# Immunomodulators; used in the treatment of covid-19

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***Abstract*-The novel coronavirus pandemic has emerged as one of the significant medical-health challenges of the current century. The World Health Organization has named this new virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Immumomodulators may effectively treat patients and reduce mortality rates. Various therapeutic compounds have been investigated and applied to mitigate the symptoms in COVID-19 patients and cure the disease. These drugs consist of IL-1, IL-6, and immunosuppressive. There is emerging data that immunomodulatory drugs could be protective at reducing certain features of SARS-CoV-2 and improving recovery. In this article we will discuss potential treatment options for SARS-CoV-2 using immunomodulatory drugs and at what stage of the condition they may be beneficial.**

***Keywords:*** **SARS-CoV-2, ILS, CRS, TNF**

## INTRODUCTION

The new member of the coronavirus family, named SARSCoV-2 or previously 2019 novel coronavirus (2019-nCoV)—a beta-coronavirus from RNA viruses—is a causative agent of a crucial respiratory infection known as COVID-19 in patients [1]. The genetic material of SARS-CoV-2, which is attach to the virus's Nucleocapsid protein, consists of 26 to 32 Kbps [1, 2]. This virus was firstly identified in December 2019 in Wuhan, Hubei Province, Mainland China [3]. In March 2020, SARS-CoV-2 spread to more than 114 countries, prompting the World Health Organization to announce a pandemic for SARS-CoV-2 [4]. The virus is hypothesized to have been originally a zoonotic virus transmitted from animals to humans, although human-to-human transmission of the 2019-nCoV has led to its spread [5]. More than 3·2 million people have been infected and more than 230000 of them have died. To date, no treatments have been definitively shown to be effective.

In this article, we summarised the current knowledge regarding antiviral and immunomodulating agent treatment strategies against COVID-19. Coronavirus are normally classified into following group like alpha, beta, gamma, and delta. SARS-CoV-2, since a beta-coronavirus, has various structural proteins. Spike protein, nucleocapsid protein, and membrane proteins are one of the most crucial structural proteins of SARS-CoV-2 that can stimulate the immune system [6, 7].

COVID-19 is generally considered as a respiratory disease that involves the lungs. It can cause common symptoms such as fever, dry cough, fatigue and headache. [8]. Although in the most patients of SARS-CoV-2 results in mild symptoms, however in some patients, this infection may cause the acute and widespread damages such as septic shock, acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS) [9, 10]. In COVID-19, like infectious diseases, fever occurs due to the release of various cytokines and their effects on the hypothalamus.

All symptoms of SARS-CoV-2(covid-19) infection occur due to the stimulation of the immune system and activation of innate and acquired immunity against corona virus [11]. When SARS-CoV-2 enters into the body, it is firstly detected by innate immunity cells and their receptors (TLR-3)) [12]. Which results in the formation of NLRP3 inflammasome and inflammatory respond [13]. CD4+and CD8+cells have a noticeable role in the synthesis of cytokines and chemokine and acquired immunity activation [16]. CD8+cells clear virus from the body by activating the cytotoxic pathways [14]. CD4+cells are involved in synthesizing and releasing chemokines and cytokines from the immune cells by differentiating into T-helper 1 cell (Th1) [15].

Cytokines and various compounds such as interleukins (ILs)-1 α/β, IL-2, IL- 4, IL-6, IL-10, IL-17 and TNF-α. [16], are produce when cells get infected by SARS-CoV-2, culminating in the migration of lymphocytes and leukocytes to the lesion site [17]. This mechanism can be lead to the overproduction of cytokines (cytokine storm), damage to normal lung cells, destruction of the lung tissue, and even serious condition or death [18, 19]. A detailed account of COVID-19 effect on the immune system as well as its immunopathology ramifications is illustrated. It is hypothesized that the application of immunomodulatory drugs can neutralized these cytokines or prevent critical conditions in patients by inhibiting the function of

harmful molecules [20]; for this reason, these drugs have been considered for the treatment of COVID-19. Still, only one particular antivirus drug called Molnupiravir is suggested for COVID-19 treatment [21].

