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Interleukin-6 blocking therapy for COVID-19: From immune pathogenesis to clinical outcomes

Fan Xiao[1,#], Ling Wu[2,#], Xiaoxia Zhu[3], Lijun Zhang[2], Dongzhou Liu[4], Lijun Wu[5], Hejian Zou[3,*], Liwei Lu[1,2,*]

[1]Department of Pathology and Shenzhen Institute of Research and Innovation, The University of Hong Kong, Hong Kong, China
[2]Department of Rheumatology, Shenzhen Hospital, The University of Hong Kong, Shenzhen, China
[3]Department of Rheumatology, Huashan Hospital and Fudan University, Shanghai, China
[4]Department of Rheumatology, Shenzhen People's Hospital, Shenzhen, China
[5]Department of Rheumatology and Immunology, People's Hospital of Xinjiang Uygur Autonomous Region, Urumqi, China

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Abstract

As a newly emerged infectious disease, the coronavirus disease 2019 (COVID-19) has caused millions of deaths, resulting in a global health challenge. Currently, several vaccines have been approved with significant benefits against disease transmission. However, effective therapies are still needed for the clinical management of infected COVID-19 patients. Available evidence has indicated elevated levels of proinflammatory cytokines, including interleukin-6 (IL-6), in COVID-19 patients, with cytokine storm involving excessive cytokine release being observed in some severe cases. Several clinical studies have shown the promising effects of IL-6-blocking strategy in treating severe COVID-19 patients, but some observational studies have reported that IL-6-blocking therapy has no effects in preventing disease progression or death among COVID-19 patients. Herein, we review recent findings on the immunopathogenesis of COVID-19, with specific emphasis on the proinflammatory function of IL-6 and discuss the therapeutic potential of IL-6-blocking therapy for the treatment of COVID-19 patients, especially those with rheumatic diseases.

Keywords

COVID-19 • interleukin-6 • rheumatic disease • treatment

Introduction

The newly emerged coronavirus disease-2019 (COVID-19) pandemic has spread rapidly across the world with broad social impact. COVID-19 has caused millions of deaths and has become a global health challenge since 2019. COVID-19 is caused by infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which leads to fever, cough, myalgia, fatigue, and even death in patients. Although recently developed vaccination strategies have shown enormous benefits against disease transmission, effective therapies for COVID-19 patients are still lacking.

Most of the COVID-19 patients show mild disease symptoms, while around 5% of patients develop severe symptoms, including respiratory failure, systemic shock, and multiorgan failures.[1] Uncontrolled excessive release of cytokines, termed as cytokine storm, is observed in critically ill COVID-19 patients with salient clinical features, including fever and respiratory failure from acute respiratory distress syndrome.[2] The pathological significance of the cytokine storm in COVID-19 has been well recognized. Effective clinical management of severe complications in COVID-19 is thus urgently needed.

Currently, substantial progress has been made in understanding the pathogenesis of COVID-19. Both innate and adaptive responses are activated during the development of COVID-19, with the critical involvement of multiple cytokines. Clinical observations have shown inflammatory infiltrates in the lung tissues of infected patients with dysregulated activation of neutrophils, monocytes, and various T cell subsets. As a result, the aberrant immune cell activation leads to excessive production of interleukin 6 (IL-6) and other inflammatory cytokines. The overproduction of these cytokines in COVID-19 patients shows similarities with macrophage activation syndrome (MAS), a subset of hemophagocytic lymphohistiocytosis and one of the major forms of cytokine storm commonly observed in patients with rheumatic diseases.

[#]Fan Xiao and Ling Wu have contributed equally to this work.

