

Exploring Interleukin-6 Inhibitor Antibodies in Combatting SARS-CoV-2 and its Mutated Variants: Challenges and Future Directions

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Abstract

The aim of this study is to investigate the efficacy of interleukin-6 (IL-6) inhibitor antibodies as a therapeutic agent to combat severe COVID-19. Given the constant evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants, the study aims to assess the potential of these inhibitors in adapting to new challenges and improving treatment outcomes. A comprehensive review of relevant literature was conducted using electronic databases such as Web of Science, PubMed, EMBASE, Scopus, and Google Scholar. The study analyzed the role of IL-6 inhibitors in combating SARS-CoV-2, focusing on their therapeutic potential in treating severe COVID-19 cases, particularly in controlling the overshooting immune response associated with cytokine storms. IL-6 inhibitors proved to be versatile and effective in attenuating severe immune responses, especially cytokine storms, which are common in advanced COVID-19 cases. The literature emphasizes their ability to regulate the immune system, reduce disease severity, and improve patient outcomes. Their efficacy in controlling the immune response and reducing disease severity makes IL-6 inhibitor antibodies a promising therapeutic strategy for severe SARS-CoV-2 and its new variants. Further research is needed to optimize their use and adaptability in evolving clinical scenarios.

Keywords

Severe acute respiratory syndrome coronavirus 2, cytokine storm, interleukin-6 inhibitors, tocilizumab, sarilumab

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Introduction

Interleukin-6 (IL-6) is a crucial cytokine that substantially impacts the control of immunological and inflammatory responses. It is generated by diverse immune system constituents, such as T cells, B cells, macrophages, and fibroblasts. Depending on the context and the specific signaling pathways triggered, IL-6 can either promote or attenuate inflammatory responses.¹ Its versatile nature, termed pleiotropy, allows IL-6 to regulate aspects of neurological and hematological system development, acute phase responses, inflammation, and immune system functions.^{2,3} In the case of viral infections, signals from infected cells are critical for mobilizing and activating the necessary innate or adaptive immune cells to fight the virus. The role of IL-6 has attracted considerable attention in the wake of the severe acute respiratory syndrome coronavirus 2

(SARS-CoV-2) pandemic. Research has shown that severe COVID-19 patients commonly have increased levels of IL-6, and these raised levels are frequently associated with more unfavorable clinical results.⁴ The immunologic profile of COVID-19-positive critically ill patients suggests hyperactivation of the humoral immune system, particularly IL-6, as a key mediator of shock, multiorgan failure, and respiration. A cytokine storm, characterized by excessive

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inflammation due to the overproduction of IL-6 and other pro-inflammatory cytokines, is possible.⁵ The exact processes leading to the surge in IL-6 levels and the subsequent cytokine storm in COVID-19 continue to be the subject of ongoing research. Preliminary studies suggest that irregularities in immune system behavior may be implicated in the progression of COVID-19. These irregularities might include a decrease in white blood cell counts, an increase in neutrophil levels, imbalances in monocytes and macrophages, as well as subdued or postponed type I interferon responses. The spike in IL-6 contributes to an overproduction of proinflammatory signaling molecules, including IL-6 itself, ultimately culminating in a cytokine storm.^{6,7}

The phrase “cytokine storm” describes the reaction of the immune system to a viral infection, which leads to the release of numerous inflammatory substances. This hyperactive immune response can damage organs and tissues and potentially lead to significant respiratory problems, multiple organ failure, and, in extreme cases, death. The main cytokines involved in this process include IL-6, IL-1, and tumor necrosis factor- α (TNF- α). Alternatively, therapeutic strategies could focus on modulating the role of IL-6 in the immune response (Figure 1).

IL-6 inhibitors are a category of drugs that specifically target the function of the cytokine IL-6, which plays an important role in the treatment of inflammatory and autoimmune diseases. They offer therapeutic benefits in conditions such as

rheumatoid arthritis, systemic juvenile idiopathic arthritis, and giant cell arteritis by reducing symptoms and improving quality of life. These inhibitors are used in the treatment of cytokine release syndrome, a severe reaction to cancer therapies, and have promise for use in the treatment of severe COVID-19 patients and other inflammatory diseases. IL-6 inhibitors are effective in relieving symptoms, preventing organ damage, and improving patient well-being by reducing inflammation.^{10–12} Table 1 illustrates the randomized clinical trial of selected IL-6 inhibitors.

In the treatment of severe COVID-19 cases and to attenuate the intensity of cytokine storms, drugs targeting IL-6, such as tocilizumab and sarilumab, have been used to regulate the immune response. Tocilizumab and sarilumab are both recombinant humanized monoclonal antibodies that inhibit the IL-6R, thereby attenuating the IL-6-mediated systemic and local effects observed with COVID-19.¹⁹ Tocilizumab and sarilumab are generally reserved for patients with severe inflammation and have shown promising results in reducing the need for mechanical ventilation and in some cases improving treatment outcomes.²⁰ More study is required to completely comprehend the complex function of IL-6 in COVID-19 and to maximize the use of IL-6 inhibitors as targeted therapeutics. Overall, IL-6 is an important therapeutic target in the treatment of SARS-CoV-2 infection, with potential pathways for reducing the severity and improving the prognosis of COVID-19 patients.