Although the pathogenesis of COVID-19, the end result of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is still not completely understood, a proposed four-stage classification system of escalating phases represents a useful construct for a structured approach to clinical phenotyping, choice of therapy, and clinical outcome [22, 23]. Stage I (early infection) begins at the time of viral inoculation and establishment of infection. Patients may or may not manifest non-specific symptoms (i.e. malaise, fever, sore throat, dry cough), and treatment is often symptomatic. Stage II is characterized with the aid of using hyper responsiveness of the immune system. Patients developed viral pneumonia and possibly hypoxia, and markers of systemic inflammation are multiplied. The third stage is characterized by a hypercoagulable state. Patients with hypoxia are likely to progress to stage IV, the most severe stage, in which multiorgan failure occurs.

Most sufferers additionally expand lymphopenia and pneumonia with bilateral infiltrations on chest computed tomography (CT) scan [24–25]. Systemic proinflammatory cytokines and biomarkers which includes interleukin (IL)-1, IL-2, IL-6, and IL-7, tumour necrosis factor (TNF)-α, granulocyte–macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein 1-α, C-reactive protein (CRP), ferritin, and D-dimer are significantly high in this stage [26, 27]. The presence of multiple pro inflammatory cytokines in advanced stages of disease was also observed in prior epidemics, such as those caused by SARS-CoV and MERSCoV, suggesting a cytokine release syndrome (CRS) or 'cytokine storm'-mediated immunopathology [28, 29].

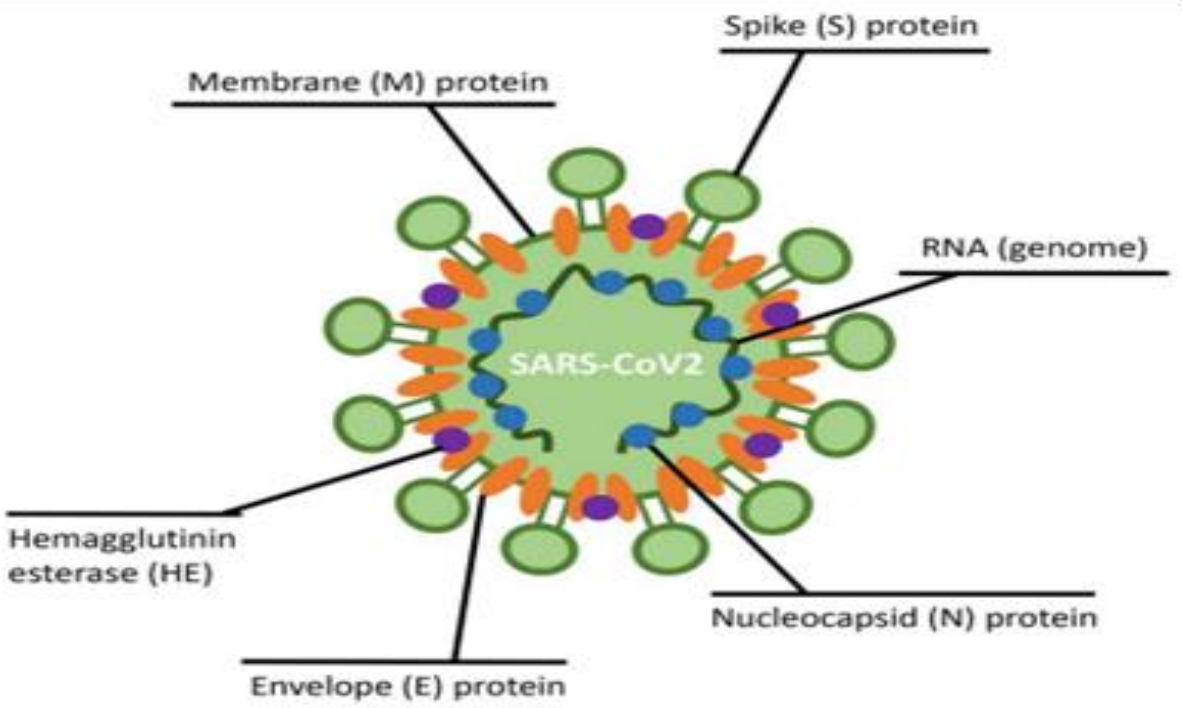


Fig. 1. Structure of SARS-CoV2. The spike protein (S) facilitates binding to the trans-membrane ACE2 host receptor; the envelope (E) protein together with the membrane (M) protein form the viral envelope and determine its shape; the hemagglutinin esterase (HE) protein may resemble another cell entry mechanism of novel CoVs; the nucleocapsid (N) protein in bound to the RNA genome of the virus to form the nucleocapsid.

