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REVIEW ARTICLE

COVID-19 infection and rheumatoid arthritis: mutual outburst cytokines and remedies

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ABSTRACT

In March 2020, COVID-19 infection caused by SARS-CoV-2 has been declared to be a global pandemic, where its complications, severity and mortality are reported to be due to the released inflammatory cytokines or the so-called cytokine storm. This is quite similar to that observed in the autoimmune and chronic inflammatory rheumatic disease, rheumatoid arthritis (RA). It was hypothesized that RA patients are at a higher risk of acquiring COVID-19; however, recent studies reported that they are not when compared to the rest of the population. In this review, we aim to highlight the mutual pathological features, cytokine profiles and risk factors between COVID-19 and RA. Also, many researchers are currently working to explore therapeutic agents that could aid in the eradication of COVID-19 infection. Due to the similarity between the inflammation status in COVID-19 and RA, many anti-rheumatic drugs such as hydroxychloroquine, tocilizumab, baricitinib and anakinra were proposed to be therapeutic modalities for COVID-19 infection.

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1. COVID-19 infection

Coronaviruses (CoVs) compromise a family of large positive single-stranded RNA viruses that may cause respiratory diseases in humans[1]. CoVs nomenclature is based on their morphology as spherical virions with a core-shell and large bulbous surface projections, meaning in Latin "virus with a crown"[2]. SARS-CoV-2 belongs to the subgroup of beta-coronaviruses and is very closely related to the severe acute respiratory distress syndrome virus (SARS-CoV), that was reported in 2002[3–5]. Last December, COVID-19 infection caused by SARS-CoV-2 virus was first reported in the Huanan seafood market in Wuhan, China[6]. A few months later, the World Health Organization (WHO) has declared it to be a global pandemic. The mode of transmission of SARS-CoV-2 is through infectious droplets produced by coughing or sneezing that could be present in the air[7], and could spread across distances and remain viable on surfaces[8].

SARS-CoV-2 uses multiple host receptors for cell entry in the lungs such as angiotensin-converting enzyme 2 (ACE2) and the cellular serine protease TMPRSS2[9–13]. ACE2 is expressed in various organs including lung and alveolar epithelial cells which makes it more susceptible to COVID-19 viral infection[14]. Upon infection with SARS-CoV-2, there is a downregulation of ACE2 receptor expression along with increased production of angiotensin II by the related enzyme ACE and enhanced activity of the renin-angiotensin system thus inducing pulmonary vascular permeability and lung damage[15,16].

The clinical symptoms could vary from fatigue, fever, headache, dyspnea, nasal congestion, nausea, diarrhea and cough[3]. The most severe complication of COVID-19 is pneumonia that could consequently lead to acute respiratory distress syndrome (ARDS) accompanied by neutrophilia, lymphopenia, and thrombocytopenia[17–20]. Being a viral infection that is typically associated with a strong immune response and inflammation, markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and proinflammatory cytokines are elevated[17]. Extreme high concentrations of cytokines could lead to the so-called "cytokine storm" as observed in severe cases of COVID-19 patients and were correlated with disease severity, viral replication and lung injury[12,21]. The cytokines profile observed in COVID-19 was found to show some similarities to that of secondary hemophagocytic lymphohistiocytosis (sHLH), the hyperinflammatory syndrome associated with an excessive cytokine and multi-organ failure[22,23]. These inflammatory cytokines and chemokines include IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte colony-stimulating factor (G-CSF), tumor necrosis factor-alpha (TNFα), CCL2, CCL3, and CXCL10[12,21]. Furthermore, an elevation of ferritin level and presence of proinflammatory state was reported in sHLH, or the so-called macrophage activation syndrome (MAS), which is quite similar to that observed in COVID-19[24].

COVID-19 complications could be due to the CRS and the extravagant immune response against the SARS-CoV-2 virus[21,25,26], suggesting that management of this storm is quite critical. One would speculate that rheumatoid arthritis

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(RA) patients may be at higher risk of COVID-19 infection, due to the inflammation status and the use of immunomodulatory drugs. However, recent data has shown that the prevalence of COVID-19 in RA patients is the same as in the general population. In this review, we aim to highlight the mutual features between COVID-19 and the chronic inflammatory rheumatic disease, rheumatoid arthritis (RA), as well as the possible use of anti-rheumatic drugs as a therapeutic modality for COVID-19 infection.