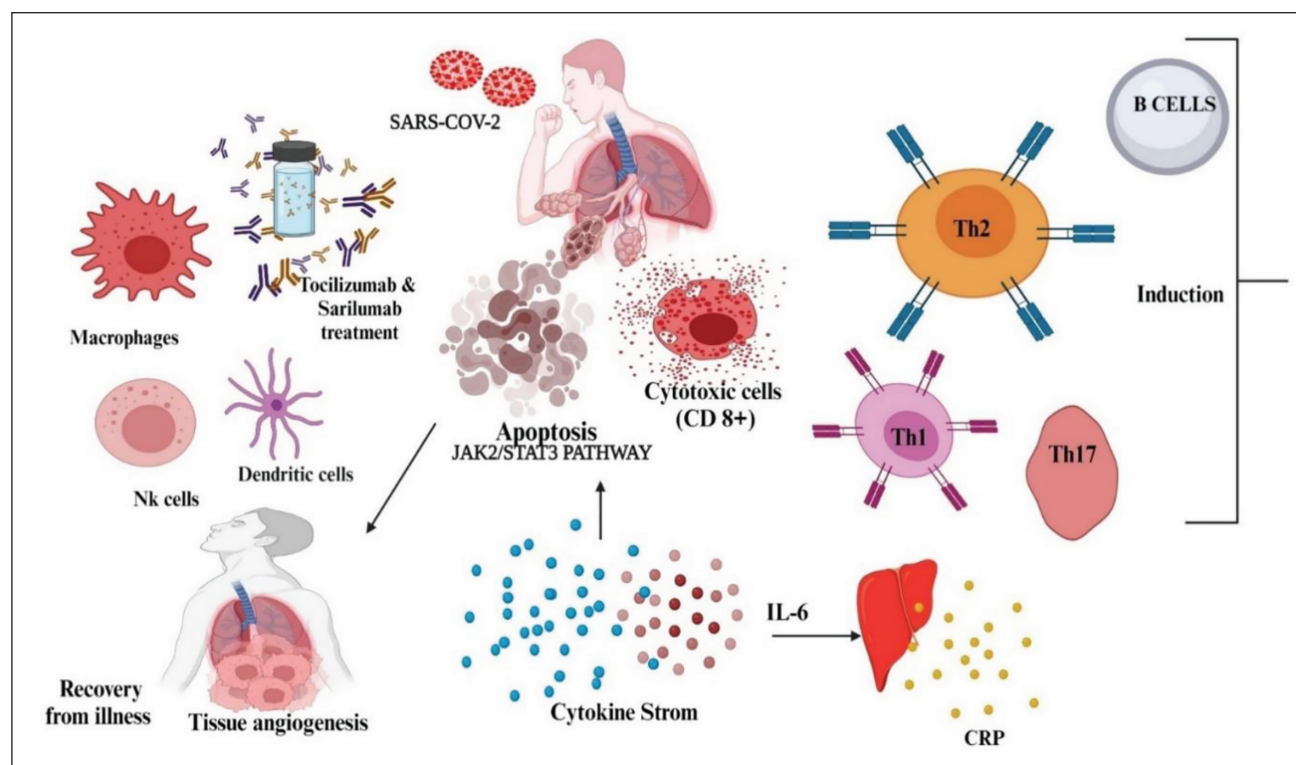


Figure 1. Schematic Illustration of the Mechanistic Action of Monoclonal Antibodies Against SARS-CoV-2 Infection.

Note: CRP, C-reactive protein; IL-6, interleukin-6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Interleukin (IL)-6 Inhibitor and Selected Randomized Clinical Trials.

