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COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons

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ABSTRACT

The outbreak of the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) responsible for coronavirus disease 2019 (COVID-19) has developed into an unprecedented global pandemic. Clinical investigations in patients with COVID-19 has shown a strong upregulation of cytokine and interferon production in SARS-CoV2-induced pneumonia, with an associated cytokine storm syndrome. Thus, the identification of existing approved therapies with proven safety profiles to treat hyperinflammation is a critical unmet need in order to reduce COVID-19 associated mortality. To date, no specific therapeutic drugs or vaccines are available to treat COVID-19 patients. This review evaluates several options that have been proposed to control SARS-CoV2 hyperinflammation and cytokine storm, including antiviral drugs, vaccines, small-molecules, monoclonal antibodies, oligonucleotides, peptides, and interferons (IFNs).

1. Covid-19 pathogenesis

COVID-19, caused by the SARS-CoV-2 virus, is a potentially fatal disease that represents a major global public health concern. The SARS-CoV2 virus infects the lower respiratory tract and causes pneumonia in humans, with symptoms that appear milder than SARS or MERS infection, but ultimately becomes a lethal disease of hyperinflammation and respiratory dysfunction [1]. By SARS-CoV2 infection and disease can be approximately divided into three phases: I. an asymptomatic phase with or without detectable virus; II. a non-severe symptomatic phase with upper airway involvement; and III. a severe, potentially lethal disease with hypoxia, ‘ground glass’ infiltrates in the lung, and progression to acute respiratory distress syndrome (ARDS) with high viral load (Fig. 1) [2].

The coronavirus genome encodes four major proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E). The S protein is responsible for viral entry into target ACE2 expressing cells of the body. Approximately 75 percent of the SARS-CoV2 genome is identical to the SARS-CoV genome, and the amino acid residues required for receptor binding are the same between these two viruses; both viruses use the angiotensin converting enzyme 2 (ACE2) receptor to infect airway epithelial cells and endothelial cells. [3].

ARDS is the main cause of death in COVID-19 disease, and appears to cause similar immunopathogenic features in SARS-CoV and MERS-CoV infections [4]. One of the main features of ARDS is the cytokine storm - an uncontrolled systemic inflammatory response resulting from the release of pro-inflammatory cytokines and chemokines by immune effector cells [5]. High blood levels of cytokines and chemokines have been detected in patients with COVID-19 infection, including: IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFa, and VEGFA [5]. The ensuing cytokine storm triggers a violent inflammatory immune response that contributes to ARDS, multiple organ failure, and finally death in severe cases of SARS-CoV2 infection, similar to SARS-CoV and MERS-CoV infections [5]. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines [4] (Fig. 2) [7]. The direct cause of death from acute COVID-19 involves cytokine storm damage to lungs and multiple organs of the body: heart, kidney and liver, leading to multiple organ exhaustion [8,9,11,12].

2. Interferons as a potential therapy for COVID-19

New therapeutic interventions will likely require a long lead time for the development of approved drugs. Thus, in light of the dire need and urgency to identify the treatment and control of COVID-2019, a repurposing of IFNs and other approved drugs is a potential option in drug development for the control of coronavirus infection. The potential drug options for SARS-CoV-2 infection include the use of enzyme inhibitors, nucleosides, host-targeted agents, convalescent plasma and IFNs [13,14]. Interferons (IFN) enhance the immune system in several ways, by exhibiting various biological functions including antiviral, antiproliferative, immunomodulatory and developmental activities [15] (Fig. 3). IFNs employed therapeutically are manufactured using recombinant DNA technology and multiple clinically approved IFNs are available: IFN α-2a (Roferon), IFN α-2b (Intron A), IFN α-n1 (Wellferon), IFN α-n3 (Alferon), IFN α-con 1 (Infergen), IFN β-1a (Rebif), IFN β-1b (Betaferon), IFN β -1a (Aovnex), IFN β -1b (Betaseron), IFN α -2a (Pegasys), IFN α -2b (PegIntron), IFN α-P-2b (Sylatron), and IFN γ-1b (Acimmune) [18,19].

In a recent study with MERS-CoV infected patients, the combination of Remdesivir and IFNbeta revealed superior antiviral activity, compared to the effect of lopinavir and ritonavir [20]. Treatment of these patients with oral ribavirin and subcutaneous pegylated IFN alpha-2a demonstrated significant improvement in survival, provided that adequate monitoring and assessment was available [21,22]. Remdesivir and IFN beta may likewise prove useful in the treatment of COVID-19 [14-16], particularly since recent clinical trials have demonstrated that Remdesivir shortened the length of time in hospital intensive care for Covid-19 patients.

