

REVIEW ARTICLE



## The immune dysregulations in COVID-19: Implications for the management of rheumatic diseases

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### ABSTRACT

The pandemic of COVID-19 has caused global social impact and high health risk. Clinical observations have suggested that elevated levels of inflammatory mediators are associated with disease severities in COVID-19 patients, in which the immunological profiles indicate the hyperactivation of innate immune cells and dysregulated adaptive immune responses. The increasing prevalence and disease progression of COVID-19 has emerged as a pressing challenge for the management of rheumatic patients with immune dysregulations. Here we review the immune dysregulations in COVID-19 and discuss the management of COVID-19 patients with rheumatic diseases.

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### Introduction

The newly emerged pandemic coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread around the world with high health risk and great social impact. Currently, the transmission and pathophysiology of COVID-19 remain partially understood [1]. Various factors may affect the susceptibility and severity of COVID-19. Growing evidence has indicated higher risks of COVID-19 infections in Black, Asian and minority ethnic populations than Caucasians [2–4]. Recent studies have suggested that DNA polymorphisms in angiotensin-converting enzyme 2 (ACE2) and TMPRSS2, two key host factors for SARS-CoV-2 entry, are associated with the genetic susceptibility of COVID-19 [5]. Moreover, the expressions of ACE2 and TMPRSS2 show significant variability among different populations. Asians show significantly higher ACE2 expression scores than admixed American and European populations [6], which might be associated with the different susceptibility between Asians and Caucasians. Furthermore, it has been shown that the higher risks of severe COVID-19 in Black, Asian and minority ethnic populations are not explained by variations in cardiometabolic factors, 25(OH)-vitamin D levels or socio-economic factors [2]. Other factors including age and comorbidities may play important roles in determining disease severity and outcome in Asians and Caucasians. Currently, the pre-clinical and clinical studies on ethnic differences of COVID-19 patients are still lacking. Thus, further studies are needed to determine the ethnic disparity of

COVID-19 patients and the underlying socioeconomic and biological factors involved. Although most of the COVID-19 patients exhibit mild disease symptoms, around 5% of patients develop severe symptoms including respiratory failure, systemic shock and multi-organ failure [1,7,8]. Recent studies have shown that SARS-CoV-2-infected patients exhibit increased levels of proinflammatory mediators, which are associated with disease severities [9,10]. Emerging evidence indicates that both dysregulated innate and adaptive immune responses contribute to the disease progression and clinical course of COVID-19 [11]. In particular, the uncontrolled excessive release of cytokines, termed as cytokine storm, is one of the leading causes of multi-organ failure and death in critically ill COVID-19 patients.

There has been increasing attention to the management of COVID-19 in rheumatic patients with dysregulated immune responses [12,13]. Up to date, available data are still not sufficient for a full assessment on COVID-19 risks and disease outcomes in rheumatic patients with immunosuppressive therapies. Here we review the immunological features of COVID-19 and discuss their implications for the management of patients with concurrence of COVID-19 and rheumatic diseases.

### Clinical and laboratory features of COVID-19

Although the majority of COVID-19 patients exhibit a good prognosis with mild to moderate symptoms, a subpopulation of critically ill patients with COVID-19 develop acute respiratory distress syndrome (ARDS) and multiple organ

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injuries, which eventually lead to death [9]. Most of these severe patients showed salient clinical features of cytokine storm, including fever and respiratory failure from ARDS. Laboratory examination revealed substantially higher serum levels of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and TNF- $\alpha$  in patients requiring intensive care, suggesting an association of cytokine storm with disease severities and poor outcome [9]. Available studies suggest that the excessive production of inflammatory cytokines is closely associated with clinical symptoms and ARDS during COVID-19 development. The overproduction of inflammatory cytokines including IL-6, IL-1 $\beta$  and TNF- $\alpha$  has been shown to contribute to pulmonary injury and extra-pulmonary organ dysfunction, which are also observed in severe COVID-19 patients with clinical signs of multi-organ failures [14].

