatol 2014;66:2675–84. doi:10.1002/art.38745.

[68] Smolen JS, Genovese MC, Takeuchi T, Hyslop DL, Macias WL, Rooney T, et al. Safety Profile of Baricitinib in Patients with Active Rheumatoid Arthritis with over 2 Years Median Time in Treatment. J Rheumatology 2018;46:7–18. doi:10.3899/jrheum.171361.

[69] Curtis JR, Xie F, Yun H, Bernatsky S, Winthrop KL. Real-world comparative risks of herpes virus infections in tofacitinib and biologic-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1843–7. doi:10.1136/annrheumdis-2016-209131.

[70] Pawar A, Desai RJ, Gautam N, Kim SC. Risk of admission to hospital for serious infection after initiating tofacitinib versus biologic DMARDs in patients with rheumatoid arthritis: a multidatabase cohort study. Lancet Rheumatology 2020;2:e84–98. doi:10.1016/s2665-9913(19)30137-7.

[71] Caporali R, Zavaglia D. Real-world experience with tofacitinib for treatment of rheumatoid arthritis. Clin Exp Rheumatol 2019 37(3):485-495.

[72] Biggioggero M, Becciolini A, Crotti C, Agape E, Favalli EG. Upadacitinib and filgotinib: the role of JAK1 selective inhibition in the treatment of rheumatoid arthritis. Drugs Context 2019;8:212595. doi:10.7573/dic.212595.

[73] Jamilloux Y, Jammal TE, Vuitton L, Gerfaud-Valentin M, Kerever S, Sève P. JAK inhibitors for the treatment of autoimmune and inflammatory diseases. Autoimmun Rev 2019;18:102390. doi:10.1016/j.autrev.2019.102390.

[74] Winthrop KL. The emerging safety profile of JAK inhibitors in rheumatic disease. Nat Rev Rheumatology 2017;13:234–43. doi:10.1038/nrrheum.2017.23.

[75] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, et al. Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. Acs Central Sci 2020. doi:10.1021/acscentsci.0c00272.

[76] Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen K-Y. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov 2016;15:327–47. doi:10.1038/nrd.2015.37.

[77] Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. J Korean Med Sci 2020;35:e79. doi:10.3346/jkms.2020.35.e79.

[78] Mulangu S, Dodd LE, Davey RT, Mbaya OT, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. New Engl J Medicine 2019;381:2293–303. doi:10.1056/nejmoa1910993.

[79] Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 2017;9:eaal3653. doi:10.1126/scitranslmed.aal3653.

[80] Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269–71. doi:10.1038/s41422-020-0282-0.

[81] Widjaja I, Wang C, Haperen R van, Gutiérrez-Álvarez J, Dieren B van, Okba NMA, et al. Towards a solution to MERS: protective human monoclonal antibodies targeting different domains and functions of the MERS-coronavirus spike glycoprotein. Emerg Microbes Infec 2019;8:516–30. doi:10.1080/22221751.2019.1597644.

[82] Wang C, Li W, Drabek D, Okba NMA, Haperen R van, Osterhaus ADME, et al. A human monoclonal 1 antibody blocking SARS-CoV-2 infection. Biorxiv 2020:2020.03.11.987958. doi:10.1101/2020.03.11.987958.

[83] Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: implications for rheumatology. Nat Rev Rheumatology 2020;16:155–66. doi:10.1038/s41584-020-0372-x.

[84] Inglot AD. Comparison of the Antiviral Activity in vitro of some Non-steroidal Anti-inflammatory Drugs. J Gen Virol 1969;4:203–14. doi:10.1099/0022[illegible]1317-4-2-203.

[85] Keyaerts E, Vijgen L, Maes P, Neyts J, Ranst MV. In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Co 2004;323:264–8. doi:10.1016/j.bbrc.2004.08.085.

[86] Paton NI, Lee L, Xu Y, Ooi EE, Cheung YB, Archuleta S, et al. Chloroquine for influenza prevention: a randomised, double-blind, placebo controlled trial. Lancet Infect Dis 2011;11:677–83. doi:10.1016/s1473-3099(11)70065-2.