Address for correspondence:
*Hejian Zou, MD, Department of Rheumatology, Huashan Hospital and Fudan University, Shanghai, China. E-mail: hjzou@fudan.edu.cn
*Liwei Lu, PhD, Department of Pathology, The University of Hong Kong, Hong Kong, China. E-mail: liweilu@hku.hk

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IL-6 is a key cytokine involved in MAS and cytokine storm. IL-6 shows pleiotropic functions with broad effects on both immune and nonimmune cells. Mounting evidence has demonstrated the critical involvement of IL-6 in the development of rheumatic diseases, including rheumatoid arthritis, systemic juvenile idiopathic arthritis, and Castleman disease.[3, 4] IL-6 induces the production of cytokines and chemokines by endothelial cells and epithelial cells, which leads to the recruitment of more immune cells to the inflammatory sites during the pathogenesis of rheumatic diseases. Furthermore, in the development of rheumatic diseases, IL-6 regulates the differentiation and activation of various T cell subsets, including Th1 cells, Th17 cells, and regulatory T cells.[3] Available studies have shown that neutralizing antibodies against IL-6 and IL-6 receptors are promising biological agents for treating patients with rheumatic diseases.[5]

Based on recent data from clinical trials and observational studies, IL-6-blocking therapy has shown promising therapeutic potential for severe COVID-19 patients.[6] In this review, we summarize recent findings on the immunopathology of COVID-19 and discuss the therapeutic potential of IL-6-blocking therapy for COVID-19. Moreover, we discuss the epidemiological studies on managing rheumatic diseases under the current COVID-19 pandemic with emphasis on the clinical benefits of anti-IL-6 therapy.

Immunopathology of Covid-19

Existing evidence indicates that both innate and adaptive immune cell populations are closely involved in the occurrence and progression of COVID-19. Observational studies on autopsy samples have revealed extensive neutrophil infiltration in the lung tissues of COVID-19 patients.[7] Moreover, the neutrophil extracellular trap (NET), which is released by neutrophils in response to pathogens and danger signals, is rapidly formed upon SARS-CoV-2 infection.[8] The released NETs may further cause damage to distant organs mediated by immunothrombosis.[8] In various infectious diseases, monocytes and macrophages play critical roles at the early stages of infections. In severe COVID-19 patients, the systemic and continuous elevation of various inflammatory cytokines, including IL-6, shows similarities with the cytokine storm responses observed in MAS, suggesting a role of dysregulated activation of macrophages in COVID-19-associated hyperinflammation. Single-cell RNA sequencing (scRNA-seq) analysis of bronchoalveolar fluid samples from severe and mild COVID-19 patients revealed a dominant proportion of mononuclear phagocytes, which was associated with the severity of the disease.[9] Various factors – including damage-associated molecular patterns (DAMPS), released from infected epithelial cells of the lung, and pathogen-associated molecular patterns (PAMPs) from viruses – may trigger the activation and production of cytokines by macrophages during SARS-CoV-2 infection.[10] Although a transient reduction of peripheral monocytes in blood was observed in severe COVID-19 cases,[10, 11] the roles of monocytes and macrophages in lung inflammation and excessive cytokine production during COVID-19 pathogenesis need further investigations.

The activation and effector responses of B and T cells have been characterized in COVID-19 patients. Notably, a weak immune response to SARS-CoV-2 infection is detected in asymptomatic individuals, while children with SARS-CoV-2 infection often exhibit a more effective humoral immune response than adult patients.[12] Although sustained humoral immunity is observed in recovered patients who had symptomatic COVID-19,[13] the protective effects of SARS-CoV-2-specific antibody responses might be limited in some patients.[14, 15] It has become clear that follicular helper T (Tfh) cells play an important role in B cell activation and are essential for generating high-affinity antibodies,[16] which are closely associated with the generation of neutralizing antibodies against SARS-CoV-2.[17] The frequencies of antigen-specific circulating Tfh cells against the M, N, and S structural proteins of SARS-CoV-2 are positively correlated with neutralizing antibody responses.[18] Convalescent individuals with severe COVID-19 manifestations showed higher neutralizing antibody titers and Tfh cell frequencies when compared with convalescent patients with mild COVID-19 episodes.[19] Remarkably, both Tfh cells and germinal center B cells were found to be diminished in the thoracic lymph nodes and hilar lymph nodes of COVID-19 patients.[14, 20] During COVID-19 development, Tfh cell differentiation was blocked in the germinal centers of lymphoid tissues, which was associated with a lack of prominent germinal center formations and impaired antibody responses in severely ill COVID-19 patients.[14] In various diseases such as autoimmune diseases, B cells and Tfh cells are important cellular sources of cytokines including IL-6.[21] IL-17 plays an important role in the pathogenesis of infectious and rheumatic diseases.[22, 23] Increasing evidence shows that IL-17-producing Th17 cells are critically involved in the development of COVID-19.[24] In SARS-Cov2-infected patients with a detectable cytokine storm in the plasma, a significant skewing of T cell activation toward Th17 phenotypes is observed,[25] in which neutrophils may play a role.[26] Thus, the contributions of B cells, Tfh cells, and Th17 cells, as well as other T cell subsets, to the dysregulated cytokine network in COVID-19 warrant further investigations.[27]