Similar features of markedly elevated cytokine levels are often observed in patients with rheumatic diseases including systemic juvenile idiopathic arthritis, adult Still's disease and systemic lupus erythematosus (SLE). Macrophage activation syndrome (MAS), a subset of hemophagocytic lymphohistiocytosis, is one of the major forms of cytokine storm and is usually associated with fever, pancytopenia, coagulopathy, hyperferritinemia, multi-organ injuries and high mortality in patients with rheumatic diseases [15,16]. These similarities between COVID-19 and rheumatic diseases may provide insights into the understanding of disease pathogenesis and potential therapeutics of COVID-19 [17]. Further studies will contribute to the effective treatment of COVID-19 concurrent with rheumatic diseases, particularly in those at high risks of cytokine storm.

### Immunological features of COVID-19

SARS-CoV-2 viral infection activates both innate and adaptive immune responses [11]. The hyperactivation of various immune populations results in massive production of inflammatory cytokines and chemokines, which finally leads to cytokine storm and tissue damage. The dysregulated cytokine profiles in COVID-19 patients showed similarities to MAS in which inflammatory macrophages were recognized as a key player [8]. Further analysis with single-cell RNA sequencing detected a dominant proportion of inflammatory monocyte-derived macrophages with high expression of cytokines and chemokines in bronchoalveolar lavage fluid from severe COVID-19 patients with ARDS, suggesting an involvement of inflammatory mediators produced by macrophages in the pulmonary system [18]. Moreover, a greater abundance of IL-1 $\beta$ <sup>+</sup> monocytes with high inflammatory gene expression were detected in early recovered COVID-19 patients [19]. The activated macrophage-derived IL-6 and IL-1 $\beta$  are known to be potent mediators for recruiting neutrophils and T cells. Extensive neutrophil infiltration in pulmonary capillaries were observed in autopsy samples from the lungs of a COVID-19 patient [20]. The neutrophil extracellular traps secreted by neutrophils in response to cytokines stimulation may contribute to enhanced inflammatory response and cytokine secretion [20].

For adaptive immune response, lymphopenia is frequently observed in COVID-19 and some rheumatic diseases such as rheumatoid arthritis and SLE [10,21]. Reduced functional diversities of T cells and enhanced T cells exhaustion were detected in COVID-19, which may indicate the severe progression of COVID-19 [22]. Notably, patients with COVID-19 showed significantly higher levels of CD4 T cell-derived GM-CSF and IL-6 expression than those in healthy subjects [23]. Moreover, the frequencies of GM-CSF- and IL-6-secreting CD4 T cells were increased in patients with severe pneumonia, in which Th1 cells with co-expression of IFN- $\gamma$  and GM-CSF were detected, suggesting a role of aberrant Th1 cells in hyperinflammation during severe SARS-CoV-2 infection [23]. Elevated Th17 responses and IL-17 levels are associated with the development of various autoimmune diseases. Similarly, an increased frequency of CCR6<sup>+</sup> Th17 cells was detected in COVID-19 associated with ARDS [24]. Together, lines of available evidence suggest that the massive production of IL-6 and IL-1 $\beta$  in lung tissue may provide an important niche for Th17 cells differentiation and IL-17 production in COVID-19.

Severe COVID-19 and rheumatic disease-associated MAS have shown similarities in terms of clinical and immunological characteristics (Table 1) [25]. It has been suggested that MAS-associated cytokine storm in COVID-19 might be the key to SARS-Cov2 viral control in severe patients. Although severe COVID-19 and MAS patients exhibit similar clinical features, a recent study has shown that MAS patients exhibit thrombocytopenia characteristics while severe COVID-19 patients are characterized by lymphopenia and neutrophilia [26]. Moreover, the two groups of patients also showed lung involvement with radiological differences [26]. MAS is often observed in patients with rheumatic diseases including systemic juvenile idiopathic arthritis (SJIA), which develops in more than 10% of SJIA patients with high mortality. Viral infection is a common trigger of MAS with rapid development of systemic inflammation. Dysregulated cytokine profiles are critically involved in both severe COVID-19 and MAS. It has been shown that elevated levels of TNF- $\alpha$ , IL-6, and IL-1 $\beta$  trigger a cascade of inflammatory responses that lead to systemic inflammation in MAS patients [25]. Notably, clinical observations have also shown increased levels of these cytokines with potential effects on pulmonary injury and extra-pulmonary organ dysfunction in severe COVID-19 patients [9]. It has been proposed that respiratory SARS-Cov2 infection induces activation of both STAT3 and NF- $\kappa$ B and further activate the IL-6 amplifier, which induces the production of various inflammatory cytokines and chemokines including IL-6 [27,28]. The increased production of IL-6 and other cytokines further recruits and activates both innate and adaptive immune cells including neutrophils, macrophages and T cells, leading to systemic overproduction of cytokines and damages of multiple organs. Currently, further investigations are needed to determine the exact roles of IL-6 and other cytokines in severe COVID-19 pathogenesis. Extensive studies have shown dysregulated immunological profiles in both rheumatic disease-associated MAS and severe COVID-19