2. Rheumatoid arthritis

Rheumatoid arthritis is a chronic and systemic autoimmune disease affecting multiple joints that could lead to progressive disability, systemic complications, socioeconomic costs and burden. RA is accompanied by systemic manifestations such as cardiovascular diseases that might lead to high mortality and morbidity. It is characterized by joint inflammation associated with hyperplasic synovium, cytokine and chemokine production, detection of autoantibodies like rheumatoid factor (RF) and anticitrullinated peptide antibody (ACPA). Moreover, these are accompanied by osteoclastogenesis, angiogenesis and systemic manifestations affecting the cardiovascular, pulmonary, neurovascular and skeletal symptoms[27]. Furthermore, symmetric polyarticular arthritis and persistent inflammation in the synovium might lead to pannus formation and thus joint destruction[28]. Early diagnosis and immediate effective therapy are crucial for the prevention of joint deterioration, functional disability and unfavorable, even fatal disease outcomes. An approach which is known as T2T (treat to target) can be implemented when the target is the disease activity remission or low disease activity.

Therapy of RA aims at improving the patient's quality of life and joint function as well as reducing the inflammatory state, pain and disease progression[28,29]. There are several pharmacological agents known as disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate, sulfasalazine, and hydroxychloroquine that slow down the progression of RA[30]. Several cytokines and chemokines play a role in the pathogenesis of RA through regulation of inflammation, autoimmunity and joint destruction, including IL-1, IL-6, IL-12, IL-17, IL-18, IL-23, and TNFα as well as the chemokines CCL2, CCL3, CCL4, CXCL8 and CXCL10[31,32]. Hence, the biologicals agents mainly act by dampening the host inflammatory response. The biological agents are engineered drugs that target specific inflammatory cells, cytokines and receptors that mediate RA inflammation and tissue damage. Thus, they reduce the symptoms associated with RA and disease progression[33]. These agents include IL-1 receptor antagonist (anakinra), rituximab (anti-CD20, B cell depleting agent) and TNF antagonists (infliximab, etanercept, golimumab, adalimumab), IL-6 receptor blockers (tocilizumab) and the JAK inhibitors (Upadacitinib, baricitinib and tofacitinib)[34,35]. Such biologics have shown to be highly effective in reducing RA symptoms, leading to amelioration of physical function and quality of life[36,37].

3. Common factors between COVID-19 and rheumatoid arthritis

Despite the multiple differences between COVID-19 and RA in terms of etiology, epidemiology, clinical features, organ involvement, and prognosis, they seem to have some similarities in the pathogenesis and risk factors associated with the disease. For example, some external microorganisms could cause acute and chronic arthritis, either by the direct presence in the joints or the aberrant autoimmune reaction induced by the host. On the other hand, the absence of the commensal bacteria present in the microbiome was found to lead to disease amelioration due to reduction in the pro-inflammatory Th17 response[38–42]. On the other hand, patients suffering from inflammatory arthritis are at high risk of infections as it could lead to disease flares[43–45]. Additionally, RA patients often have co-morbidities such as diabetes mellitus, cardiovascular disease and pulmonary diseases which further increases the risk of viral infections[43,46,47]. This increased risk of infection is associated with certain risk factors similar to those reported in COVID-19[43,48,49].

One of the most consistent associated comorbidities in RA is hypertension[50]. Recent data indicated that hypertension was significantly associated with the increased risk of adverse outcomes in COVID-19 patients and that hypertension is an independent risk factor for predicting the severity and mortality of COVID-19 patients[51]. Additionally, the prevalence of diabetes mellitus is controversial among RA, but definitely, RA patients are more predisposed to developing both insulin resistance and type 2 diabetes mellitus[52–54]. The second most common comorbidity associated with a worse outcome in COVID-19 patients is diabetes[55–57], probably due to higher ACE2 expression in diabetic patients[58].

Regarding risk factors, old age seems to increase the likelihood of RA development. This could be due to the dramatic changes in the lymphocyte populations and phenotypes that could possibly cause an increase in reactivity to self-tissue antigens[28]. Similarly, age over 65 years might increase the risk of acquiring COVID-19 infection[59]. Another reported risk factor is smoking where smokers were reported to experience seropositive, erosive RA disease with extraarticular manifestations[60]. This could be attributed to the effect of the posttranslational modifications such as citrullination of the mucosal proteins including collagen, fibrinogen, enolase and fibrinogen[61–63]. Likewise, smoking increases the risk and severity of COVID-19, which could be attributed to lung injury and reduced lung capacity[64].

