Review Article

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The dual sides of interferon induction in COVID-19 treatment

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Abstract

Coronavirus disease of 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has created a pandemic with immense impacts on different aspects of human life globally. Generally, type I and II interferons are essential cytokines to combat viral infections including COVID-19. However, SARS-CoV-2 adopts evasion mechanisms to overcome interferon-mediated antiviral responses and neutralizes a key human defensive strategy. The aim of this mini-review is to survey both beneficial and non-beneficial effects of interferon during COVID-19 disease course. The indication of interferon-α2b or interferon β-1a has shown benefit at the early stages of COVID-19 in some clinical trials; though, interferon administration could only help in the incubation period or before the peak viral load. The incubation period and the duration from the symptom onset till the peak viral load has been estimated 5-6 and 2-3 days, respectively. On the other hand, an increase of interferon level in the disease's late stages leads to delayed recovery and probably increased mortality rates due to the upregulation of ACE-2 expression in human airway epithelial cells, leading to the facilitation of virus entry into the host cells. Besides, it promotes the overactivation of inflammatory responses, which often happens in the disease's pulmonary phase causing the cytokine storm. In this stage, antiviral agents might not work, and anti-inflammatory drugs, including corticosteroids (dexamethasone or prednisolone), tocilizumab (an IL-6 inhibitor), or anakinra (a recombinant IL-1 receptor antagonist), are beneficial. Some other proposed drugs such as TNF-α inhibitors and JAK inhibitors need further investigations in future studies.

Keywords: Anti-inflammatory, Antiviral, Coronavirus, Cytokine storm, Pandemic, SARS-CoV-2

1. Introduction

Nearly a year ago, a novel coronavirus outbreak started in Wuhan, China, causing an immense impact on different aspects of human life globally (2). The infective agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a positive-sense, single-stranded RNA virus, and a member of the coronaviruses family, surrounded by a lipid bilayer envelope (1).

SARS-CoV-2 has shown mainly airborne transmission similar to influenza and rhinoviruses. It can be spread by droplets that were produced by cough, sneeze, or talking (3). These droplets can be produced in different sizes. Investigations found that the spread distance of small droplets

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can be about 12 feet (4).

The relation of the immune system functioning with SARS-CoV-2 pathogenesis has been investigated in many studies. Interferon is the core of the most popular pathways that should be scrutinized in this regard, since type I and II interferons are essential cytokines to combat viral infections (5). Recent studies suggest that SARS-CoV-2, similar to its ancestors SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus), adopts evasion mechanisms to overcome interferon-mediated antiviral responses; as a result, one of our most potent defensive strategies becomes paralyzed. On the other hand, several studies declared an increase of interferon level in disease's late stages leads to delayed recovery and increased mortality rates. The aim of this mini-review is to survey both beneficial and non-beneficial effects of interferon therapy during different stages of SARS-CoV-2 infection (6, 7).

2. Therapeutic approaches to combat COVID-19

There are three main strategies to reduce the viral load of SARS-CoV-2; blocking de novo infection, inhibiting viral replication, and promoting cytotoxicity approaches. Blocking de novo infection pertains to the incubation period, which happens before the appearance of the symptoms. Supporting the immune defensive system in this period would be very beneficial. However, due to the lack of symptoms, it fits more with preventive approaches. Multiple studies have focused on the incubation period of SARS-CoV-2 and the perfect timing to initiate different treatment strategies (8, 9). Kim et al. designed a mathematical model and suggested that the first two mentioned mechanisms are most effective when applied before peak viral load (maximum three days after symptoms onset). None of these ways are useful after the initial infection stages, when the disease's pulmonary phase has started. On the other hand, the third strategy i.e. promoting cytotoxic approaches showed mild effects when applied before peak viral load, but unlike other approaches, was still promising even after the mentioned time (8).

Estimation of the incubation period is so critical in developing a treatment strategy. To overcome the barriers of data collecting through conventional methods (such as interviews), Ejima et al. designed a model using viral load data to estimate this period with high certainty. The results suggested that the peak viral load occurs in 2-3 days after symptom onset and the incubation period is almost 5-6 days (Figure 1) (9).