The cytokine dysregulation and influx of inflammatory myeloid cells can cause to lung infiltration and critical symptoms, including sepsis, shock, respiratory failure, acute respiratory distress syndrome (ARDS), multiorgan system dysfunction, and death [30]. Since lymphopenia is often observed in early and late stages of COVID-19 patients, the CRS can also additionally in all likelihood be mediated by leukocytes other than T cells [31]. The cytokine storm is thought to resemble secondary hemophagocytic lymph histiocytosis (sHLH) [11]. The macrophage activation syndrome (MAS)-like

pulmonary immunopathology characteristic of COVID-19, above and beyond the direct endothelial damage from SARS-CoV-2, may explain the high degree of micro- and macro thrombotic findings in this patient population [32].

Cytokine storm, along with viral evasion of cellular immune responses, may play an important role in disease progression. Thus, tackling the immune response with immunomodulatory agents may be important as addressing viral replication to prevent the progression to multiorgan dysfunction (Fig. 1). Herein, we discussed the role of specific and non-specific immunomodulating agents, including neutralizing monoclonal antibodies, corticosteroids, and different molecules in the management of severe COVID-19, and their impact on survival and clinical symptoms. [33]

Classification of Immune System

The immune system is generally divided into innate and adaptive components. The innate immune system provides non-specific resistance to pathogens, while adaptive immunity is characterized through antigen specificity and immunologic memory.

Immunomodulators are drugs that stimulate or suppress the immune system. Mainly two immune systems, (along with immunomodulators), work together to prevent and control infection. CP (convalescent plasma), IL interleukin, GM-CSF granulocyte–macrophage colony-stimulating factor, IVIG intravenous immunoglobulin, JAK Janus kinase, NK natural killer, RAASi renin–angiotensin–aldosterone system inhibitors, rhuGM-CSF recombinant human granulocyte–macrophage colony stimulating factor, TNF tumor necrosis factor.

A substance that stimulates or either suppresses the immune system and help the body fight with cancer, infection, or other diseases. Specific immunomodulating agents, such as that monoclonal antibodies, cytokines, and vaccines, affect specific parts of the immune system. Nonspecific immunomodulating agents, such as BCG and levamisole, affect the immune system in a general way. Also called as immune system modulator. Immune-modulating agents are a type of immunotherapy that enhance the body's immune response against cancer.[41]