There are many discrepancies between RA and COVID-19 in terms of etiology, disease progression, risk factors and demographic factors. For instance, it seems that the gender susceptibility between RA and COVID-19 is quite the opposite. Women are more prone to RA possibly due to the X chromosomes or their female hormones as suggested by some studies where estrogen and prolactin stimulate autoantibody production[28,65,66]. In contrast, males are more at risk for worse outcomes and high mortality with COVID-19, which could be due to higher expression levels of ACE2[67].

Another common feature among RA and COVID-19 infection is vasculitis. Systemic rheumatoid vasculitis is among the most serious complications of RA. It is characterized by inflammation of mid-size arteries and capillaries, which could lead to deep cutaneous ulcers, gangrene, and neuropathy, which is associated with poor outcomes and mortality[68]. Recently, some case reports highlighted the presence and association of vasculitis in COVID-19 patients[69,70]. Also, the development of RA is accompanied by a disturbance of the coagulation system and elevation in the blood coagulation state and fibrinolysis, which is probably due to excessive stimulation of inflammatory pathways[71,72]. Likewise, coagulopathies were observed in COVID-19 infection as reported by the prominent elevation of D-dimer and fibrin/fibrinogen-degradation products. This was proposed to be a result of the hypoxia and the inflammatory response to SARS-CoV-2 causing thrombo-inflammation and thrombosis[73].

Most importantly, the cytokine imbalance in COVID-19 infection is quite similar to that observed in inflammatory rheumatic diseases. This includes the pro-inflammatory and pyrogenic IL-1, IL-6 and TNF-α cytokines, similar to what has been previously observed in other coronavirus infections SARS and MERS (middle east respiratory syndrome), as well as the inflammatory chemokines CCL2 and CXCL10[21,25,32,74]. It has been observed that a reduction in $CD4^+$ and $CD8^+$ T cells is found in severe COVID-19 patients along with higher serum levels of TNF-α, IL-1 and IL-6[20]. It is worth mentioning that IL-6 is one of the crucial inflammatory mediators in COVID-19 as its levels are correlated with SARS-CoV-2 viral load[75]. Besides, COVID-19 and RA share another feature, i.e. genetic host characteristics such as IL-6 gene polymorphisms, that can contribute to SARS-CoV-2 susceptibility and RA[76,77]. Such gene markers could be used as predictors of response to anti-IL-6 treatment during the COVID-19 pandemic[78].

4. Is there an increased risk of COVID-19 in patients with rheumatoid arthritis?

The shared immune and genetic mechanisms as well as clinical aspects between inflammatory diseases and COVID-19, propose that SARS-CoV-2 could be a trigger for the development of excessive inflammatory disorders, especially in susceptible individuals[79]. Therefore, arthritis patients should be informed to maintain their treatments during the pandemic, adhere to self-protection principles for COVID-19, and consult their rheumatologists in case of any doubt of infection, preferably *via* telemedicine if available[80]. There are various risk factors associated with COVID-19, such as pulmonary and cardiovascular diseases as well as diabetes mellitus[81,82]. However, it remains unclear if chronic rheumatic diseases such as RA increase the risk of COVID-19 compared to the general population[83]. Such a risk has been proposed to be due to the immune dysregulation and the use of chemical and biological anti-rheumatic agents that generally increase the risk of infections due to the state of being immunocompromised along with associated comorbidities[25,84–86]. In particular, RA patients suffered from a malfunction in the thymus, increased turnover of peripheral T cells and dysfunction of circulating T cells, which make these patients more prone to infections[87–89]. Additionally, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, which might be used as an adjunct treatment to reduce arthritic pain[90], have been demonstrated to induce ACE2 overexpression and hence might increase the SARS-CoV-2 infection susceptibility. These worsen the clinical course or even mask some symptoms that aid in the diagnosis of COVID-19[91]. Other studies claimed that NSAIDs are not associated with the odds of hospitalization, unlike glucocorticoid exposure which seems to increase the hospitalization chances in patients with rheumatic diseases[92].

