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Review Article

Immune Targeted Therapies for COVID-19 Infection: A Narrative Review

Bahareh Forouzani-Haghighi[1], PharmD; Alireza Rezvani[2,3], MD; Afsaneh Vazin[1], PhD

[1]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran;
[2]Department of Hematology and Medical Oncology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;
[3]Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Alireza Rezvani, MD;
Hematology Research Center, Headquarters of Shiraz University of Medical Sciences, Zand Blvd., Postal code: 14336–71348, Shiraz, Iran
Tel: +98 9122418127
Email: ar.rezvani@hotmail.com
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Abstract

In December 2019, the coronavirus disease-2019 (COVID-19) outbreak emerged in Wuhan, China. The World Health Organization officially declared it a pandemic on March 11, 2020. Reports indicated that the associated mortality of the infection is quite higher in the elderly, individuals with specific comorbidities (such as diabetes mellitus), and generally the ones with a compromised immune system. A cohort study in Wuhan, China, reported a dysregulated immune response in 452 patients with laboratory-confirmed COVID-19. As a result of this suppressed immune response, an increase in neutrophil to lymphocyte ratio, T lymphopenia, and a decrease in $CD4^+$ T cells were all common laboratory findings, especially in severe cases.

On the other hand, there is substantial evidence of T cell exhaustion in critically ill patients. Accordingly, the immune system seems to play an important role in the prognosis and pathogenesis of the disease. Therefore, 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 ● Immunotherapy ● COVID-19 ● Immune checkpoint inhibitors ● T-lymphocytes

What's Known

- Coronavirus disease-2019 infection is associated with a greater mortality rate in the elderly, patients with specific comorbidities (such as diabetes mellitus), and generally those with a compromised immune system.
- Immune responses play an important role in the prognosis and pathogenesis of the disease.

What's New

- Immunoregulatory treatments such as immune checkpoint inhibitors, interferons, and CD200 inhibitors have a promising outlook in the treatment of coronavirus disease-2019 infection.

Introduction

In December 2019, the coronavirus disease-2019 (COVID-19) outbreak emerged in Wuhan, China.[1] On March 11, 2020, the World Health Organization (WHO) officially declared it a pandemic.[2] Up to March 2022, WHO reported 434 million cases of infection and 5.9 million deaths worldwide, and the virus is still spreading rapidly.[3] On imaging, the disease presented as moderate to severe pneumonia with clinical symptoms such as cough, dyspnea, fever, and bilateral lung infiltrates.[4] The presence of moderate to severe lymphopenia (especially T cells), in laboratory tests further suggests a dysregulated immune response in these patients.[5]

According to the reports, the associated mortality rate of the infection was quite higher in the elderly, individuals with specific comorbidities (such as diabetes mellitus), and those with a compromised immune system in general.[6] These patients often had a weaker prognosis and required more frequent admission to an intensive care unit and ventilator support.[7] Cancer

patients account for a considerable proportion of the high-risk population, due to cancer and chemotherapy-induced immune suppression. Moreover, these patients are at a higher risk of experiencing severe complications.[8] To avoid immune suppression in this situation, some specialists recommend delaying surgery and adjuvant chemotherapy for patients with stable condition.[9]

Current studies also claimed that the prevalence of COVID-19 infection is higher among cancer patients undergoing conventional chemotherapy than those receiving immunotherapy, such as checkpoint inhibitors.[10] This finding could be attributed to the limited sample size, and subsequent studies with a larger sample size found no statistically significant difference in the prevalence of this viral infection between chemotherapy and immunotherapy patients.[11] However, another hypothesis is that the 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.[12] Among various anti-cancer protocols, immune checkpoint inhibitors (ICIs) are one of the treatment alternatives for specific cancers such as melanoma, lung, renal, and other chemo-resistant tumors. Unlike chemotherapy, members of this class are not associated with immune suppression due to their immune regulatory effects.[13] Antibodies against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) such as ipilimumab and tremelimumab were the first class of immune checkpoint inhibitors to be introduced, but severe autoimmune reactions restricted their use.[14] Currently, antibodies against programmed cell death protein 1 (PD-1) and its ligand PD-L1 are more favorable than CTLA-4 inhibitors due to their milder side effects.[15] This class includes the monoclonal antibodies nivolumab, pembrolizumab (anti-PD-1), atezolizumab, durvalumab, and avelumab (anti-PD-L1).[16]

Therefore, immunomodulatory pathways seem to have an essential role in the pathogenesis of the disease.[17] This study aims to review the evidence of immune response dysregulation and the potential immunoregulatory treatments in COVID-19 infection.