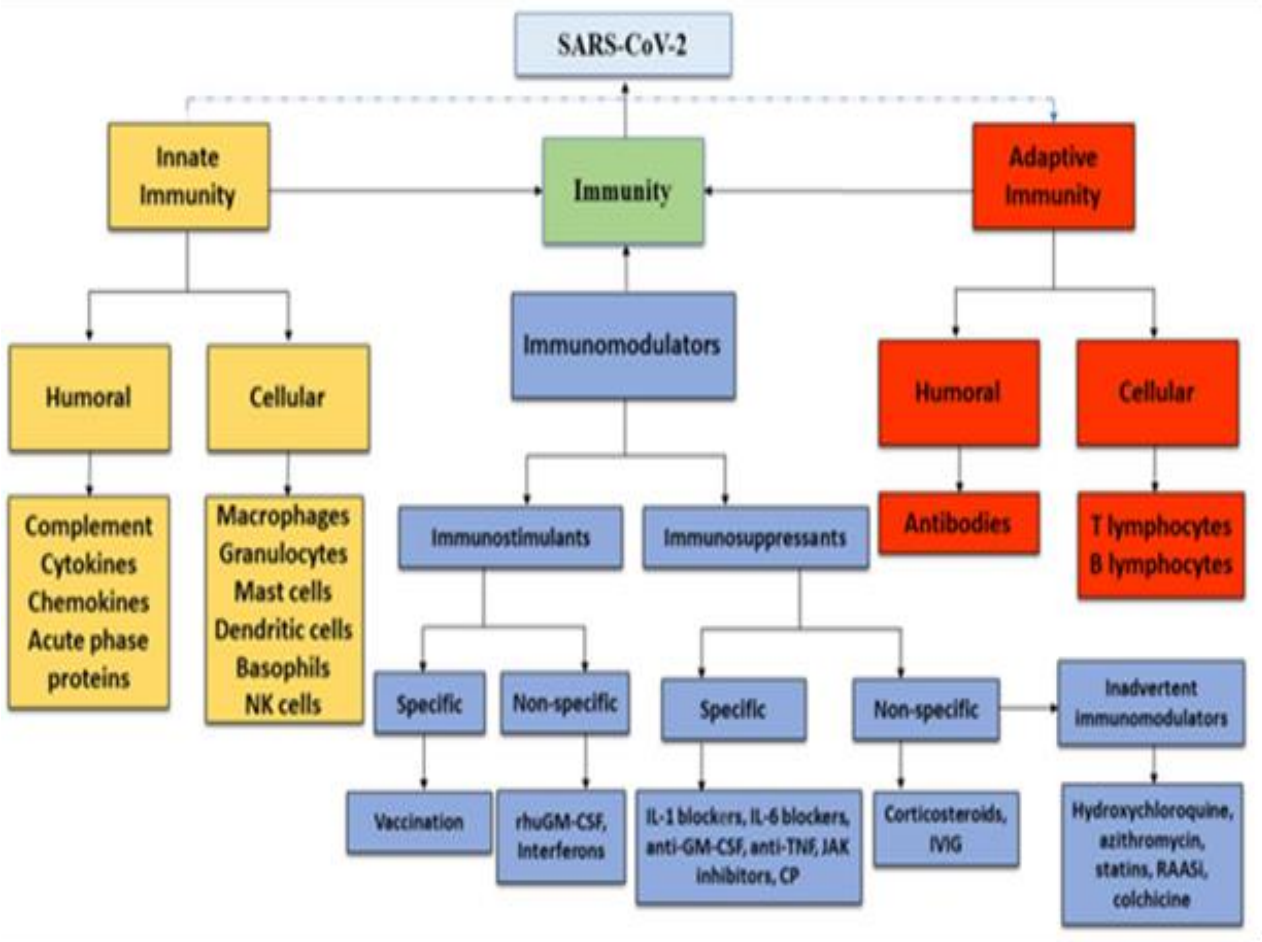

Fig. 2 The immune system is classically divided into innate and adaptive components. The innate immune system provides nonspecific resistance to pathogens, whereas adaptive immunity is characterized by antigen specificity and immunologic memory. Immunomodulators are drugs that either stimulate or suppress the immune system. The two immune systems, along with immunomodulators, work together to prevent and control infection. CP convalescent plasma, IL interleukin, GM-CSF granulocyte–macrophage colony-stimulating factor, IVIG intravenous immunoglobulin, JAK Janus kinase, NK natural killer, RAASi renin–angiotensin–aldosterone system inhibitors, rhuGM-CSF recombinant human granulocyte–macrophage colony stimulating factor, TNF tumor necrosis factor

Immunomodulatory Agents

Immune system plays important role in the etiology and pathophysiological mechanisms underlying many diseases. Immunomodulators are the chemical representatives that modify the immune response or the functioning of the immune system by altering, restraining and initiating mechanistic concept of adaptive immunity. [34]

Immunomodulating agent are biological or synthetic substances that can stimulate, suppress or modulate any aspect of the immune system in clouding both adaptive and innate arms of the immune system.

Immunomodulators are drugs that can be support the immune function by modify, in a beneficial way. They are used to treat conditions such as multiple sclerosis, rheumatoid arthritis, multi myeloma, cancer, Kidney transplant rejection, and covid-19. [35]

Once a pathogen enters the body, it is addressed by two lines of defense: innate immunity and adaptive immunity (Fig.2) [36]. Innate immunity encompasses is a number of soluble and cell-based antimicrobial factors and is triggered very early after infection. Adaptive immunity, which consists of pathogen-specific antibody and T cells, develops later and contributes to both clearing of infection and immunity against subsequent infection. Innate and adaptive immunity worked together to detect and eliminate pathogens. Immunomodulatory drugs can be stimulated (immunostimulants), suppress (immunosuppressants) or modulate various aspects of the immune system, including both adaptive and innate immune systems [37]. Immuno-stimulators are often prescribed to enhance the immune response against infectious diseases, however, morbidity and mortality in severe COVID-19 is associated with hyper-inflammation [38] and interfering with cytokine signaling using immunomodulatory strategies may significantly reduce hyper-inflammation in these patients. The action of the immunomodulators can be specific or non-specific [39, 40].

