# Immune targeted therapies for COVID-19 Infection: A Promising Outlook

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December 29, 2020

**Abstract**

In December 2019, the coronavirus disease-19 (COVID-19) outbreak emerged in Wuhan, China. On March 11, 2020, the WHO (World Health Organization) officially declared it a pandemic. Reports indicated that the associated mortality of the infection is quite higher in the elderly, patients with specific comorbidities (like diabetes mellitus), and generally the ones with a compromised immune system. A cohort study of 452 patients with laboratory-confirmed COVID-19 in Wuhan, China, reported a dysregulated immune response in these patients. As a result of this suppressed immune response, the increase of neutrophil to lymphocyte ratio (NLR), T lymphopenia, and decrease of CD4+ T cells was considered as common laboratory findings, especially in severe cases. On the other hand, there is also clear evidence of T cell exhaustion in severely ill patients. So, the immune system seems to play an important role in disease prognosis and pathogenesis. This study aims to review the evidence on the immune response dysregulation in COVID-19 infection and the potential role of immunoregulatory treatments such as immune checkpoint inhibitors, interferons, and CD200 inhibitors in altering disease prognosis, especially in critically ill patients.

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**Keywords:** Immune targeted therapy, COVID-19, Immune Checkpoint Inhibitors, T cell Exhaustion

**How did you gather the information you considered in your review?**

Relevant databases such as Scopus, Medline, Embase, ISI Web of Knowledge, Cochrane central register of controlled trials, Cochrane database systematic reviews, and Google Scholar were searched.

**What is the 'take-home' message for the clinician?**

Immune targeted therapies can be a promising outlook for the treatment of COVID-19 infection, as there are strong evidence of dysregulated immune responses during this infection.

**Introduction:**

In December 2019, the coronavirus disease-19 (COVID-19) outbreak emerged in Wuhan, China(1). On March 11, 2020, the WHO (World Health Organization) officially declared it a pandemic. Up to October 30, 2020, WHO has reported 44.8M cases of infection and 1.1M deaths globally, and the virus is yet rapidly spreading(2). The disease presented as moderate to severe pneumonia with clinical symptoms such as cough, dyspnea, fever, and bilateral lung infiltrates on imaging. Laboratory exams also present moderate to severe lymphopenia (especially T cells), suggesting for dysregulated immune response in these patients(3).

Reports indicated that the associated mortality of the infection is quite higher in the elderly, patients with specific comorbidities (like diabetes mellitus), and generally the ones with a compromised immune system. These patients have a poorer outcome typically and require intensive care unit admission and ventilation support more often(4). Among the high-risk individuals, cancer patients account for a large percent of this group due to cancer and chemotherapy-induced immune suppression. Moreover, these patients have a higher risk of experiencing severe events. Some experts suggest postponing any surgery and adjuvant chemotherapy for stable patients to prevent subsequent immune suppression in this situation(5).

Current studies also claim that the prevalence of COVID-19 infection is higher among cancer patients undergoing conventional chemotherapy than those receiving immunotherapy, such as checkpoint inhibitors. This result might be due to the small sample size, and further studies with a larger sample size report an insignificant difference in the prevalence of this viral infection between patients receiving chemotherapy and immunotherapy(6). However, another hypothesis is that this lower prevalence of the COVID-19 spread among patients receiving checkpoint inhibitors could be due to the augmentation of immune system activity by these drugs (7). Among various anti-cancer protocols, immune checkpoint inhibitors (ICIs) are one of the treatment options for specific cancers such as melanoma, lung, renal, and other chemo-resistant tumors. Unlike chemotherapy, this class's members are not associated with immune suppression due to their immune regulatory effects. The antibodies against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) such as ipilimumab and tremelimumab were the first class of immune checkpoint inhibitors introduced, but the severe autoimmune reactions limited their use. Currently, antibodies against programmed cell death protein 1 (PD-1) and its ligand PD-L1 are more favorable over CTLA-4 inhibitors due to their milder adverse reactions. The monoclonal antibodies nivolumab, pembrolizumab (anti-PD-1), atezolizumab, durvalumab, and avelumab (anti-PD-L1) are the members of this class(8).