Treatment	Research Findings	References
Tocilizumab	The study was conducted between November 2020 and January 2022 at Peking University First Hospital, Beijing, China. A total of four patients between the ages of 35 and 59 were admitted to the hospital. Three were diagnosed with acute leukemia, and one with multiple myeloma. Severe infections and cytokine storms occurred in all four patients during the agranulocytosis phase. Regardless of anti-biotic treatment, all patients had elevated IL-6 levels and suffered hypotension or organ damage. They were administered tocilizumab, an adjuvant treatment that targets the IL-6 receptor. After treatment with tocilizumab, three of the four patients experienced a significant improvement in their condition, while one patient died of multiple organ failure due to anti-biotic resistance. This suggests that tocilizumab may be an effective adjuvant therapy to alleviate systemic inflammation and organ damage in such patients, although more extensive studies are needed to confirm these results.	13
Tocilizumab versus olokizumab versus sarilumab	The aim of the study was to investigate the efficacy and safety of olokizumab, tocilizumab, and sarilumab in the treatment of patients with rheumatoid arthritis who do not respond adequately to methotrexate or cannot tolerate it. In six randomized, controlled trials with a total of 4,439 patients, all three drugs, as well as adalimumab, proved to be significantly more effective than a placebo in achieving a response rate of 20% according to the criteria of the American College of Rheumatology (ACR20). The results showed that tocilizumab had the highest probability of achieving the ACR20 response rate, followed by sarilumab, olokizumab administered every 2 weeks, olokizumab administered every 4 weeks, adalimumab 40 mg, and finally placebo. The consistency of this efficacy pattern was observed in both ACR50 and ACR70 response rates. In terms of safety, placebo had the fewest adverse events and discontinuations, while the IL-6 inhibitors (tocilizumab, sarilumab, and olokizumab) ranked second in terms of safety.	14
Tocilizumab and sarilumab	This systematic review specifically examined the effectiveness and safety of IL-6 receptor antagonists (tocilizumab and sarilumab) in treating adult patients with severe or critical COVID-19. The analysis assessed data from 11 randomized clinical trials, including a total of 5,028 people. The findings indicate that IL-6 receptor antagonists have the potential to decrease the duration of intensive care unit and hospital stays in these patients, without considerably elevating the likelihood of serious adverse events. Nevertheless, these therapies did not result in a substantial decrease in the overall mortality rate at 7-, 14-, and 28-day intervals.	15
Rituximab versus tocilizumab	This 48-week phase four randomized controlled trial (RCT) aimed to compare the efficacy of rituximab and tocilizumab in 164 RA patients who exhibited inadequate response to anti-tumor necrosis factor (anti-TNF) therapy. The study assessed which medication demonstrated superior improvement in symptoms and disease activity during the trial. The study also assessed the safety and tolerability of both medications, contributing to the advancement of tailored therapy regimens for rheumatoid arthritis.	16
Sarilumab	The open-label extension study EXTEND demonstrated that patients with rheumatoid arthritis who transitioned from intravenous tocilizumab to subcutaneous sarilumab, or continued with subcutaneous sarilumab, did not encounter any new safety concerns, and maintained clinical effectiveness for a period of 96 weeks. Furthermore, the treatment consistently had a beneficial effect on different clinical indicators. The study's findings offer assurance that changing the method of delivering IL-6 receptor inhibitors from intravenous to subcutaneous in patients with RA does not impact the safety or effectiveness of the treatment. This supports the notion that these medicines are versatile and consistently successful.	17
Tocilizumab and methotrexate	In RA patients with poor response to methotrexate, tocilizumab in combination with methotrexate showed more immediate and better clinical efficacy in reducing inflammation than in patients who were switched from methotrexate to tocilizumab alone. The study randomized 223 patients, 83% completed 52 weeks. The group treated with tocilizumab in addition to methotrexate had a lower rate of clinically significant radiographic progression, indicating more effective prevention of joint deterioration than the group switched to tocilizumab alone.	18

Note: RA, rheumatoid arthritis.

Overview of IL-6 and Its Role in the Immune Response

IL-6 is a central cytokine in the immune system that plays a multifaceted role in the regulation of immune reactions. It can stimulate immune activity during infection or injury but also acts to regulate this response to prevent excessive inflammation. This dual role makes IL-6 an important factor in balancing the body's defense mechanisms. It is synthesized by several cell types including macrophages, T cells, B cells, and fibroblasts, and has a variety of functions in the immune system. IL-6 controls the immediate response phase and influences the production of immediate response proteins, such as C-reactive protein (CRP), in the liver. These proteins are involved in the early phases of the immune response. Furthermore, this cytokine plays a crucial role in hematopoiesis. Recognized as a proinflammatory cytokine, IL-6 is critical for mobilizing and activating immune cells in response to infection or tissue damage. The extensive effects of this extend to multiple immune system cells. IL-6 is vital in the adaptive immune response, as it enhances antibody production and the growth of effector T cells, growth of effector T cells.²¹ The receptor system for IL-6 consists of two key elements: the IL-6R, which binds to the ligand, and the gp130 component, which is required for signal transduction. This dual-component structure is crucial for the initiation of the cell response to IL-6. After binding to its receptor, IL-6 triggers various intracellular signaling pathways, with the JAK/STAT system playing a particularly important role. This activation leads to the triggering of various transcription factors that control gene expression related to inflammation, immune activation, and tissue repair, as discussed by Uciechowski and Dempke.²²