Interleukin (IL) -1 Receptor Antagonists

Anakinra is a recombinant human IL-1 receptor antagonist indicated for rheumatoid arthritis (RA) and cryopyrin associated periodic syndromes [42]. It works to inhibiting the proinflammatory cytokines IL-1α and IL-1β [43]. In before studies, anakinra was shown to be effective in treating MAS, which presents as a fulminant cytokine storm [44]. This may suggest a role for anakinra in combating CRS symptoms in COVID-19 patients. Re-analysis of data from a phase III randomized control trial revealed that IL-1 receptor blockade with anakinra was associated with significant improvement in the survival of patients with sepsis [45]. There are currently no published control clinical trials supporting the efficacy or safety of anakinra in treating COVID-19. In a small case-series of nine patients with moderate to severe COVID-19 pneumonia, the use of anakinra was well-tolerated and effective in improving clinical and biological markers [46].

IL-6 Receptor Antagonists

Abnormally high levels of IL-6 are an indicator of poor result in COVID-19 patients with pneumonia and ARDS [47]. Tocilizumab is a recombinant humanized anti-human IL-6 receptor monoclonal antibody that can specifically bind the membrane-bound IL-6 receptor (mIL6R) and soluble IL-6 receptor (sIL6R), thereby inhibiting signal transduction [48]. Tocilizumab is currently FDA-approved for the management of RA, giant cell arthritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis [49]. It is also approved for the management of chimeric antigen receptor (CAR) T-cell-induced CRS [50], making it a possible therapeutic option for CRS of severely ill COVID-19 patients who have extensive lung lesions and high IL-6 levels [51].