According to this evidence, immunomodulatory pathways seem to play an important role in disease pathogenesis.

Generally, different mechanisms must be designed to defeat the host cell immune response for a successful pathogen invasion. On the other side, excessive host cell immune response might also result in the overproduction of inflammatory and proinflammatory cytokines, leading to uncontrolled cellular and tissue damage. The Immune system interacts with pathogens by expressing special receptors like Toll-like receptors (TLRs) family and nucleotide-binding oligomerization domain-like receptors responsible for producing chemical mediators that induce anti-virulence genes. Immune cells also prevent excessive inflammatory response by expressing inhibitory receptors at the same time (9). Inhibitory receptors superfamily consist of two major subgroups includes the immunoglobulin (Ig) and calcium-dependent carbohydrate-binding (C-type) lectin family(10). CD200 receptor1 (CD200-R1) is a transmembrane glycoprotein receptor that belongs to the Ig superfamily and is expressed on the surface of certain T cells and myeloid cells. The interaction between CD200 and its receptor (CD200-R1) leads to the downregulation of myeloid cells and immune response modulation (11). The immune response modulation mediated by CD200: CD200-R interaction results in suppressing certain inflammatory cytokines, e.g., interferons, tumor necrosis factor, and nitric oxide synthase, to limit inflammation cascade. However, there is a question here; Do anti-inflammatory signals always represent protective effects from cell injury? (12).

Unsurprisingly, the modulatory effects of the CD200: CD200-R signaling pathway is a double-edged sword, meaning that although the restriction of the inflammatory response prevents cells from further damages, the pitfall is that parasites, bacterial and viral pathogens can also focus on activating this signaling pathway as an opportunity to disarm the immune system and invade the host cells(13).

Considering the immune-suppressing nature of COVID-19 infection, focusing on immunoregulating therapies such as immune checkpoint inhibitors, interferons, and other medications in this category like anti-CD200 monoclonal antibodies can be notably useful. This study aims to review the evidence on the immune response dysregulation in COVID-19 infection and the potential immunoregulatory treatments.

**Methods:**

Relevant databases such as Scopus, Medline, Embase, ISI Web of Knowledge, Cochrane central register of controlled trials, Cochrane database systematic reviews, and Google Scholar were searched. The following keywords were used in searching related articles: "COVID 19", "Coronavirus Pandemic 2019", "Cancer," "Immunotherapy," "Immune Checkpoint Inhibitors," "T Cell Exhaustion," and "immune system." Titles, abstracts, and full text of articles were reviewed in this study. Congress abstracts and newspaper articles were excluded.

**Results:**

**1.Evidence of the dysregulated immune response in COVID-19 infection:**

A cohort study of 452 patients with laboratory-confirmed COVID-19 in Wuhan, China, reported a dysregulated immune response in these patients. As a result of this suppressed immune response, the increase of neutrophil to lymphocyte ratio (NLR), T lymphopenia, and decrease of CD4+ T cells were considered as common laboratory findings, especially in severe cases. However, there was no significant change in the number of CD8+ cells and B cells. According to these data, lymphocyte damage, especially T lymphocytes, seems to be one of the most important disease pathogenesis factors. It is suggested that the amount of lymphocyte injury (mainly T lymphocyte) and subsequent cellular immune suppression are a critical factor in disease progression(14).

Furthermore, another study in Wuhan, China, also confirmed the relationship between T cell count and disease prognosis. According to this research, patients with a total T cell count lower than 800/μl generally require more aggressive interventions and ICU admission(15).

**2.CD200-R inhibitors role in coronavirus infection:**

Molecular studies indicated that some pathogens bypass the host cell's immune system by exploiting CD200: CD200-R signaling pathway. The animal studies in mice showed that type 1 interferon (IFN 1) production in response to TLR-7 signaling has a key role in coronavirus clearance, and the CD200: CD200-R suppression prevents virus clearance by limiting IFN1 production (16). So, Using CD200 signaling inhibitors like Samalizumab in the early stages of Covid-19 infection might help restrict the virus invasion. Further clinical studies are necessary to make a conclusion on CD200 inhibitors efficacy in limiting specific viral infections as they are novel agents that generally have not been involved in long term clinical trials, and supportive details of using these agents are lacking.