Compelling evidence has indicated elevated levels of proinflammatory cytokines, including IL-6, IL-1β, and tumor necrosis factor (TNF)-α, in severe COVID-19 patients requiring intensive care.[28] ScRNA-seq analysis also showed higher levels of IL-6 expression in patients with severe and critical SARS-CoV-2 infection when compared with expression levels in patients with moderate infection.[29] Moreover, it has been revealed that these cytokines are important mediators of pulmonary injury and extrapulmonary organ dysfunction, observed in some severe COVID-19 patients. The maximal

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level of IL-6 highly predicts the need for mechanical ventilation in COVID-19 patients, suggesting that IL-6 levels are associated with COVID-19 disease progression and severity.[30] Inflammatory monocytes with high IL-6 expression and IL-6-producing T cells with dysregulated Th1 responses are detected in severe COVID-19 patients.[31] While histological findings have shown massive infiltration of inflammatory infiltrates in lung tissues of infected patients, the overproduction of IL-6 may contribute to local inflammatory responses and tissue damage during SARS-CoV-2 infection. It is clear that IL-6 serves as a key regulator of adaptive immune populations, including Th17 cells and Tfh cells. The massive amount of IL-6 may contribute to a microenvironmental niche for T-cell activation and differentiation in lung tissue. Together, these clinical and immunological features of COVID-19 support the notion that IL-6-targeted therapies may represent promising therapeutic strategies for the treatment of COVID-19 patients.

Il- 6-Blocking Therapy for Covid-19

Several clinical trials have shown the promising effects of the IL-6-blocking strategy in severe COVID-19 patients. In a small-scale clinical trial, Xu *et al*. showed that IL-6 receptor blockade with tocilizumab immediately improved the clinical manifestations of severe and critical COVID-19 patients.[32] Most of the patients exhibited absorbed lung lesion opacity and normalized numbers of lymphocytes after tocilizumab treatment.[32] Importantly, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) and Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) studies showed that treatments with IL-6 receptor antagonists, including tocilizumab and sarilumab, in large-scale randomized clinical trials improved the clinical outcomes of critically ill patients with COVID-19.[33, 34] In a prospective meta-analysis study, administration of IL-6 antagonists was associated with lower 28-d all-cause mortality when compared with placebo treatment in clinical trials of patients hospitalized for COVID-19.[35] Based on the available clinical evidence, tocilizumab was authorized for emergency use by the US Food and Drug Administration (FDA) for the treatment of certain hospitalized patients with COVID-19.[36] Tocilizumab treatment was also formally included in the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (7th edition) of the National Health Commission of China.[37] In a recent report, Liu *et al*. reviewed the clinical records, laboratory results, and chest computed tomography scans of five geriatric severe COVID-19 patients who were treated with tocilizumab.[38] Most of the patients (4/5) showed clinical improvements and were discharged from the hospital after treatment, suggesting that tocilizumab may serve as an effective therapy for severe COVID-19 patients. As the elderly are susceptible to SARS-CoV-2 infection and vulnerable to glucocorticoid-related side effects, this study may help physicians to better understand the efficacy and outcomes of tocilizumab applications in severe geriatric COVID-19 patients. Furthermore, the 6-month follow-up results showed that the discharged patients were generally in good condition, suggesting the long-term safety of tocilizumab in the treatment of COVID-19.