IL-6 has a function in stimulating the proliferation and development of B cells, as well as facilitating the production of antibodies, as described by Maeda et al.²³ Furthermore, IL-6 plays a role in regulating T cell functions and facilitates the transformation of immature CD4⁺ T cells into Th₁₇ cells, which are recognized for their ability to generate IL-17, a crucial component in protecting against extracellular pathogens. IL-6 can also prevent the growth of regulatory T cells (Tregs), which maintain the tolerance level of the immune system and prevent overwhelming immune responses, as mentioned by Li et al.²⁴ and Tanaka et al.¹ Beyond its typical functions, IL-6 has links to several pathological conditions. Rheumatoid arthritis, systemic lupus erythematosus and chronic inflammation are autoimmune diseases associated with excessive or unbalanced production of IL-6. It also supports tumor cell survival, proliferation, and angiogenesis.²⁵ Targeting IL-6 has become a treatment approach for various disorders due to its varied functions. IL-6 inhibitors work by blocking the IL-6R, thereby interrupting the JAK/STAT signaling pathway. This interruption reduces the production of proinflammatory cytokines, which play a central role in inflammatory and autoimmune processes. By suppressing the production of cytokines

and the recruitment of immune cells, these inhibitors help to regulate the excessive immune response that occurs in diseases such as rheumatoid arthritis, cytokine release syndrome, and other inflammatory diseases. This targeted mechanism not only relieves inflammation but also protects tissue from damage caused by excessive immune activation. Monoclonal antibodies specifically targeting IL-6 or its receptor have been developed and approved for the treatment of diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, and cytokine release syndrome associated with certain cancer immunotherapies. By influencing inflammation, activating immune cells, and supporting tissue repair, IL-6 plays a central role in the immune response. Dysregulation of IL-6 molecule can result in numerous health challenges, underscoring its significance in both research and therapeutic avenues.

IL-6 and Antigen-presenting Cells (APCs): A Classical Network of Immune Response

An essential element of the immune system that plays a role in both initiating and controlling immune responses is the APCs. They consist of B cells, macrophages, and dendritic cells (DCs). To trigger an immune response, APCs collect antigens, refine them, and pass them on to T cells and other immune cells.^{26,27}

Macrophages

Macrophages are crucial components in the human immune system, fulfilling multiple roles, such as ingesting and breaking down microorganisms, removing cellular debris and dead cells, and activating additional cells contributing to immune functions. Table 2 illustrates the specific activities of macrophages during SARS-CoV-2 infections. In response to various triggers like infections, tissue injuries, or the existence of other inflammatory agents, macrophages can generate IL-6. When macrophages release IL-6, it can increase inflammation by attracting and activating various immune cells such as neutrophils and T cells.^{38–40} Macrophages play a key role in regulating both normal and disease-related activities, and they monitor both innate and adaptive immune responses. SARS-CoV-2 manipulates monocytes and macrophages to suppress the host immune response, facilitating the progression of COVID-19. Systemic effects of the virus include acute respiratory distress syndrome (ARDS), widespread intravascular coagulation, edema, and pneumonia.^{41,42}

Macrophages, which serve as the first line of defense in our respiratory system, are equipped with detectors known as pattern recognition receptors (PRRs), including toll-like receptors (TLRs), which identify viral elements. When these macrophages encounter SARS-CoV-2, they can be activated. In severe cases of COVID-19, the immune response can become overly aggressive, leading to a condition known as cytokine release syndrome or cytokine storm, as described by

Table 2. The Effector Functions of Macrophages in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection.

S. No.	Effector Function	Description	References
1.	Phagocytosis	Engulf and internalize SARS-CoV-2 particles, leading to their degradation within the cell. After degradation, the cell can also present fragments of the viral antigens, on its surface.	28
2.	Antigen presentation	This presentation triggers additional immune system elements, including T and B cells. These cells are critical for orchestrating a targeted and specialized immune response against SARS-CoV-2 by activating an adaptive immune response.	29, 30
3.	Cytokine production	Release cytokines (e.g., IL-1, IL-6, TNF-alpha) to regulate inflammation and attract other immune cells to the site.	31
4.	Nitric oxide (NO) production	Generate nitric oxide, which possesses anti-viral properties and aids in controlling viral replication.	32
5.	Reactive oxygen species (ROS) production	Produce reactive oxygen species to eliminate infected cells and combat the virus.	33
6.	Induction of inflammation	Initiate and regulate inflammation to combat the virus and recruit immune cells.	34
7.	Tissue repair and remodeling	Engage in the process of resolving inflammation and promoting tissue healing in order to restore compromised lung tissue.	35
8.	Modulation of immune response	Help balance the immune response to prevent excessive inflammation and immunopathology.	36
9.	Clearance of debris	Remove apoptotic cells and cellular debris to maintain tissue integrity and prevent secondary infections.	37

Note: IL, interleukin; TNF, tumor necrosis factor.

Knoll et al.⁴³ This condition is characterized by a significant increase in proinflammatory cytokines, particularly IL-6. Macrophages and other immune cells can exacerbate this cytokine storm by producing high levels of IL-6. Consequently, IL-6 measurements are an indicator of the severity of COVID-19. As Vainer et al. found, higher levels of IL-6 in the blood correlate with poorer treatment outcomes and higher mortality rates.⁴⁴ Monitoring IL-6 levels is crucial for physicians to make informed treatment decisions, such as administering anti-inflammatory drugs like tocilizumab, which directly targets IL-6 signaling pathways.