**Table 1.** Comparisons of severe COVID-19 and MAS.

Comparisons	Severe COVID-19	MAS
Clinical and laboratory features	<ol style="list-style-type: none"> <li>1. ARDS, fever, hyperferritinemia (around 800 ng/mL), respiratory failure, dyspnea, etc [55].</li> <li>2. Lymphopaenia and neutrophilia [26].</li> <li>3. There is no sufficient evidence that rheumatic patients have increased risks.</li> </ol>	<ol style="list-style-type: none"> <li>1. Fever, pancytopenia, coagulopathy, hyperferritinemia (usually over 10<sup>4</sup> ng/mL), dyspnea, etc [16].</li> <li>2. Thrombocytopenia and higher H-score [26].</li> <li>3. High incidence in rheumatic patients (SJIA, AOSD, etc.) [56].</li> </ol>
Cytokine profiles	Increased levels of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , G-CSF, IP-10, MCP-1, MIP-1A etc. [9]	TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IFN $\gamma$ , IL-18 [57]
Immunological profiles	<ol style="list-style-type: none"> <li>1. Existence of activated macrophages and neutrophils in lung tissues [18,20].</li> <li>2. Functional exhaustion of NK cells and CD8 T cells [22,30].</li> <li>3. Skewed T cell receptor repertoire and broad T cell expansion [31].</li> <li>4. Extrafollicular B cell activation [32].</li> </ol>	<ol style="list-style-type: none"> <li>1. Aberrant activation of macrophages.</li> <li>2. Impaired functions of NK cells and CD8 T cells [56].</li> <li>3. Dysregulated T cell expansion and activation [58].</li> </ol>
Therapies	<ol style="list-style-type: none"> <li>1. Glucocorticoid therapies have shown different effects. Methylprednisolone and Dexamethasone reduced risks of severe COVID-19 patients [7,41].</li> <li>2. IL-1 and IL-6 blocking agents have shown some benefits in clinical trials [47,48].</li> </ol>	<ol style="list-style-type: none"> <li>1. Immunosuppressive agents including glucocorticoid are commonly used.</li> <li>2. The effects of IL-1 and IL-6 blocking agents are not fully known. Some SJIA patients still have risks for MAS with these therapies [59].</li> </ol>

COVID-19: coronavirus disease 2019. MAS: macrophage activation syndrome. ARDS: acute respiratory distress syndrome. TNF- $\alpha$ : Tumor necrosis factor  $\alpha$ . G-CSF: Granulocyte colony-stimulating factor. IP-10: interferon-inducible protein 10. MCP-1: monocyte chemoattractant protein-1. MIP: macrophage inflammatory proteins. NK cells: natural killer cells. IFN $\gamma$ : Interferon  $\gamma$ . SJIA: systemic juvenile idiopathic arthritis. AOSD: adult onset Still's disease.

patients [14–16]. One of the major characteristic of MAS is the activation of macrophages. Moreover, MAS patients have shown impaired cytotoxic functions of NK cells and CD8 T cells, which result in insufficient lysis of macrophages and sustained production of cytokines. In severe COVID-19 patients, inflammatory macrophages and neutrophils infiltration have been detected in bronchoalveolar lavage fluid and lung tissues, indicating the involvement of these cells during local inflammation [18,20]. It has been shown that SARS-CoV-2 infection leads to decreased numbers and impaired functions of various immune cell populations including dendritic cells, T cells and NK cells in peripheral blood of acute COVID-19 patients [29,30]. Further analysis of immunological responses has shown increased interferon response, skewed T cell receptor repertoire and broad T cell expansion in severe COVID-19 patients, suggesting a dynamic nature of immune responses during COVID-19 development [31]. It has been found that severe COVID-19 patients exhibit hallmarks of extrafollicular B cell responses which is similar to that in active SLE patients [32]. Although B cell activation and serum IgM, IgG and IgA responses in COVID-19 have been partially characterized, future studies are needed to investigate functional changes of B cell subsets and antiviral antibody responses in severe COVID-19 pathogenesis [33,34].