[87] Roques P, Thiberville S-D, Dupuis-Maguiraga L, Lum F-M, Labadie K, Martinon F, et al. Paradoxical Effect of Chloroquine Treatment in Enhancing Chikungunya Virus Infection. Viruses 2018;10:268. doi:10.3390/v10050268.

[88] Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69. doi:10.1186/1743-422x-2-69.

[89] Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Ag 2020:105938. doi:10.1016/j.ijantimicag.2020.105938.

[90] Savarino A, Trani LD, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis 2006;6:67–9. doi:10.1016/s1473-3099(06)70361-9.

[91] . Chinese Clinical Trial Registry. 2020.

[92] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020:2020.01047. doi:10.5582/bst.2020.01047.

[93] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis 2020. doi:10.1093/cid/ciaa237.

[94] Diao B, Wang C, Tan Y, Chen X, Liu Y, Ning L, et al. Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19). Medrxiv 2020:2020.02.18.20024364. doi:10.1101/2020.02.18.20024364.

[95] Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome. Crit Care Med 2016;44:275–81. doi:10.1097/ccm.0000000000001402.

[96] Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment os severe COVID-19 patients with tocilizumab. ChinaXiv:20200300026. 2020

[97]http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19. Accessed 17th March 2020

[98] Wang W, He J, Lie puvi, Huang liyan, Wu S, lin yongping, et al. The definition and risks of Cytokine Release Syndrome-Like in 11 COVID-19-Infected Pneumonia critically ill patients: Disease Characteristics and Retrospective Analysis. Medrxiv 2020:2020.02.26.20026989. doi:10.1101/2020.02.26.20026989.

[99] Haga S, Yamamoto N, Nakai-Murakami C, Osawa Y, Tokunaga K, Sata T, et al. Modulation of TNF-alpha-converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF-alpha production and facilitates viral entry. P Natl Acad Sci Usa 2008;105:7809–14. doi:10.1073/pnas.0711241105.

[100] Wang W, Ye L, Ye L, Li B, Gao B, Zeng Y, et al. Up-regulation of IL-6 and TNF-alpha induced by SARS-coronavirus spike protein in murine macrophages via NF-kappaB pathway. Virus Res 2007;128:1–8. doi:10.1016/j.virusres.2007.02.007.

[101] Sorrell FJ, Szklarz M, Azeez KRA, Elkins JM, Knapp S. Family-wide Structural Analysis of Human Numb-Associated Protein Kinases. Struct Lond Engl 1993 2016;24:401–11. doi:10.1016/j.str.2015.12.015.

[102] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet Lond Engl 2020;395:565–74. doi:10.1016/s0140-6736(20)30251-8.

[103] Bekerman E, Neveu G, Shulla A, Brannan J, Pu S-Y, Wang S, et al. Anticancer kinase inhibitors impair intracellular viral trafficking and exert broad-spectrum antiviral effects. J Clin Investigation 2017;127:1338–52. doi:10.1172/jci89857.

[104] Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020. doi:10.1016/s1473-3099(20)30132-8.

[105] Pu S-Y, Xiao F, Schor S, Bekerman E, Zanini F, Barouch-Bentov R, et al. Feasibility and biological rationale of repurposing sunitinib and erlotinib for dengue treatment. Antivir Res 2018;155:67–75. doi:10.1016/j.antiviral.2018.05.001.

[106] Richardson P, Griffin I, Tucker C, Smith D, Oechsle O, Phelan A, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. Lancet Lond Engl 2020;395:e30–1. doi:10.1016/s0140-6736(20)30304-4.

[107] Ferguson FM, Gray NS. Kinase inhibitors: the road ahead. Nat Rev Drug Discov 2018;17:353–77. doi:10.1038/nrd.2018.21.

[108] Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 2018;128:3041–52. doi:10.1172/jci98814.

[109] Virtanen AT, Haikarainen T, Raivola J, Silvennoinen O. Selective JAKinibs: Prospects in Inflammatory and Autoimmune Diseases. Biodrugs Clin Immunother Biopharm Gene Ther 2019;33:15–32. doi:10.1007/s40259-019-00333-w.