Dendritic Cells (DCs)

DCs are characterized as specialized immune cells that are essential for recognizing and fighting external entities such as pathogens. Table 3 details their function in the immune system's response to SARS-CoV-2. As experts in antigen handling, DCs seize and process antigens and introduce them into other components of the immune system to trigger and drive the immune response, as noted by Liu et al. Upon encountering pathogens or when exposed to inflammatory stimuli, DCs can release IL-6, an integral component of immune defense.⁴⁸

IL-6 is crucial for the mobilization and activation of additional immune cells, such as T and B cells, and for directing these cells to the required sites. In this context, as highlighted

by Xu et al., the interaction between DCs and T cells can lead to the release of IL-6.⁵⁴ This cytokine, along with other cytokines, plays an important role in shaping the subsequent immune response and determines the outcome for the activated T cells. In addition, DCs undergo maturation and activation when they encounter antigens or inflammatory stimuli. During this phase, they can secrete IL-6, which acts as an autocrine or paracrine signal, supporting their own maturation process and stimulating nearby immune cells, as described by Jones et al.⁵⁵ DCs also play a role in immune regulation during SARS-CoV-2 infection. They can promote the development of Tregs, which help to suppress excessive immune responses and prevent tissue damage. This regulatory function is important for maintaining immune homeostasis and preventing immunopathology. DCs can secrete various cytokines, including IL-6, in response to SARS-CoV-2 infection.⁵⁶ IL-6, along with other cytokines, helps to orchestrate the immune response by promoting inflammation, activating immune cells, and regulating the balance between proinflammatory and anti-inflammatory processes.

B Cells

B cells are distinct leukocytes that are crucial to the immune response. As constituents of the adaptive immune system, these components possess specialized abilities to identify infections and orchestrate a customized response. Upon

Table 3. Roles of Dendritic Cells in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection Effector Activities.

S. No.	Effector Function	Description	References
1.	Antigen presentation	Dendritic cells are essential to capture viral antigens—fragments of the virus—and present them on their cell surface through molecules of the major histocompatibility complex (MHC). This process enables T cells to recognize these viral components and thus trigger an immune response.	45
2.	Cytokine secretion	Dendritic cells produce various cytokines that includes IL-6, IL-12, IL-23, and interferons (IFN-alpha, IFN-beta), to modulate the immune response. These cytokines can enhance inflammation, activate other immune cells, and regulate the differentiation of T cells.	46
3.	Co-stimulation of T cells	Dendritic cells are equipped with co-stimulatory molecules such as CD80 (B7-1) and CD86 (B7-2), which bind specifically to compatible receptors (CD28) on T cells. The binding of these molecules between dendritic cells and T cells generates an important additional signal. This additional signal is essential for triggering and promoting the growth and activity of T lymphocytes following their exposure to an antigen.	47
4.	T cell priming	Dendritic cells specialize in antigen presentation and are crucial for activating naïve T cells. During a SARS-CoV-2 infection, these cells collect viral antigens from the respiratory system and then move to the adjacent lymph nodes, where they serve to activate and prime T cells.	48, 49
5.	Induction of adaptive immunity	The activation of CD4+ T cells supports the B cells in generating antibodies. CD8+ T cells are stimulated to destroy virus-infected cells. This combined immune response is essential for the effective elimination of viruses.	50, 51
6.	Tolerance induction	Dendritic cells also play a role in promoting immune tolerance. They can induce regulatory T cells (Tregs) that help suppress excessive inflammation and prevent damage to healthy tissues during the immune response of SARS-CoV-2 infection.	52
7.	Memory T cell formation	Dendritic cells play a crucial role in the development of memory T cells, which persist even after the initial infection has subsided. These memory T cells provide sustained immunity and can respond more quickly and effectively when the virus reappears.	53

Note: IFN, interferon; IL, interleukin.

encountering exogenous pathogens such as bacteria or viruses, B cells undergo activation and subsequently generate antibodies. Table 4 depicts the effector functions of B cells in SARS-CoV-2 infection. Antibodies are specialized proteins that bind to specific antigens, the unique molecular recognition features that appear on the surface of invading pathogens. Each B cell carries receptors tailored to recognize a specific antigen. In response to various triggers such as infection, tissue injury, or signals that activate the immune system, B cells can produce IL-6. IL-6 has diverse effects on different immune cells and can influence both innate and adaptive immune responses.⁶⁴

IL-6 can stimulate the growth and differentiation of B cells themselves, promoting their activation and antibody

production. It can also contribute to the activation and differentiation of other immune cells, such as T cells and macrophages. Upon infection with SARS-CoV-2, B cells are activated to produce specific antibodies targeting the virus. These antibodies can bind to the spike protein of the virus, neutralizing it and preventing it from infecting host cells. B cells also contribute to the formation of long-term immune memory against SARS-CoV-2, which is important for protection against future infections.⁶⁵ IL-6 produced by various immune cells, including B cells, is mainly produced in response to SARS-CoV-2 infection. In the context of COVID-19, the disease caused by SARS-CoV-2, IL-6 levels can increase dramatically, leading to an overly aggressive inflammatory response often referred to as a cytokine storm.^{6,20}

Table 4. The Effector Functions of B Cells in Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection.