### Management for COVID-19 patients with rheumatic diseases

Current studies of COVID-19 among rheumatic patients with immunomodulatory therapies have significant implications for the prognosis and management of these patients. Up to date, there is no sufficient evidence indicating an increased risk of COVID-19 occurrence or poor outcome within rheumatic patients (Table 2) [35]. Recent studies reported similar clinical features and comparable lengths of hospital stay and mortality rates between rheumatic and non-rheumatic COVID-19 patients [36,37]. However,

another retrospective study showed that the patients with rheumatic disease were more susceptible to COVID-19 infection than the general population [38]. Nevertheless, further studies are urgently needed to determine the effects of immunosuppressive agents on SARS-CoV-2 infection in rheumatic patients and whether the comorbidities associated with rheumatic diseases have any significant impacts on COVID-19 disease initiation and progression.

The broadly used immunosuppressive agents including glucocorticoids and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) may potentially ameliorate the hyperinflammation-associated symptoms in COVID-19, but extra caution is required for the administration of these immunosuppressive agents due to their possible side effects associated with severe bacterial and opportunistic infections. The use of hydroxychloroquine or chloroquine in COVID-19 patients is currently controversial. Recent evidence suggested that hydroxychloroquine did not prevent COVID-19 development in SLE patients [39,40]. Notably, glucocorticoid therapies show different effects in various groups of COVID-19 patients. A retrospective cohort study involving 201 COVID-19 patients revealed that standard doses of methylprednisolone treatment markedly reduced the risk of death in severe patients, particularly those with ARDS [7]. Moreover, dexamethasone treatment was found to reduce the mortality of severe COVID-19 patients [41]. Clinical observations on the association between steroids therapies and good prognosis suggest that anti-inflammatory steroids treatment at the right window time may prevent COVID-19 progression to severe forms [42]. However, a proportion of COVID-19 patients with corticosteroid therapy showed no improvement [43]. Available data indicate that ibuprofen use is not associated with exacerbated disease development and worse clinical outcomes in a retrospective cohort study of COVID-19 patients [44]. Currently, the continued use of hydroxychloroquine and glucocorticoids in rheumatic patients with or without SARS-CoV-2 exposure is recommended by the

**Table 2.** Current findings and implications for the management of rheumatic diseases with COVID-19.

	Important Findings	Implications
Clinical features	Rheumatic and non-rheumatic COVID-19 patients showed similar clinical features and comparable mortality rates [36,37]. Comparable incidence rates and clinical course between rheumatic patients with immunosuppressive treatments and general population [60–63]. Low numbers of COVID-19 infection in SLE patients from the Asia Pacific Lupus Collaboration cohort [64]. Chronic arthritis patients with DMARDs treatments were not at increased risk of severe COVID-19 [65]. Higher incidence of COVID-19 in rheumatic patients than non-rheumatic patients [38].	Rheumatic patients may not have higher risks of COVID-19 than general population.  Rheumatic patients might be more susceptible COVID-19.
Therapies	HCQ did not prevent COVID-19 development in SLE patients [39,40]. Methylprednisolone, dexamethasone and steroids reduced the risks of severe COVID-19 [7,41,42]. Corticosteroid therapy showed no improvement in a proportion of COVID-19 patients [43]. Ibuprofen use was not associated with exacerbated disease development and worse clinical outcome [44]. IL-6 receptor blockade with tocilizumab improved clinical outcome in severe COVID-19 patients [47,48].	Continued use of HCQ and glucocorticoids in rheumatic patients with or without SARS-CoV-2 exposure is recommended. NSAID use may be continued in patients without severe respiratory symptoms [35,45].  IL-6 receptor inhibition could be continued in selected patients based on shared decision-making [35,45].

COVID-19: coronavirus disease 2019.

SLE: systemic lupus erythematosus.

DMARD: disease-modifying anti-rheumatic drugs.

HCQ: hydroxychloroquine.

NSAID: nonsteroidal anti-inflammatory drug.