[110] Borden EC, Sen GC, Uze G, Silverman RH, Ransohoff RM, Foster GR, et al. Interferons at age 50: past, current and future impact on biomedicine. Nat Rev Drug Discov 2007;6:975–90. doi:10.1038/nrd2422.

[111] Schoggins JW, Wilson SJ, Panis M, Murphy MY, Jones CT, Bieniasz P, et al. Corrigendum: A diverse range of gene products are effectors of the type I interferon antiviral response. Nature 2015;525:144. doi:10.1038/nature14554.

[112] Fleming S. Viral Inhibition of the IFN-Induced JAK/STAT Signalling Pathway: Development of Live Attenuated Vaccines by Mutation of Viral-Encoded IFN-Antagonists. Nato Adv Sci Inst Se 2016;4:23. doi:10.3390/vaccines4030023.

[113] Ayllon J, García-Sastre A. Current Topics in Microbiology and Immunology. Curr Top Microbiol 2014;386:73–107. doi:10.1007/82_2014_400.

[114] Jia D, Rahbar R, Chan RWY, Lee SMY, Chan MCW, Wang BX, et al. Influenza virus non-structural protein 1 (NS1) disrupts interferon signaling. Plos One 2010;5:e13927. doi:10.1371/journal.pone.0013927.

[115] Conigliaro P, Triggianese P, Martino ED, Fonti GL, Chimenti MS, Sunzini F, et al. Challenges in the treatment of Rheumatoid Arthritis. Autoimmun Rev 2019;18:706–13. doi:10.1016/j.autrev.2019.05.007.

[116] Favalli EG, Raimondo MG, Becciolini A, Crotti C, Biggioggero M, Caporali R. The management of first-line biologic therapy failures in rheumatoid arthritis: Current practice and future perspectives. Autoimmun Rev 2017;16:1185–95. doi:10.1016/j.autrev.2017.10.002.

[117] Edwards CJ, Galeazzi M, Bellinvia S, Ringer A, Dimitroulas T, Kitas G. Can we wean patients with inflammatory arthritis from biological therapies? Autoimmun Rev 2019;18:102399. doi:10.1016/j.autrev.2019.102399.

Table 1. Potential role of anti-rheumatic drugs in COVID-19 infection

	PROS	CONS
Chloroquine Hydroxychloroquine	Anti-viral effect (increase of endosomal pH required for virus/cell fusion, inhibition of toll-like receptor activity, interference with terminal glycosylation of the cellular receptor ACE 2)	-
IL-6 inhibitors	Treatment of cytokine storm manifestations during ARDS	Lack of definite criteria to identify patients to be treated Potential community-acquired pneumonia due to immunosuppression
Baricitinib	Interference with viral penetration into the cell by blocking NAK-mediated endocytosis Treatment of cytokine storm manifestations during ARDS	Impairment of IFN anti-viral response Increased risk of secondary HZV infections
TNF-inhibitors	Interference with viral penetration into the cell	Slight increase in viral infection risk
NSAIDs	-	Facilitation of viral penetration by overexpression of ACE2 Delay in diagnosis due to fever masking
Corticosteroids	-	Increased risk of viral infection Increased mortality and risk of secondary bacterial or fungal infection

ACE2 = angiotensin converting enzyme 2, ARDS = acute respiratory distress syndrome, NAK = numb-associated kinase; HZV = Herpes Zoster virus,
IFN = interferon, NSAIDs = nonsteroidal anti-inflammatory drugs

Ennio Giulio Favalli[1], Francesca Ingegnoli[1,2], Orazio De Lucia[1], Gilberto Cincinelli[2], Rolando Cimaz[2,3], Roberto Caporali[1,2]

[1] Division of Clinical Rheumatology, ASST Gaetano Pini-CTO Institute, Milan, Italy

[2] Department of Clinical Sciences and Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, Università degli Studi di Milano, Milano, Italy

[3] Division of Pediatric Rheumatology, ASST Gaetano Pini-CTO Institute, Milan, Italy