S. No.	Effector Function	Description	References
1.	Antibody production	B cells, play a crucial role in generating antibodies that specifically target viral antigens, including the spike; and nucleocapsid proteins of the SARS-CoV-2 virus. By neutralizing the virus, these antibodies hinder its ability to infect cells.	57
2.	Memory B cell formation	Exposure to SARS-CoV-2 triggers the differentiation of certain B cells into memory B cells. These memory B cells retain the ability to recognize SARS-CoV-2 and ensure long-term immunity against future infections. Upon reinfection with the virus, these memory B cells rapidly trigger a stronger and more specific antibody response, which forms the basis for the immunity induced by the vaccine.	58
3.	Antibody class switching	B cells have the capability to engage in class switching, altering the kind of antibody they generate. In relation to SARS-CoV-2 infections, this class switching is crucial for the creation of various antibody types, including IgM, IgG, IgA, and so on. IgM is produced earlier in the infection, while IgG and IgA provide longer-lasting protection.	59
4.	Antibody dependent cellular cytotoxicity (ADCC)	Antibodies can also facilitate the phagocytosis (engulfing) of virus particles and infected cells by immune cells, such as macrophages. This process helps to clear the virus from the body.	60, 61
5.	Immune complex formation	B cell-derived antibodies can form immune complexes with viral antigens. These complexes can enhance the immune response by activating complement proteins and promoting the recruitment of immune cells to the site of infection. However, excessive immune complex formation can also contribute to inflammation and tissue damage	62
6.	Regulation of immune response	B cells can modulate the immune response by secreting cytokines and by accommodating with other cells of the immune system. They contribute to establishing the equilibrium between pro-inflammatory and anti-inflammatory activities during a SARS-CoV-2 infection.	63

Note: IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

While B cells contribute to fighting SARS-CoV-2 by producing specific antibodies, IL-6 plays a crucial role in controlling the inflammatory response. Uncontrolled IL-6 production can exacerbate the severity of COVID-19, which is why IL-6 inhibitors are being investigated as potential therapeutic options.

Therapeutic Antibodies in SARS COV-2 Viral Infection

Studies have investigated the use of antibodies specifically targeting IL-6 as a means of controlling severe cases of COVID-19 caused by the SARS-CoV-2 virus. IL-6, a cytokine with proinflammatory properties, plays a role in the

functioning of the immune system and is thought to be associated with the increased inflammation observed in certain cases of COVID-19, as mentioned by Atal and Fatima.⁶⁶ Tocilizumab and sarilumab, originally developed for the treatment of rheumatoid arthritis, were used to treat severe cases of COVID-19 in the early stages of the pandemic. These antibodies work by suppressing the inflammatory response in COVID-19 by inhibiting the IL-6R.

Tocilizumab

Tocilizumab is a monoclonal antibody (mAb) that suppresses the immune system and is used to treat rheumatoid arthritis. According to a new study, tocilizumab effectively reduces the

inflammatory marker cytokine IL-6 and may reduce cytokine storm. The advantages and disadvantages of tocilizumab are represented in Table 5. Tocilizumab works by preventing the protein IL-6 from being activated. Tocilizumab reduces inflammation and symptoms associated with these diseases by reducing the function of IL-6, which promotes inflammation in the body. Tocilizumab has been used to treat certain SARS-CoV-2 patients, particularly those who have acquired severe respiratory problems and show signs of systemic inflammation. Tocilizumab works by inhibiting the function of IL-6, a cytokine that is often elevated in severe cases of COVID-19.^{78–80} Tocilizumab is used to treat COVID-19 assuming to lower IL-6 levels and modulate the immune response may help mitigate cytokine storm and reduce inflammation in the airways.

Sarilumab

Sarilumab is a mAb used to treat certain inflammatory diseases by blocking the IL-6R. Sarilumab binds to the IL-6R, effectively interrupting the IL-6 signaling cascade, a cytokine known for its proinflammatory role and involvement in immune activities and helps to alleviate inflammation.⁸¹ Sarilumab was originally developed for patients with

moderate-to-severe rheumatoid arthritis (RA) who did not respond well to other options, such as disease-modifying anti-rheumatic drugs (DMARDs) or tumor necrosis factor (TNF) inhibitors.⁸² Sarilumab has attracted considerable attention because of its prospective usefulness in treating the hyperinflammatory episodes commonly seen in patients with moderate-to-severe COVID-19 pneumonia. As a high-affinity antibody targeting the IL-6R, sarilumab is emerging as a potentially effective therapeutic strategy for these critical health scenarios. It is very important to note that; the IL-6 inhibitors target the IL-6 cytokine, which plays a role in the inflammatory response. Mutated lineages of the SARS-CoV-2 virus, such as the variants of concern, may exhibit different characteristics in terms of transmissibility, and severity of illness. The impact of IL-6 inhibitors on these mutated lineages would depend on various factors, including the specific variant's interaction with the immune system, and the overall immune response of an individual. While IL-6 inhibitors may still be effective against these mutated lineages, their efficacy may be influenced by the specific mutations present in the variant. Ongoing research on clinical studies is being conducted to assess the effectiveness of IL-6 inhibitors against different variants of SARS-CoV-2. Regarding the mutated lineages of SARS-CoV-2, IL-6 inhibitor antibodies have

Table 5. Advantages and Disadvantages of Tocilizumab.