**3.Interferons role in COVID-19 Infection:**

Interferons are one of the key mediators in limiting viral invasion to the cells, but activation of inhibitory responses like CD200:CD200R1 signaling pathway by specific viral pathogens such as COVID-19 limit their antiviral activity(17). As mentioned before, using novel agents such as CD200 inhibitors might not yet be optimized for this situation. So, how about taking one step further in the signaling pathway and trying interferons for supporting the virus clearance system?

Intrinsic viral resistance of the cells is highly dependent on IFN I & IFN III. One of the cellular attack strategies by coronavirus is to suppress the IFN response (18). As expected, a serum analysis study of

COVID-19 patients revealed suppressed levels of type I & type III interferon and elevated inflammatory and proinflammatory cytokines and chemokines (19). However, some researchers suggest that the virus induce a late interferon response rather than a complete absence (20). An animal study on a mouse model of SARS-CoV infection also showed that IFN-1 was detectable in the lung until several hours after the viral load peak(21). A small COVID-19 patients cohort revealed surprising results. In this study, a strong association between IFN-$\alpha$ and viral load, as well as disease severity, was discovered. This study concluded that high interferon levels in the late stages of the infection could not successfully bring down the viral load, and interferon probably acts optimally in the early stages of the disease (22).

So, according to all these details, can IFN be a therapeutic strategy in COVID-19 infection?

Actually, the efficacy of the interferons as a therapeutic option for COVID-19 is a subject of debate. Numerous in vitro and in vivo studies candidate IFN-I as a promising therapeutic option for SARS and MERS infections (23). The knowledge from SARS-CoV and MERS-CoV studies on interferon efficacy can be a valuable guide for determining interferons' position in COVID-19 treatment guidelines. Several randomized clinical trials are registered to test this. These studies include the DisCoVeRy trial (NCT04315948, the first clinical trial by the WHO Solidarity consortium) that is aimed to evaluate the therapeutical efficacy of subcutaneous injection of IFN-b1a in combination with lopinavir-ritonavir, lopinavir-ritonavir alone, hydroxychloroquine, or remdesivir. Another phase II clinical trial on inhaled IFN-b1a as a single agent is ongoing in the UK (NCT04385095) (24). A retrospective study of 77 COVID-19 patients in Wuhan, China compared nebulized IFN-a2b with arbidol or a combination of the two and claimed that nebulized IFN-a2b significantly reduced the level of inflammatory markers, interleukin-6 and C-reactive protein (CRP) as well as the duration of the detectable virus (25). A case series in Hubei Province evaluated the efficacy of recombinant IFN-a nasal drops in preventing COVID-19 incidence. In this study, 2944 healthcare workers received the IFN-a nasal drop. After 28 days, the rate of COVID-19 infection among them was zero (26). Fortunately, the primary results of ongoing clinical studies on interferons are encouraging. However, studies on different animal models and larger sample sizes are required to obtain more precise details on the safety and efficacy of IFN-I as a therapy in COVID-19.

**4. Immune Checkpoint Inhibitors Role in COVID-19 Infection:**

One of the most important clinical challenges during the COVID-19 pandemic is the management of patients who need to receive anti-cancer therapy due to significant immunosuppressive effects of conventional chemotherapy agents. Immune checkpoint inhibitors like anti-PD-1/PD-L1 or anti-CTLA-4 have been introduced in past decades as novel anti-cancer agents for specific carcinomas like non-small cell lung cancer and melanoma, colorectal cancer, and others. This class's immunomodulatory property is a considerable advantage over conventional chemotherapy agents as they are not associated with significant immunodeficiency during treatment (27). For example, one of the concerns with conventional chemotherapy agents is the reactivation of past viral infections or contributions to the spread of current concomitant viral infections like HIV and HCV due to their immunosuppressive side effects. However, a large number of clinical trials proved that immune checkpoint inhibitors are not associated with this risk, So they can be safe and effective in treating virally related or unrelated cancer patients with active COVID-19 infection (28).

Another hypothesis is that these agents might be useful in treating active COVID-19 infection, even in non-cancerous patients, due to their profound immunomodulatory effects and especially T cells activation (29).