Cell Entry Mechanism

For a successful pathogen invasion, different mechanisms must be employed to overcome the host cell immune response.[18] Excessive host cell immune response, on the other hand, might also result in the overproduction of inflammatory and proinflammatory cytokines, leading to uncontrolled cellular and tissue damage.[19, 20] Immune cells also suppress excessive inflammatory responses by simultaneously expressing inhibitory receptors.[21] The immunoglobulin (Ig) and calcium-dependent carbohydrate-binding (C-type) lectin families are two major subgroups of the inhibitory receptors superfamily.[22] CD200 receptor1 (CD200-R1) is a transmembrane glycoprotein receptor of the Ig superfamily that is expressed on the surface of certain T cells and myeloid cells.[23] The interaction between CD200 and its receptor (CD200-R1) leads to myeloid cell downregulation and immune response modulation.[24]

The immune response modulation mediated by CD200: CD200-R interaction results in the suppression of certain inflammatory cytokines, such as interferons, tumor necrosis factor, and nitric oxide synthase, thereby limiting the inflammatory cascade.[25] However, one concern remains: Do anti-inflammatory signals always represent protective effects against cell injury?[26]

The modulatory effects of the CD200: CD200-R signaling pathway are a double-edged sword, which means that although the restriction of the inflammatory response prevents cells from further damages, parasites, bacterial and viral pathogens can use this signaling pathway to disarm the immune system and invade the host cells.[27]

Considering the immunosuppressive nature of COVID-19 infection,[28] focusing on therapies such as immune checkpoint inhibitors, interferons, and other medications in this class such as anti-CD200 monoclonal antibodies can be quite beneficial.[29]

Evidence of the Dysregulated Immune Response in COVID-19 Infection

There are some controversies about the immune status of patients with COVID-19, and the immune status of all the patients is not the same.[30] However, in some patients, particularly in severe cases, there is a clear evidence of dysregulated immune function.[31] A cohort study in Wuhan, China, reported that 452 patients with laboratory-confirmed COVID-19 had a dysregulated immune response. As a result of the suppressed immune response, an increase in neutrophil to lymphocyte ratio (NLR), T lymphopenia, and a decrease of $CD4^+$ T cells were 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 findings, lymphocyte damage, especially T lymphocytes, seems to be one of the most important factors in the pathogenesis of the diseases. The amount of lymphocyte damage (mainly T lymphocyte) and

the subsequent cellular immune suppression are thought to be critical factors in disease progression.[32]

Furthermore, another study conducted in Wuhan, China, confirmed the relationship between T cell count and disease prognosis. According to this research, patients with a total T cell count less than 800/μl require more aggressive interventions and ICU admission.[33]

Immunologic Targets for COVID-19 Treatment

Regarding the critical role of the immune status in the prognosis and pathogenesis of COVID-19 infection, immunologic targets such as the implicated mediators of viral entry and antiviral defense system of the host cell could be a promising therapeutic target for COVID-19 treatment by blocking the mechanism of viral entry and reinforcing the viral clearance. The potential immunologic targets are summarized in table 1.

CD200-R Inhibitors Role in Coronavirus Infection

Molecular studies indicated that some pathogens bypass the immune system of the host cell by exploiting CD200: CD200-R signaling pathway.[38] The animal studies in mice revealed that the production of interferon type 1 (IFN-I) in response to TLR-7 signaling plays an important role in coronavirus clearance, and the CD200: CD200-R suppression prevents virus clearance by limiting IFN-I production.[39] Samalizumab is a recombinant humanized monoclonal antibody against CD200 receptor, which has been investigated for the treatment of multiple myeloma and chronic lymphocytic leukemia.[40] According to the mechanism of action, using CD200 signaling inhibitors such as samalizumab in the early stages of Covid-19 infection might help restrict the virus invasion. Further clinical investigations are required to determine the efficacy of CD200 inhibitors in restricting specific viral infections, as they are novel agents that generally have not been involved in long-term clinical trials, and supportive information of employing these agents is not available.

Interferons Role in COVID-19 Infection

Interferons are one of the key mediators in restricting viral invasion into the cells,[41] but activation of inhibitory responses such as the CD200:CD200R1 signaling pathway by specific viral pathogens such as COVID-19 limit their antiviral effectiveness.[42, 43] As mentioned before, using novel agents such as CD200 inhibitors might not be optimized in this context. Thus, how about taking the signaling pathway one step further and trying interferons for supporting the virus clearance system?