IL-6 Inhibitor	Advantages	References	Disadvantages	References
Tocilizumab	1. Tocilizumab particularly targets the IL-6, which is a crucial factor in generating inflammation.	[67]	1. An immunosuppressive drug that can weaken the immune system. This increases the risk of serious and potentially life-threatening infections such as bacterial, viral, and fungal infections.	[73]
	2. Effective against autoimmune and inflammatory conditions, including rheumatoid arthritis, juvenile idiopathic arthritis, cytokine release syndrome (CRS) associated with CAR-T cell therapy.	[68]	2. Treatment may experience infusion-related reactions during or shortly after treatment with tocilizumab. These reactions may include fever, chills, headache, dizziness, and skin rash.	[74]
	3. Promising in treating severe COVID-19 cases by modulating the excessive inflammatory response known as cytokine storm. It is also used to reduce the risk of mechanical ventilation and improve outcomes in critically ill COVID-19 patients.	[69]	3. It may cause a transient elevation of liver enzymes, which may indicate liver inflammation.	[75]
	4. Intravenous (IV) and subcutaneous (SC) formulations are available for patients and healthcare providers options for administration.	[70,71]	4. It can cause changes in blood cell counts, including a decrease in neutrophils, platelets, and red blood cells.	[76]
	5. Tocilizumab has a relatively quick onset of action.	[72]	5. Occasionally, associated with an increased risk of gastrointestinal perforation.	[77]

Note: CAR-T, chimeric antigen receptor T-cell; IL-6, interleukin-6.

primarily been used to treat severe cases of COVID-19 regardless of the specific lineage. However, it is important to note that the effectiveness of IL-6 inhibitors may vary depending on the specific mutation or variant of the virus. Certain variants of concern, such as the B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma), and B.1.617.2 (delta) variants, have been associated with increased transmissibility and, in some cases, increased disease severity. These variants have acquired multiple mutations, including those in the spike protein of the virus, which is the primary target of neutralizing antibodies like IL-6 inhibitors.⁸³

It is very important to know that IL-6 inhibitors target the release of IL-6, which plays a role in the inflammatory response. Mutant lineages of the SARS-CoV-2 virus, such as the variants of concern, may have different characteristics in terms of transmissibility and severity of disease. The effect of IL-6 inhibitors on these mutant lineages would depend on several factors, including the interaction of the specific variant with the immune system and the overall immune response of an individual.⁸⁴ While IL-6 inhibitors may also be effective against these mutant lines, their efficacy may be influenced by the specific mutations in the variant. Ongoing research and clinical investigations are being conducted to assess the effectiveness of IL-6 inhibitors in combating different forms of SARS-CoV-2. IL-6 inhibitor antibodies have predominantly been employed for the treatment of severe instances of COVID-19; however, their application is not restricted to a specific viral lineage. Nevertheless, it is crucial to underscore that the effectiveness of these inhibitors can fluctuate depending on the specific mutation or variation. The emergence of variants, namely, B.1.1.7 (alpha); B.1.351 (beta); P.1 (gamma); and B.1.617.2 (delta), has raised significant concerns due to their heightened transmissibility and potential to cause more severe illness under specific circumstances.⁸⁵ The observed variants have experienced numerous changes, including modifications in the spike protein, which serves as the primary target for neutralizing antibodies like IL-6 inhibitors.

Perspectives and Challenges on IL-6 Inhibitor Antibodies

IL-6 is a critical factor in the pathogenesis of various diseases, such as rheumatoid arthritis, systemic juvenile idiopathic arthritis, Castleman disease, and cytokine release syndrome (CRS).^{86,87} Therapeutic antibodies, such as monoclonal antibodies and IL-6 inhibitor antibodies, are used to treat a variety of diseases, with a focus on autoimmune and inflammatory diseases. Pharmaceutical treatments capable of suppressing the action of IL-6 have been developed with the intention of mitigating inflammatory responses and regulating the activity of IL-6 in relation to these pathological situations. Although IL-6 inhibitors show promise in the therapeutic context, there are several obstacles and limitations to their use.