However, several recent studies report that patients diagnosed with rheumatic diseases, especially patients with chronic inflammatory arthritis taking chemical and bDMARDS, are not at a higher risk of acquiring COVID-19 infection compared to the rest of the population[5,93–97]. This goes in line with previous reports during SARS and MERS, where patients with autoimmune diseases did not show any increase in mortality rates[93,98]. On the other hand, a case report has proposed that patients with rheumatic immune diseases are more likely to progress into severe/critical COVID-19, as these two diseases overlap in pathogenesis and therapeutic agents used[99]. Moreover, a study by Akiyama et al. showed that the prevalence of COVID-19 in patients with autoimmune diseases was higher than in other populations. Additionally, the use of glucocorticoids increased the risk of severe outcomes, whereas anti-TNF therapy reduced the risk of severe COVID-19[100]. Initially, patients with rheumatic disease and COVID-19 infection were reported to be more likely to require mechanical ventilation but had the same hospitalization rate[101]. However, an update of this study indicated that patients with rheumatic disease are not at a higher risk of hospitalization, intensive care unit admission, mechanical ventilation or death[102].

5. Remitters: anti-rheumatic and anti-COVID-19 agents

Currently, many researchers across the globe are investigating potential therapeutic agents that can be utilized for the treatment of COVID-19. The standard care comprises supplemental oxygen, ventilation, and antibiotic agents[103]. Until now, several attempts include the use of plasma containing antibodies from recovered COVID-19 patients to severe and deteriorating patients infected with COVID-19[104]. Moreover, anti-viral agents that have previously worked against other RNA viruses such as remdesivir and lopinavir/ritonavir showed potential therapeutic efficacy against SARS-CoV-2 virus *in vitro*[105–108]. However, other studies have suggested that lopinavir/ritonavir did not reduce mortality, hospitalization duration, or clinical progression in hospitalized COVID-19 patients (Chinese Clinical Trial Register number, ChiCTR2000029308)[103,106]. Furthermore, the RECOVERY trial showed that lopinavir/ritonavir did not cause any reductions in 28-day mortality, duration of hospitalization, or risk of progressing to invasive mechanical ventilation or death[109]. Therefore, WHO decided to discontinue the use of lopinavir/

ritonavir in hospitalized COVID-19 patients; however, this does not include non-hospitalized COVID-19 patients[110].

As mentioned earlier, there is a similarity in the cytokine imbalance of COVID-19 and inflammatory rheumatic disorders, thus some of the anti-rheumatic drugs had been redirected in the treatment of this pandemic. Furthermore, many of the anti-rheumatic drugs especially the biological agents, are currently under investigation to be used in the treatment protocols for COVID-19[111,112]. It is well known for decades that steroids such as prednisolone can be used in RA as it reduces pain and flares of synovitis as well as modify the progression of disease *via* affecting joint tenderness[113,114]. Corticosteroids may be recently introduced for COVID-19 therapy, as the corticosteroid dexamethasone was suggested to have anti-inflammatory and immunosuppressive roles by limiting the activity of inflammatory cytokines, T and B cells. Furthermore, dexamethasone may reduce the mortality of severe, intubated COVID-19 patients[115,116]. The RECOVERY trial further supported the use of dexamethasone which resulted in decline in mortality rate among the COVID-19 patients receiving either invasive mechanical ventilation or oxygen alone[117].

During the initial phase of the COVID-19 pandemic, hydroxychloroquine and chloroquine have been suggested to inhibit SARS-CoV-2 replication and activity, especially in the cases of COVID-19 pneumonia[107,108,118]. This is attributed to the previously reported antiviral mechanism of action of chloroquine against various viruses including H5N1 avian influenza, Zika, Ebola, and SARS-CoV[119–122]. Chloroquine acts by increasing the endosomal pH required for the fusion of virus and host cell as well as interfering with the glycosylation of the cellular receptor ACE2, thus negatively influencing the virus-receptor binding[118,122,123]. Hydroxychloroquine is a more potent derivative than chloroquine and was suggested for the management of SARS-CoV-2 infection[124]. This could be due to its multiple mechanisms of action: anti-viral, immunomodulatory, anti-inflammatory and anti-thrombotic that are needed to resolve the clinical symptoms in COVID-19 infection[124,125]. However, if the use of hydroxychloroquine is uncontrolled, side effects such as retinopathy and potential cardiac damage could be observed[126,127]. Initial *in vitro* studies revealed hydroxychloroquine to reduce SARS-CoV-2 viral load[128,129]. Moreover, hydroxychloroquine could block antigen presentation to CD4+ T cells, and cause a reduction in the production of type I IFNs, TNF-α, IL-6, GM-CSF, and IL-1β[130,131]. Recently, WHO has announced that hydroxychloroquine will not be included in the international Solidarity clinical trial of COVID-19 therapy for hospitalized patients[110]. This was due to the evidence proven by multiple studies where there were no observed differences in the clinical status or mortality for mild-moderate hospitalized COVID-19 patients receiving hydroxychloroquine with or without macrolide therapy compared to standard care (ClinicalTrials.gov number, NCT04322123)[132–134]. However, it is worth mentioning that hydroxychloroquine could have a beneficial effect in the therapy of non-hospitalized COVID-19 patients as well as being under investigations to be used in a prophylactic approach for COVID-19[135,136]. Nevertheless, hydroxychloroquine did not show a preventive effect against SARS-CoV-2 infection in patients with rheumatological conditions[92,137,138].