IFN-I and IFN-III are critical for the intrinsic viral resistance of the cells. One of the cellular attack strategies by coronavirus is to suppress the IFN response.[44] As expected, a serum analysis study of COVID-19 patients revealed decreased levels of type I and type III interferon as well as higher levels of elevated inflammatory and proinflammatory cytokines and chemokines.[45] However, some researchers suggested that the virus induced a late interferon response rather than a complete absence.[46] An animal study on a SARS-CoV-infected mouse model found that IFN-I was detectable in the lung for several hours after the viral load peak.[47] A small cohort of patients with COVID-19 showed surprising results. This study found a strong association between IFN-α and viral load and disease severity. This study concluded that high levels of interferon in the late stages of the infection were ineffective in reducing the viral load, and that interferon probably was most effective in the early stages of the disease.[48] Hence, with all of this information, can IFN be employed as a therapeutic strategy in COVID-19 infection?

Actually, the efficacy of the interferons as a

Table 1: Summary of clinical studies on immunoregulatory treatments for COVID-19 infection

Author	Drug Group	Study Center	Tested Drug	Study Population	Outcomes
Sallard et al.[34]	Interferons	Various sites in Europe	Subcutaneous injection of IFN-β1a in combination with oral lopinavir, ritonavir, ribavirin	Hospital treatment of COVID-19 patients	Decreased severity of infection
Sallard et al.[34]		United Kingdom	Inhaled IFN-β1a as a single agent	Hospital treatment of COVID-19 patients	Reduction in developing severe disease
Zhou et al.[35]		Wuhan, China	Intranasal IFN-α2a in combination with arabitol	Hospital treatment of COVID-19 patients	Reduction in clinical symptoms
Meng et al.[36]		Hubei, China	Intranasal IFN-α2	Healthcare workers	Preventive effect on infection
El Bairi et al.[37]	Immune Checkpoint Inhibitors	Spain	Tocilizumab plus pembrolizumab	Hospital treatment of COVID-19 patients	Decreased time to clinical improvement

IFN: Interferon; UK: United Kingdom

therapeutic option for COVID-19 is a subject of debate. Numerous *in vitro* and *in vivo* studies suggested IFN-I as a promising therapeutic approach for SARS and MERS infections. The obtained information from SARS-CoV and MERS-CoV studies on interferon efficacy can be a useful guide for determining the position of interferons in COVID-19 treatment guidelines.[49] Several randomized clinical trials have been registered to test this hypothesis. The DisCoVeRy trial (NCT04315948, the first clinical trial by the WHO Solidarity consortium) is one of these studies. Its goal was to evaluate the therapeutical efficacy of subcutaneous injection of IFN-b1a in combination with lopinavir-ritonavir, lopinavir-ritonavir alone, hydroxychloroquine, or remdesivir. In the United Kingdom, another phase II clinical trial on inhaled IFN-b1a as a single agent is ongoing (Synaigen with NCT04385095).[34] In a retrospective study of 77 COVID-19 patients in Wuhan, China, researchers compared nebulized IFN-α2b with arbidol or a combination of the two and claimed that nebulized IFN-a2b significantly reduced the level of inflammatory markers such as interleukin-6 and C-reactive protein (CRP), as well as the duration of the detectable virus.[35] A case series in Hubei Province was conducted to assess the efficacy of recombinant IFN-α nasal drop in preventing COVID-19 incidence. In this study, 2944 healthcare personnels received the IFN-α nasal drop. After 28 days, the rate of COVID-19 infection among them was zero.[50] Fortunately, the preliminary findings of ongoing clinical trials on interferons are encouraging, and only a few adverse reactions are reported. In a randomized clinical trial of the efficacy and safety of interferon β-1a in the treatment of severe COVID-19, 19% of patients experienced injection-related reactions such as fever, chills, headache, and fatigue, which were responsive to supportive therapy (acetaminophen) and a change in injection time to late night. The authors suggested that the incidence of interferon adverse reaction in COVID-19 patients is lower than in multiple sclerosis patients. The study also found no evidence of hepatotoxicity, nephrotoxicity, or any other organ failure caused by interferon β-1a use that caused treatment interruption. The Summary of clinical trials outcomes on the use of Interferon in COVID is presented in table 1.