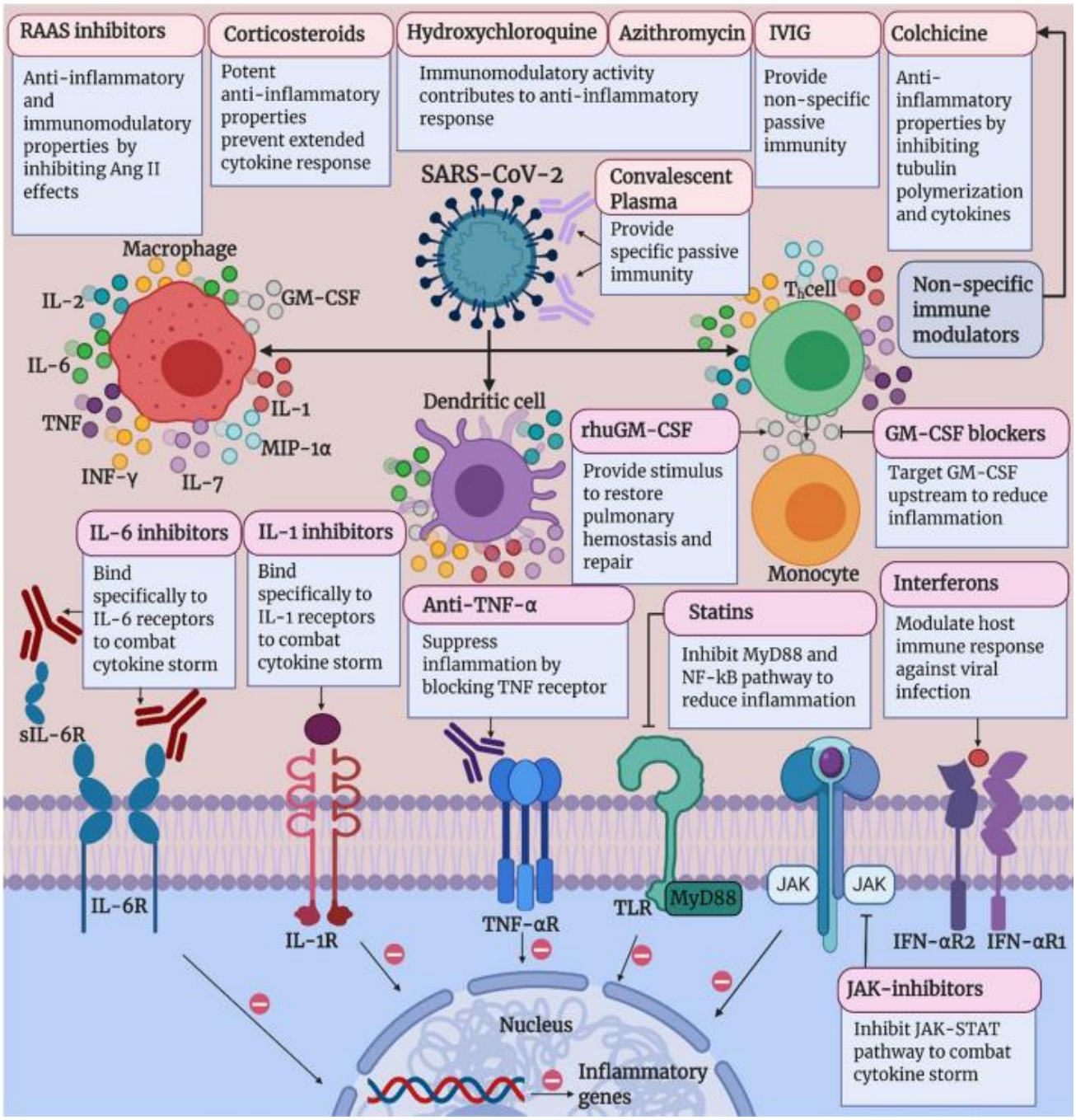


Fig. 3 Schematic representation of the immunomodulators' site of action. Hydroxychloroquine, azithromycin, statins, RAASi and their combinations have not been reliably shown to be of benefit in hospitalized patients with COVID-19, and therefore are represented here to define a potential pathophysiological target for therapy. This should not be seen as endorsement for use of such agents. The use of hydroxychloroquine and azithromycin in COVID-19 patients may be associated with harm. Whether such agents are beneficial in other stages of infection remains a matter of study. Created with biorender.com. Ang II angiotensin II, GM-CSF granulocyte–macrophage colon stimulating factor, IFN interferon, IL interleukin, IL-6R interleukin-6 receptor, IVIG intravenous immunoglobulin, JAK Janus kinase, JAKSTAT Janus kinase-signal transducer and activator of transcription, MIP-1α macrophage inflammatory protein 1-α, MyD88 myeloid differentiation primary response 88, NF-κB nuclear factor-κB, RAAS renin–angiotensin–aldosterone system, rhuGM-CSF recombinant human granulocyte–macrophage colony-stimulating factor, sIL-6R soluble IL-6 receptor, TLR toll-like receptor, TNF tumor necrosis factor reserve