American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) based on the considerations of progressive rheumatic disease activities and increased risks of disease flares after abrupt discontinuation (Table 2) [35,45]. However, COVID-19 patients with severe respiratory symptoms are recommended to discontinue NSAIDs use [45].

Available evidence has indicated that cytokine storm is one of the leading causes of mortality for severe COVID-19. COVID-19 patients with rheumatic diseases showed higher incidences of respiratory failure and were more likely to require intensive care admission and mechanical ventilation than non-rheumatic patients, suggesting a role of rheumatic disease-associated hyperinflammation in severe COVID-19 development. Both clinical and immunological features of cytokine storm during COVID-19 development suggest that cytokine-targeted therapies including blockade of IL-6, IL-1, IL-17 and TNF $\alpha$  may represent promising therapeutic strategies for the treatment of severe COVID-19 patients [46]. Most of these biologic agents have been widely applied in treating autoimmune diseases with satisfactory benefits. Preliminary clinical data showed therapeutic benefits of both IL-6 receptor and IL-1 receptor blockades in severe COVID-19 patients [47,48]. Up to date, several large scale clinical trials have been initiated to investigate the safety and efficacy of cytokine-targeted therapies in the treatment of severe COVID-19 patients. IL-6 receptor blockade with tocilizumab was found to significantly improve the clinical outcome in 21 patients with severe and critical COVID-19 in a preliminary single-arm study [47]. Moreover, tocilizumab treatment was associated with decreased risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia [49]. However, the efficacy, optimal dosages and intervention timing of IL-6 blockade treatment in COVID-19 need to be further assessed in larger randomized clinical trials. The strategy of targeting IL-6 pathway

has demonstrated clinic success in various rheumatic diseases including rheumatoid arthritis, juvenile idiopathic arthritis and adult-onset Still's disease [50]. During the concurrence of COVID-19 and rheumatic diseases, IL-6 receptor inhibition could be continued in selected patients based on shared decision-making [45]. However, due to very limited clinical data to support the continued use of other non-IL-6 biologic agents, it has been recommended that non-IL-6 biologic immunosuppressants should be temporarily stopped with the aim to restore anti-infection immunity within a short period [45]. Further clinical studies on other anti-rheumatic drugs including JAK inhibitors, anti-TNF- $\alpha$  agents, and colchicine may benefit COVID-19 patients with or without rheumatic diseases [51]. Considering the risks of rapid deterioration of COVID-19 in some COVID-19 patients, a close monitoring of disease progression would be critically important, especially in the rheumatic patients at high risks of developing cytokine storm and respiratory failure. Future studies on the immune pathogenesis and clinical characteristics of rheumatic patients with COVID-19 will have significant implications for assessing the risk of infection in patients on immunosuppression and improving the management of these patients.

Vaccines against SARS-CoV-2 is one of the most important strategies for combating COVID-19. The current COVID-19 vaccine pipeline involves multiple technology platforms including inactivated virus, recombinant protein and RNA vaccines [52]. Currently, more than 30 COVID-19 vaccine candidates have progressed to clinical trials [52]. Effective vaccination is of key significance for both rheumatic patients and non-rheumatic populations to minimize COVID-19 risks. Previous experience in RA patients with DMARDs treatments suggested that vaccines including live-attenuated ones might be safer than previously thought [53]. Although much attention has been paid to the safety and efficacy of vaccination in rheumatic patients with treatments



of immunosuppressive agents, it has been recommended that non-live vaccines can be safely provided to patients with autoimmune inflammatory rheumatic diseases while live-attenuated vaccines could be considered with caution [54]. However, further clinical studies are warranted to provide valuable insights in understanding the safety, immunogenicity, and efficacy of newly developed vaccines in both general population and rheumatic patients.

### Conclusion and future perspectives

Current studies have suggested that the hyperactivation of various immune cell populations and excessive cytokines production are closely associated with disease progression and clinical manifestations of COVID-19, in which the cytokine storm is one of the key factors contributing to the high mortality of SARS-CoV-2 infected patients. Although available data indicate comparable COVID-19 occurrence and disease outcome between rheumatic and non-rheumatic COVID-19 patients, further investigations on the immune dysregulations and clinical management of COVID-19 in patients with rheumatic diseases are urgently needed for early diagnosis and effective treatment of this disease.

### Conflict of interest

None.

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