Management of Cytokine Release Syndrome (CRS)

Immunotherapies, such as chimeric antigen receptor T-cell (CAR-T) therapy, can induce CRS, a potentially fatal complication. IL-6 inhibitors have been used effectively to treat CRS by reducing the excessive immune response induced by CAR-T cells.^{88,89}

Potential in COVID-19 Treatment

The potential therapeutic application of IL-6 inhibitors in the treatment of severe instances of COVID-19 has been investigated in scientific research. The use of these inhibitors has the potential to impede the progression of respiratory problems and multiorgan failure by reducing the profound systemic inflammation usually known as a cytokine storm. However, clinical evidence for their efficacy against COVID-19 is still emerging.⁹⁰

Challenges and Future Directions

IL-6 inhibitors, like any immunomodulatory therapy, may have potential side effects and safety concerns. These may include an increased risk of infections, such as respiratory tract infections or opportunistic infections. Close monitoring of patients receiving IL-6 inhibitors is necessary to minimize adverse events. Response to IL-6 inhibitors may vary from patient to patient. Some patients may improve significantly, while others may not respond as well. Factors influencing differential response include disease heterogeneity, genetic variations, and other underlying comorbidities. Optimizing combination therapies, managing drug–drug interactions, and understanding the long-term effects of such combinations are the subject of ongoing research.

Combination therapies with IL-6 inhibitor antibodies are often used to improve the efficacy of treatment for various diseases. These inhibitors are often combined with other disease-modifying drugs or biologics to target multiple signaling pathways involved in the inflammatory process. For example, the combination of IL-6 inhibitors with corticosteroids has shown a synergistic effect in reducing mortality and shortening ICU stay in severe COVID-19 cases. However, this approach is associated with challenges, such as managing potential drug–drug interactions, tailoring treatments to the individual patient profile, and closely monitoring for overlapping side effects, including immunosuppression and an increased risk of opportunistic infections.

The immune response to SARS-CoV-2 is complex, with cytokine storms, which have a hyperinflammatory state, being a critical factor in severe cases. IL-6 inhibitors have been shown to be a targeted therapy to treat this immune dysregulation, particularly in patients with elevated IL-6 levels and signs of hyperinflammation. Early administration can

prevent severe disease progression; however, not all patients benefit equally. Identifying the right candidates for this treatment remains a challenge as immune responses and disease progression vary between individuals. Accurate stratification of patients based on biomarkers is essential to ensure the effective and timely use of IL-6 inhibitors. Despite their potential, IL-6 inhibitors raise concerns about their long-term safety and efficacy. While they promise to reduce inflammation during acute disease, prolonged use could lead to adverse effects such as secondary infections or impaired tissue repair. In addition, new SARS-CoV-2 variants could compromise their efficacy, requiring constant evaluation and adaptation of these therapies. Research is increasingly focused on overcoming these challenges by exploring combination therapies, optimizing dosing regimens, and tailoring treatments to individual patient profiles through advances in personalized medicine. Innovative approaches to modulate IL-6 are also gaining attention, including small molecule inhibitors, nanomedicine delivery systems, ribonucleic acid (RNA)-based therapeutics, and gene editing technologies. These strategies aim to refine IL-6 targeting, improve the precision of drug delivery, and minimize side effects. In addition, biomarker research and genetic profiling pave the way for more personalized and effective treatments. By expanding our understanding of the role of IL-6 in inflammation and disease, these advances promise to improve COVID-19 outcomes and extend to other diseases where cytokine-driven immune responses occur.

Conclusion

The reported findings on IL-6 inhibitor antibodies in SARS-CoV-2 infections and their mutant lineages allow for important insights into the challenges, opportunities, and future prospects of using IL-6 inhibitors in treating COVID-19. IL-6 is a proinflammatory cytokine that is critical to the immune response. In severe cases of COVID-19, there is often an excessive release of IL-6, resulting in a hyperinflammatory state known as a cytokine storm. Targeting IL-6 with inhibitors has been explored as a potential therapeutic strategy. Clinical studies and practical applications reveal that IL-6 inhibitors, including tocilizumab and sarilumab, effectively reduce the severity and mortality rate of COVID-19 in certain patient groups, especially in patients with severe disease and high IL-6 levels. Although IL-6 inhibitor antibodies show promise in treating severe COVID-19 disease, particularly in patients with a hyperinflammatory response, several challenges and limitations remain to be overcome, and the impact of mutant lineages and variants on the efficacy of IL-6 inhibitors needs further investigation. Further studies and clinical trials are needed to fully assess the role of IL-6 inhibitors in treating COVID-19. This will ensure that they are used as effectively as possible in the future.

Abbreviations

ARDS: Acute respiratory distress syndrome; **B.1.1.7:** Alpha variant; **B.1.351:** Beta variant; **B.1.617.2:** Delta variant; **COVID-19:** Coronavirus disease 2019; **DNA:** Deoxyribonucleic acid; **HRC:** Health Research Center; **IgA:** Immunoglobulin A; **IgG:** Immunoglobulin G; **IgM:** Immunoglobulin M; **IL-6:** Interleukin-6; **P.1:** Gamma variant; **PRRs:** Pattern recognition receptors; **RNA:** Ribonucleic acid; **SARS-CoV-2:** Severe acute respiratory syndrome coronavirus 2; **TLRs:** Toll-like receptors; **TNF:** Tumor necrosis factor.

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MAB, GG, FYS, and AYS: Conceptualization and resources; SMS: Conceptualization, investigation, validation, and drafting of the article.

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