Furthermore, due to the presence of inflammatory cytokines in the plasma and bronchoalveolar lavage fluid of COVID-19 patients, targeting such markers using bio-therapies such as IL-6 receptor blocker tocilizumab was proposed[139]. Tocilizumab is a recombinant human IL-6 monoclonal antibody that blocks its signaling pathway and the inflammatory response[140]. Tocilizumab was one of the most effective therapeutics to relieve the symptoms of RA patients and their quality of life[141,142]. Being an IL-6- receptor blocker, tocilizumab inhibits the inflammatory storm observed in COVID-19 thus halting alveolar-capillary blood-gas exchange dysfunction, pulmonary fibrosis and organ failure[143–145]. Based on this, tocilizumab can be a suitable and effective drug for COVID-19 patients, especially those with ARDS, *via* resolving fever and oxygen saturation and restoring CRP levels and lymphocytes count[146]. Tocilizumab showed controversial data on COVID-19 patients. For instance, a retrospective study by Guaraldi et al. and another multi-center observational study showed that the risk of invasive mechanical ventilation, ICU admission or death in patients with severe COVID-19 pneumonia was reduced upon tocilizumab therapy[147,148]. Similarly, tocilizumab reduced the need of mechanical ventilation or death, but did not improve the survival of COVID-19 patients with pneumonia who were not receiving mechanical ventilation[149]. On the other hand, another study highlighted that tocilizumab did not seem to be reducing the mortality of hospitalized patients with COVID-19 pneumonia (ClinicalTrials.gov number, NCT04356937)[150–152]. This was further highlighted in other studies where tocilizumab did not show to be effective in prevention of intubation or death in moderately ill hospitalized COVID-19 patients[150–153].

It is worth mentioning that excessive activity of tocilizumab can cause damage such as autoimmunity[154]. Multiple health centers have used and recommended tocilizumab for COVID-19 therapy but further studies and trials are still needed to confirm the positive therapeutic effect in COVID-19 patients[154]. Single-nucleotide polymorphisms (SNPs) in various genes have been recognized to predict response to tocilizumab therapy in RA and correlated with low DAS28 score[155–157]. Additionally, the IL-6R gene SNPs were found to be associated with response to tocilizumab therapy in RA[158,159]. It is interesting to investigate these genetic markers that can be useful in understanding SARS-CoV-2 mechanisms and hence allow targeted therapy in COVID-19 infection[78].

Another inhibitor of the IL-6 pathway is sarilumab, an inhibitor of soluble and membrane IL-6Rα receptor that could be used to reduce the severity of the pulmonary complications of COVID-19[19]. Recent reports claim that sarilumab is only effective in critical but not moderate/severe COVID-19 patients, while others have reported that sarilumab is a potential therapeutic approach resulting in a clinical benefit with good safety in severe COVID-19 patients[160]. This has been emphasized by others where clinical improvement and mortality in severe COVID-19 patients were unaffected upon