Earlier studies showed that coronaviruses including MERS, SARS, human coronavirus 229E, and avian infectious bronchitis virus (IBV)
were susceptible to IFN treatment [17,23]. In patients with MERS infection, a combination of ritonavir plus IFN α2a or IFN α-2b resulted in significantly improved survival after 14 days of treatment. The combination of ritonavir and IFNβ had no significant effect on clinical outcome in patients infected with MERS, but the combination of ribavirin (1), ritonavir (2) and IFN α-2a inhibited viremia within 48 h of treatment [13]. The use of recombinant IFNs (IFN-α, IFN-β and exogenous IFNs) in the treatment of SARS-CoV2, SARS-CoV and MERS-CoV demonstrated that IFN response inhibited protein synthesis and replication of the virus [24–26]. IFN α and γ, alone or in combination, showed partial efficacy against the animal coronaviruses, as well as inhibiting SARS-CoV replication in vitro. IFN β had the highest potency, demonstrating prophylactic protection and antiviral potential post infection [27]. Therefore, it may be worthwhile to test the safety and efficacy of human and recombinant IFNs in SARS-CoV-2-infected patients, alone or in combination with other antiviral drugs.

3. Potential combination approaches for COVID-19

At present, there are no Food and Drug Administration (FDA)-approved drugs specifically indicated for the treatment of patients with COVID-19, with the exception of the recently studied Remdesivir. It was shown that Remdesivir reduced the patients’ time in ICU from fifteen days to eleven days. Originally developed as a small molecule
compound against Ebola virus, Remdesivir acts by inhibiting the viral RNA dependent RNA polymerase. However, it is difficult to imagine how the direct antiviral properties of Remdesivir could be potently activated during the immunopathogenic ARDS phase of COVID-19 disease, suggesting that other off-target effects may be attributed to the drug. Further studies, particularly amongst patient populations at earlier stages of the disease, are warranted to resolve these issues.

A number of drugs and combinational therapies have been identified using previously approved drugs that target clathrin-mediated endocytosis, viral protease, regulate immunity, inhibit the inflammatory cytokine surge, improve pulmonary function and reduce lung viral loads (Table 1). At present, treatment of COVID-19 cytokine storm focuses primarily on support and symptomatic treatment of inflammation, cytokine storm and compromised respiratory function [28]. Recently, a number of specific anti-cytokine approaches have proven effective in the treatment of a variety of cytokine storm syndromes, and include drugs targeting interleukin-1 (IL-1), IL-6, IL-18, and interferon-gamma [29]. While randomized trials will be needed to confirm which, if any, of these therapeutics are effective in Covid-19-infected patients with cytokine storm syndrome, IL-6 blockade using anti-IL6 antibody has recently been reported, with successful outcomes in some individuals [10]. While working to prevent future outbreaks of coronavirus infections with vaccine development and new or re-purposed anti-viral medicines, it remains of utmost importance to use the knowledge at our disposal to treat those patients most at risk of dying from Covid-19-induced cytokine storms.

Declaration of Competing Interest

There are no financial or other interests related to this review that represent a conflict of interest.

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Table 1

| Name of the agent/therapy | Targeted virions infection | Target virion mechanism | References |
|---------------------------|----------------------------|-------------------------|------------|
| Thalidomide and Glucocorticoids | SARS-CoV-2 | Regulate immunity, inhibit the inflammatory cytokine surge | [30] |
| Remdesivir and IFNa2 | SARS-CoV-2 | Improves pulmonary function and reduces lung viral loads | [13] |
| Chloroquine and Hydroxychloroquine | SARS-CoV-2 | Attenuation of cytokine production and inhibition of autophagy - shown recently to be ineffective in clinical studies | [31] |
| Lopinavir and Ritonavir | HIV, MERS-CoV and SARS-CoV-2 | Protease inhibitor, inhibits 3CLpro | [13] |
| Lopinavir, oseltamivir and ritonavir | SARS-CoV-2 | Target viral protease | [32] |
| Lopinavir, ritonavir, and interferon beta | MERS-CoV and SARS-CoV-2 | Slightly reduced viral load and improved pulmonary function | [20] |
| Convalescent plasma | SARS-CoV-2, SARS-CoV and MERS-CoV | Inhibited virus entry to the target cells, suppressed viraemia by anti-SARS-CoV2 antibody | [13] |
| Hydroxychloroquine and Azithromycin | SARS-CoV-2 | Viral load reduction through inhibition of replication | [33] |
| Camostat mesilate Hydroxychloroquine | SARS-CoV-2 | Inhibitor of the host cell serine protease and angiotensin receptor blockers | [34] |
| Darunavir and Umifenovir | SARS-CoV-2 | Viral load reduction through inhibition of replication | [35] |
| Ribavirin and Interferon-α | SARS-CoV-2 | Lowered the risk of acute respiratory distress syndrome (ARDS) and death | [36] |
| Hydroxychloroquine and Nitazoxanide | SARS-CoV-2 | Adjuvant therapy in Covid-19 | [37] |
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