Although some clinical trials show favorable responses to IL-6-blocking therapies in COVID-19 patients, it should be noted that the reported treatment effects are varied because, in a randomized, double-blind, placebo-controlled trial, tocilizumab was also reported to have no significant effect in preventing intubation or death in moderately ill COVID-19 patients.[39] A randomized clinical trial and its follow-up study found that tocilizumab did not affect 28-d mortality, whereas it might be considered for treating patients with moderate-to-severe COVID-19-associated pneumonia and high C-reactive protein (CRP) levels.[40,41] The patient subgroups that are responsive to IL-6 blockage have not been identified and warrant further studies. Based on available evidence, severely ill COVID-19 patients may benefit from IL-6-blockade immunotherapy since the serum levels of IL-6 are increased in COVID-19 patients and are associated with the disease severity.[29] However, IL-6 levels are not routinely tested in many published studies. It should be considered that the baseline levels of IL-6 may be important for evaluating the therapeutic efficacies of IL-6/IL-6 receptor antagonists. Moreover, the infusion time of the biological agents targeting the IL-6/IL-6 receptor pathway is important for assessing the therapeutic effects as IL-6 may exert different functions in the inflammatory response during different disease stages.

A recent survey conducted by the COVID-19 Global Rheumatology Alliance revealed significant social, physical, and mental effects of the COVID-19 pandemic on patients with rheumatic diseases worldwide.[42] Although the risks of SARS-CoV-2 infection and disease severities in rheumatic patients, especially those with disease-modifying antirheumatic drug (DMARD) treatments, are still unclear, available epidemiological studies provide some insights related to the development of COVID-19 in rheumatic patients.[43] An OpenSAFELY study based on existing patient data showed that patients with autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, exhibited a slightly increased risk of death from COVID-19 compared to those without these diseases.[44] However, the disease activities and treatment history of these patients were not taken into consideration in this risk estimation study. Recently, a nationwide cohort study from Denmark also showed that patients with inflammatory rheumatic diseases were more likely to be infected with COVID-19 than the general population.[45] However, the notion of increased COVID-19 risks in rheumatic patients should be further confirmed as other published studies showed comparable clinical features, hospitalization rates, and mortality rates between rheumatic and nonrheumatic patients with COVID-19.[46, 47] Exposure to glucocorticoids at moderate

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or high doses (≥10 mg/d prednisolone or equivalent) is associated with a higher risk of hospitalization in rheumatic patients.[48] Notably, cytokine inhibitors appear to at least partially protect rheumatic patients from SARS-CoV-2 infection,[49, 48] suggesting a therapeutic potential of cytokine-targeted therapies for treating COVID-19.

The IL-6-blocking strategy has shown significant efficacies in various rheumatic diseases, including rheumatoid arthritis and adult-onset Still's disease.[50] The newly released guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic by the American College of Rheumatology suggests that IL-6 receptor inhibition could be continued in rheumatic patients with infection or in the setting of exposure to SARS–CoV-2 with the need for shared decision-making between patients and inpatient care teams.[51] For those rheumatic patients without exposure to or infection of SARS–CoV-2, IL-6 receptor inhibitor should be continued when available.[51] Nevertheless, further investigations on the immunopathological characteristics and clinical manifestations of rheumatic patients with COVID-19 are needed for more precise and effective therapies for the management of these patients.

Conclusion

Current studies have demonstrated that proinflammatory cytokines, including IL-6, play an important role in immunopathogenesis and disease pathology of COVID-19. Extensive evidence indicates that the overproduction of IL-6 contributes to local inflammatory response and tissue damage during SARS-CoV-2 infection. Although available clinical studies have suggested that IL-6 is a promising therapeutic target for treating severe COVID-19 patients, more randomized controlled clinical trials are still needed to determine the efficacy, optimal dosages, and intervention duration of IL-6 blockade agents for the treatment of COVID-19 patients, especially those with rheumatic diseases.

Conflict of Interest

Liwei Lu is an Editorial Board Member of the journal. The article was subject to the journal's standard procedures, with peer review handled independently of this member.

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