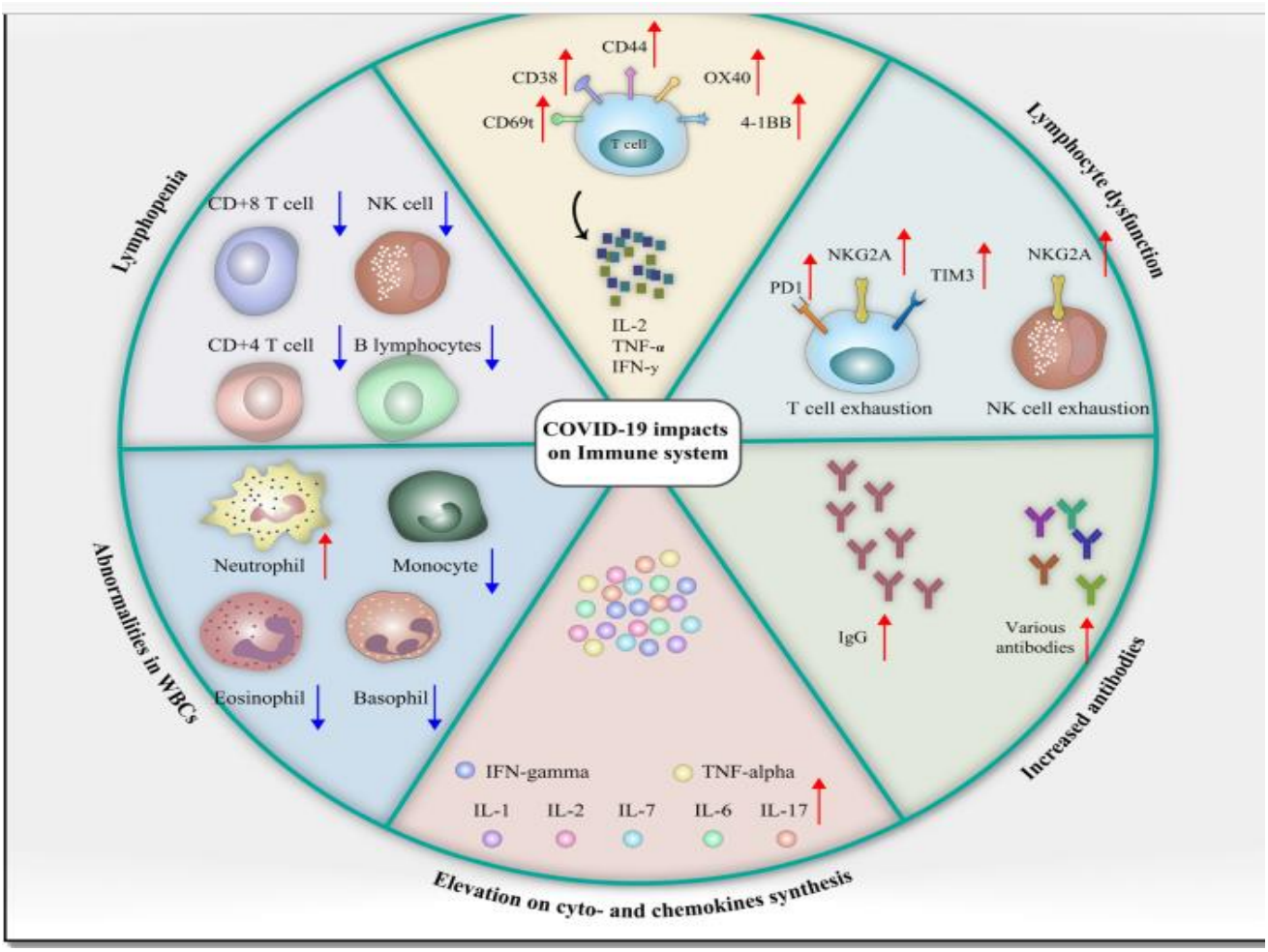


Fig.4 The investigation of COVID-19 immunopathology indicated that the infected individuals' immune patterns include increased activation of T cells, which is accomplished by the higher expression of some receptors in the T cell membrane. Lymphopenia is a critical immune pattern in COVID-19 patients. Over product cytokines and chemokines caused by SARS-CoV-2 infection may result in cytokine storm and even ARDS. Lymphocytes dysfunction, abnormalities in WBCs, and increased antibodies are also other important immunopathological patterns in COVID-19 that can be observed in detail.

Tocilizumab

Tocilizumab, another of the biologic agents more recently used to treat uveitis, is an IL-6 receptor antagonist. In previous years, it was approved for the treatment of RA and JIA. There are reports that it is successful in the treatment of uveitis. In a randomized, controlled, multicenter study, 37 patients with non-infectious intermediate uveitis, posterior uveitis, and pan-uveitis received tocilizumab infusion at one of two different doses. [52] At both doses, tocilizumab increased visual acuity and decreased vitreous haze and central macular thickness. The efficacy and safety of tocilizumab and methotrexate were evaluated in patients with RA. [53] During the 24-week follow-up period, serious infectious complications occurred in 1.4%of patients receiving tocilizumab, similar to methotrexate severe infections requiring hospitalization occurred in 24% of patients using tocilizumab. However, 52% of all patients were also receiving corticosteroid therapy, suggesting that the high incidence of infection was not due to tocilizumab alone. [54] In a study of 141,869 patients comparing tocilizumab with anti-TNF-α agents in terms of risk of serious infection, both groups had similar rates of infectious complications. [55] It was observed that 4.68% of patients treated with tocilizumab developed serious infections per year. There is currently no known relationship between tocilizumab use and the development of COVID-19 infection. There are publications reporting that for patients who require systemic immunosuppressive therapy and contract COVID-19, tocilizumab may be beneficial for both the comorbid condition and COVID-19. [61] Luo et al.4 used tocilizumab to suppress severe systemic immune

response in 15 patients with COVID-19. They stated that 11 of the patients responded well to treatment and that tocilizumab may be beneficial for severe patients at risk of cytokine storm. [56]