Recent research showed that PD-1 expression is upregulated in the early phase of COVID-19 infection, which can be a T cell exhaustion marker. This evidence suggests that certain immune checkpoint inhibitors with anti-PD-1/PD-L1 activity (e.g., nivolumab, pembrolizumab, avelumab) might reinvigorate exhausted T cells and improve virus clearance (30). There is a question here, how T cell exhaustion is implicated in disease progression?

Studies on chronic viral infections' pathophysiology revealed the association between functionally exhausted T cells and viral infection persistence. T cell exhaustion is a deterrent factor in preventing cellular damage

by extra inflammatory cytokines in immune responses. However, on the other hand, it can be an excellent opportunity for the pathogen to invade cells in the absence of sufficient immune system activity and developing a persistent infection. Viral pathogens induced early T cell exhaustion by targeting the cellular and molecular pathways that determine T cell differentiation and produce effector and memory cells(31).

As mentioned before, analytical studies on infected cells in COVID-19 patients showed higher levels of PD-1 in $CD^{4+}$ & $CD^{8+}$ T cells, especially in more severe forms of the disease that led to the patient's ICU admission. Another important finding in serum analysis of these patients is extra high levels of Interleukin-10 (IL-10), an inhibitory cytokine implicated in T cell exhaustion by inducing inhibitory effects on T cell proliferation. According to this evidence, the application of potential T cells reinvigorating agents such as immune checkpoint inhibitors in the early phase of the disease might limit the COVID-19 progression(32).

So, can these agents be the preferable anti-cancer choice in this situation or even be an independent therapeutic option for COVID-19 treatment?

Recent studies showed that although immune checkpoint inhibitors do not expose patients to immunodeficiency, which is a considerable criterion in this pandemic and might be useful for treating active COVID-19 infection, they might be associated with greater concerns that even overweight their immunomodulatory benefits.

The first concern related to these agents is the promotion of extra inflammatory events in response to different immune-activating mechanisms associated with increased cytokine-mediated toxicity (33). The incidence of immune-related adverse events (IrAEs) with these agents depends on the dose and mechanism of action. For example, ipilimumab, an anti-CTLA4 antibody, is associated with about 60% IrAEs that 10-30% of these are considered serious and life-threatening, such as hepatitis, hypophysitis, and autoimmune thrombocytopenia. Generally, anti-PD-1 antibodies (such as nivolumab or pembrolizumab) are associated with less frequent and milder immune-mediated side effects. Approximately only 10% of patients receiving these agents experience serious IrAEs such as hepatitis and pneumonitis(34). The major concern here is the possible overlap between the possible pneumatological toxicity from anti-PD-1/PD-L1 agents and the coronavirus-related interstitial pneumonia. Although interstitial pneumonia is a rare adverse reaction of immune checkpoint inhibitors, it is one of the fatal forms of reactions associated with an estimated 35% mortality and cannot be ignored(35).

In the end, what is the best recommendation? Regarding the lack of enough clinical studies on both advantages and disadvantages of these agents in the COVID-19 pandemic, the use of immune checkpoint inhibitors cannot be strongly suggested as a COVID-19 treatment protocol or definite prior choice in cancer treatment. However, the probable overlap of adverse drug reactions should not encourage oncologists to deprive patients of these agents if they are an effective treatment choice for them.

**Conclusion:**

Immune targeted therapies can be a promising outlook for the treatment of COVID-19 infection. Until now, antiviral agents were not particularly successful in controlling this massive pandemic, and there is also strong evidence of dysregulated immune responses during this infection. So, agents with immunomodulatory properties that can reinforce the immune system to clear the virus by itself can take into consideration. The CD200: CD200-R inhibitors, IFN I & III, and immune checkpoint inhibitors might be the plausible immunomodulator options.

Clinical decisions about using these agents must be based on the patient's immunological status, cost & availability, and specifically, the results of ongoing clinical studies on their safety and efficacy for the current purpose.

Fig.1 shows a summary of possible immune targeted therapies for COVID-19 infection.

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**Figure Legends:**

summary of possible immune targeted therapies for COVID-19 infecion