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 the significant immunosuppressive effects of conventional chemotherapy agents. Immune checkpoint inhibitors, such as anti-PD-1/PD-L1 or anti-CTLA-4 have been introduced as innovative anti-cancer agents in the past decades for specific carcinomas including non-small cell lung cancer and melanoma, colorectal cancer, and other cancers.[51] The immunomodulatory characteristic of this class is a considerable advantage over conventional chemotherapy agents, as they are not associated with significant immunodeficiency during treatment.[52] For example, one of the concerns with conventional chemotherapy agents is that they may reactivate previous viral infections or contribute to the spread of existing concomitant viral infections such as HIV and HCV due to their immunosuppressive side effects.[53] However, a large number of clinical trials demonstrated that immune checkpoint inhibitors were not associated with this risk. Therefore, they can be safe and effective in treating virally related or unrelated cancer patients with active COVID-19 infection.[54]

Another hypothesis is that these agents, due to their profound immunomodulatory effects and especially T cells activation, might be useful in treating active COVID-19 infection, even in non-cancerous individuals.[55]

Recent research showed that PD-1 expression is upregulated in the early stages of COVID-19 infection, which can be a T cell exhaustion marker. These findings suggest 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.[37] A question arises here: how T cell exhaustion is implicated in disease progression?

Studies on the pathophysiology of chronic viral infections found an association between functionally exhausted T cells and viral infection persistence.[56] T cell exhaustion is a deterrent factor in immune responses that prevent cellular damage caused by extra inflammatory cytokines. On the other hand, in the absence of sufficient immune system activity, it can be an excellent opportunity for the pathogen to invade cells and develop persistent infection.[57] 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.[58]

As previously stated, analytical tests on infected cells in COVID-19 patients showed higher levels of PD-1 in $CD4^+$ and $CD8^+$ T cells, especially in more severe forms of the disease that resulted in ICU admission.[59] Another

important finding in the 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 research, the application of potential T cells reinvigorating agents such as immune checkpoint inhibitors in the early stages of the disease might limit the COVID-19 progression.[60]

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

Recent studies showed that although immune checkpoint inhibitors do not cause 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 outweigh their immunomodulatory advantages.

The first concern related to these agents is that they promote extra-inflammatory processes in response to different immune-activating mechanisms, which are associated with increased cytokine-mediated toxicity.[61] The incidence of immune-related adverse events (IrAEs) is dependent on the dose and mechanism of action of these agents. For example, ipilimumab, an anti-CTLA4 antibody, is associated with about 60% IrAEs, and 10-30% of these are considered serious and life-threatening, such as hepatitis, hypophysitis, and autoimmune thrombocytopenia. Anti-PD-1 antibodies, such as nivolumab or pembrolizumab, are often associated with less frequent and milder immune-mediated side effects. Only about 10% of individuals who receive these agents experience serious IrAEs such as hepatitis and pneumonitis.[62] 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 should not be ignored.[63] Figure 1 shows a summary of potential immune targeted therapies for COVID-19 infection, and the summary of clinical trials outcomes on ICIs is shown in table 1.

Finally, 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 recommended as a COVID-19 treatment protocol or definite prior choice in cancer treatment. However, if these medications are a viable

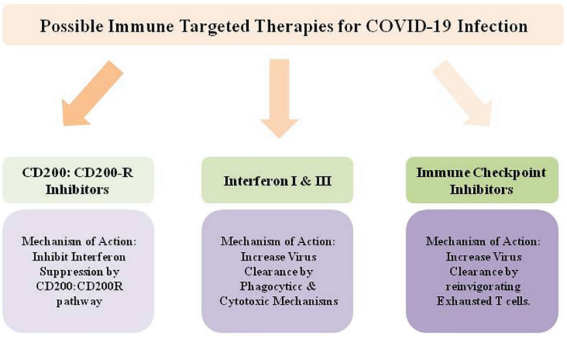

Figure 1: Possible immune targeted therapies for COVID-19 infection are illustrated.

treatment alternative for a patient, the probable overlap of adverse drug reactions should not discourage oncologists from prescribing these agents.

Conclusion

Although the immune status of COVID-19 patients is not uniform in all patients, some studies reported clear evidence of immune dysfunction, especially in severely ill patients. According to these studies, lymphocyte damage, especially T lymphocytes, seems to be an important determinator in disease pathogenesis. Regarding the significant role of the dysregulated immune response in disease pathogenesis and prognosis, immune targeted therapies can be a promising outlook for the treatment of COVID-19 infection.

Until now, antiviral agents were not particularly effective in controlling this massive pandemic. Hence, agents with immunomodulatory properties that can reinforce the immune system to clear the virus by itself should be taken into consideration. Immunomodulators such as CD200: CD200-R inhibitors, IFN-I and III, and immune checkpoint inhibitors might be some plausible options.

Clinical decisions about whether or not to use these agents should be based on the patient's immunological status, cost, availability, and specifically, the findings of ongoing clinical studies on their safety and efficacy for the current purpose.

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Authors' Contribution

B.F.H contributed to the conception, design,

acquisition of the work and Writing the work. A.R and A.V contributed to the conception, design and acquisition of the work and drafting and revising the work critically for important intellectual content. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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