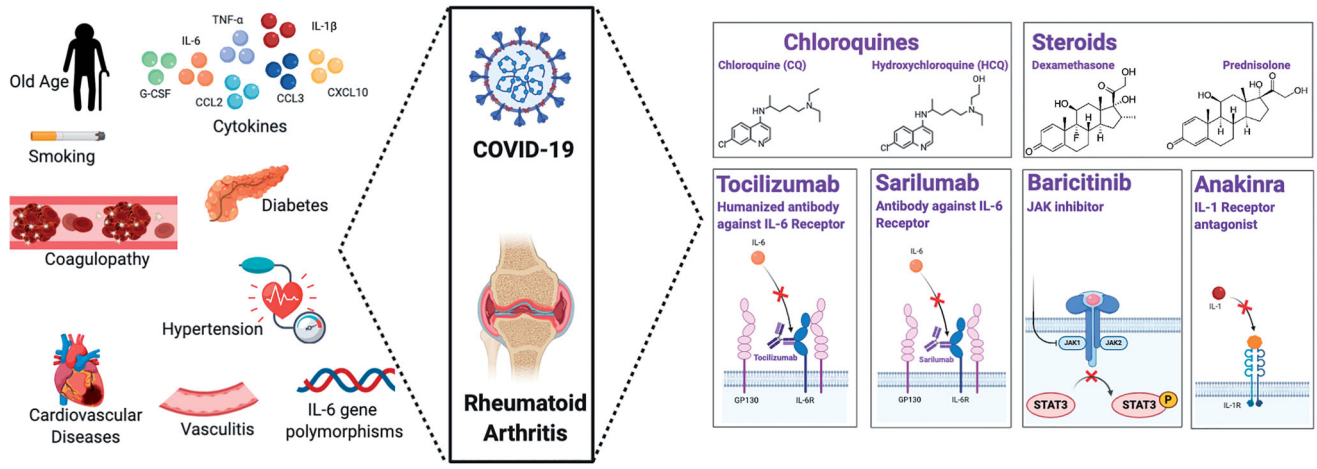

Figure 1. Mutual features between COVID-19 infection and rheumatoid arthritis. The left panel shows the cytokines, risk factors and co-morbidities associated with both diseases, while the right panel displays the remedies that may have potential therapeutic effects in COVID-19 and RA

sarilumab therapy and standard of care[161]. Nevertheless, sarilumab was associated with faster recovery in a subset of patients showing minor lung consolidation. Also, the use of IL-1 blockers was proposed as a possible therapeutic strategy for COVID-19[162].

Previously, the SARS viral spike protein was reported to induce TNF-α-converting enzyme-dependent shedding of the ACE2 ectodomain, thus affecting viral entry[163,164]. This suggests that a similar effect could be suggested in SARS-CoV-2, hence linking its mechanism of entry to TNF-α production. Therefore, the use of TNF inhibitors such as adalimumab may be effective in resolving COVID-19 infection[165–168]. Additionally, other biologic drugs such as the JAK inhibitor baricitinib that is used for treating RA patients, is suggested for controlling SARS-CoV-2 viral replication and showed positive therapeutic efficacies[139,169,170]. This could be mediated *via* the inhibition of the key regulators of endocytosis, AP2-associated protein kinase 1 (AAK1), and the binding cyclin G-associated kinase (GAK), thus blocking viral entry into the lungs[171,172]. Furthermore, JAK inhibitors could dampen the signaling pathways associated with the cytokine storm, the main player of severe symptoms of COVID-19[169]. Baricitinib in combination to remdesivir was superior to the use of remdesivir alone in improving the clinical status, among patients receiving oxygen or mechanical ventilation, with minimal side effects[173].

Colchicine, which is used for the treatment of some rheumatic conditions, was proposed for COVID-19 therapy. A possible mechanism of action could be *via* non-selective inhibition of NLRP3 inflammasome, a major inflammatory marker in the COVID-19 infection[174].

Rheumatologists play a crucial role in this COVID-19 pandemic as they are the most acquainted with these therapeutic agents such as chloroquine, hydroxychloroquine, JAK inhibitors and anti-IL-1 and IL-6 agents, that are typically prescribed in rheumatic diseases[175]. Rheumatologists should share their knowledge and experience to fight the COVID-19 pandemic. Also, they should maintain the management and counseling of patients through telemedicine, in order to avoid the abrupt withdrawal of DMARDs. This would aid in avoiding relapses, flares and development of associated morbidities of such rheumatic diseases, as recommended by EULAR and ACR organizations[80,96,176,177]. A major concern about the common remission agents of COVID-19 and RA is the possibility of a shortage of such drugs that are quite critical for the management of patients with rheumatic diseases[178].

6. Conclusions

It seems that COVID-19 infection revisits inflammatory pathways such as those found in rheumatoid arthritis. Additionally, COVID-19 and RA share mutual features and risk factors that promote the use of synthetic and biological anti-rheumatic agents, for COVID-19 therapy (Figure 1). Current and future studies are working on the efficacy of these agents in COVID-19 infection.

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Author contributions

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