Secukinumab: Secukinumab, another agent shown to be effective in autoinflammatory diseases, is an IL-17A antagonist. The results of three randomized controlled clinical trials to evaluate the efficacy of subcutaneous secukinumab in the treatment of non-infectious uveitis were analyzed and there was no significant difference in uveitis recurrence between the secukinumab and placebo groups.[57] In a study of patients with psoriatic arthritis, a dose-dependent increase in the risk of serious infection was observed, with 2.1 of 100 patients in the group receiving the highest dose of secukinumab developing a serious infection within 1 year.[58] Carugno et al.[59] described a case of COVID-19 in a patient who had been using secukinumab for 2 years due to psoriatic arthritis. They reported that the patient had a mild clinical course and that IL-17 inhibitors may even have a role in the treatment of COVID-19. In another publication, it was reported that IL-17A has a role in lung and heart damage in various diseases and that IL-17A inhibitors may be a potential treatment to prevent damage. [60] In contrast, Sharmeen et al.[61] reported that secukinumab use was associated with severe COVID-19 course. In another study, analysis of clinical course in 41 COVID-19 patients receiving IMT (including secukinumab) due to rheumatologic diseases revealed no difference from the normal population. [62]

Alemtuzumab: Alemtuzumab is a monoclonal antibody that reduces T and B lymphocyte counts by binding to CD52 on the cell surface of lymphocytes. The 12-year long-term outcomes of alemtuzumab use in multiple sclerosis patients were recently published. [63] Its efficacy has been demonstrated both clinically and on magnetic resonance imaging. There are case reports related to its use in the treatment of uveitis. In one report, alemtuzumab induced remission in a case of refractory panuveitis.88 it was also shown to induce remission in another patient with refractory intermediate uveitis and macular edema associated with multiple sclerosis. The highest risk of serious infectious complications with alemtuzumab use in patients with multiple sclerosis was reported to be the first year of treatment (3.3%/year).[64]in the same study, it was observed that the incidence of serious infections decreased in the long term (0.8%/year) in patients with 12-year follow-up. An analysis of 399 patients receiving different treatments for multiple sclerosis (including alemtuzumab) indicated that COVID-19 incidence and disease course were similar to those in the normal population. [65]

Canakinumab: This is another biologic agent that acts as an IL-1 beta inhibitor. It can be used in the treatment of psoriasis, chronic obstructive pulmonary disease, gout, and BD. Anakinra is another biologic agent that exhibits similar activity by binding to the IL-1 beta receptor. In BD patients with ocular involvement, canakinumab and anakinra have been shown to control ocular inflammation.[66] In a retrospective chart review of 475 patients receiving canakinumab and anakinra for various autoimmune and autoinflammatory diseases, it was reported that 3 patients developed severe bacterial infections, resulting in death for 2 of those patients. It has been reported that anakinra yields positive results in controlling the cytokine storm in patients with secondary hemophagocytic syndrome and has the potential to be used in severe COVID-19 cases. The results of a preliminary study indicated that canakinumab and anakinra are safe during the COVID-19 pandemic and beneficial in COVID-19 patients with cytokine storm. [67]

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## CONCLUSION

COVID-19 is increasingly being recognized as a syndrome of viral replication and host inflammatory response. Effective pharmaco-immunomodulating strategies may help alleviate syndrome progression, especially in the more advanced stages of COVID-19. Although vaccines can be successful in immunizing individuals against COVID-19, they seem to be not suitable for hospitalized patients with severe and critical conditions. Immune dysfunction and especially over activation of the immune system and lymphopenia are two significant problems in COVID-19 patients. In this regard, the application of immunomodulatory drugs has been considered to reduce the mortality rate in COVID-19 patients. In the present review article, mechanism of action for several pivotal immunomodulatory and immunosuppressant agents pertaining to different drug groups was examined and discussed. More studies and extensive trials are warranted to ensure the extent of effectiveness or ineffectiveness of these medications. We reviewed the roles of immunomodulation as potential COVID-19 pharmacological modalities based on the existing data and proposed several new immunologic targets to be tested in the foreseeable future. The outcomes of this study, however, can assist physicians and scientists in designing future studies and having better treatment guidelines. At present, several new pharmacological targets are being investigated and in the near future, they are expected to contribute to the COVID-19 management.

Disclosure

The authors report no conflicts of interest in this work.

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