3. Interferon dual role in COVID-19

Following the recognition of SARS-CoV-2 by the immune system cells, the level of both types of interferon is elevated. Type I interferons induce the expression of interferon-stimulated genes (ISGs) and, as a result, promote the antiviral innate immune responses. ISGs take direct actions against viruses by targeting some crucial stages of the viral life cycle, such as penetration into the host cells, replication, protein translation, and assembly of new virus particles. They also contribute to the priming of immune cells, especially antigen-presenting cells (APCs), natural killer cells (NKs), B cells, and T cells. Type II interferon, known as interferon-γ, plays its role by linking the innate immune response and activation of the adaptive immune response, including B and T cells. According to Lee et al., interferon-α2b therapy reduced the duration of viral shedding, markers of acute inflammation such as C-reactive protein (CRP) and interleukin (IL)-6 seemed to dampen, and the average hospital stay for patients decreased (5, 6, 10, 11).

In an open-label randomized clinical trial, interferon β-1a was administered to adults diagnosed with COVID-19. The discharge rate was improved significantly on day 14, and the 28-day mortality was also dramatically lowered in the interferon group. Totally improved survival rates were reported. However, the clinical response was not significantly different between the groups (12).

In a recent study, 242 of 446 analyzed COVID-19 patients received interferon-a2b, a type I interferon. Administration of interferon in early stages of the disease was considered to be beneficial and decreased the rate of viral replication. On the other hand, late-stage interferon administration led to upregulation of ACE-2 expression in human airway epithelial cells, which means the facilitation of virus entry into host cells. The recovery time was not associated with interferon therapy

(13).

Other adverse effects of a delayed increase in interferon level include accumulation of inflammatory monocyte-macrophages, extensive vascular leakage, and compromised T cell responses against the virus. Accumulation of monocyte-macrophages leads to the release of inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-1ß, IL-6, inducible nitric oxide synthase (iNOS), and all of these events results in lethal pneumonia (14, 15).

4. Management of cytokine storm

Around days seven to 10, an exacerbation occurs in COVID-19 patients' clinical status (Figure 1), including aggravation of fever, dyspnea, and an increase in the level of acute-phase proteins (ferritin and CRP). It is believed that this deterioration is due to the higher levels of proinflammatory cytokines including TNF-α, IL-1ß, IL-6, IL-18, and interferon-γ, leading to cytokine storm (16).

SARS-CoV-2 stimulates an immune response by the secretion of the above-mentioned proinflammatory cytokines, accompanied by weak interferon-γ production. The produced inflammatory cytokines cause infiltration of neutrophils and macrophages into the lung tissue. Alongside this, the virus forces Th1 cells to secrete IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF). GM-CSF activates other monocytes to produce more IL-6, TNF-α, and other proinflammatory cytokines. Consequently, the cytokine storm happens. It was shown that the severity of COVID-19 was associated with the level of these inflammatory cytokines, T cell lymphopenia, and dynamic cytokine storm (17).

In COVID-19 patients, acute respiratory distress syndrome (ARDS) might happen despite the decrease in the viral load. This suggests that the exacerbation is due to the excessive immune response, not the viral virulence. Therefore, it could imply that in the cytokine storm phase, antiviral agents might have no indication (16).

It can be concluded that interferon treatment should be considered only in the early stages of the disease in which the viral infection and replication is the main issue. On the other hand, anti-inflammatory drugs, rather than interferons, are therapeutic candidates for disease's late phases or the pulmonary phase (11). The suggested anti-inflammatory drugs include corticosteroids, such as dexamethasone, whose efficiency in improving the survival rate of hospitalized COVID-19 patients was confirmed in RECOVERY (Randomized Evaluation of COVid-19 thERapY) trial, as a large randomized, controlled clinical trial (18, 19). Dexamethasone might be replaced with prednisolone. A clinical trial held in Northwell Health system on 5,776 COVID-19 patients with cytokine storm showed that corticosteroids monotherapy

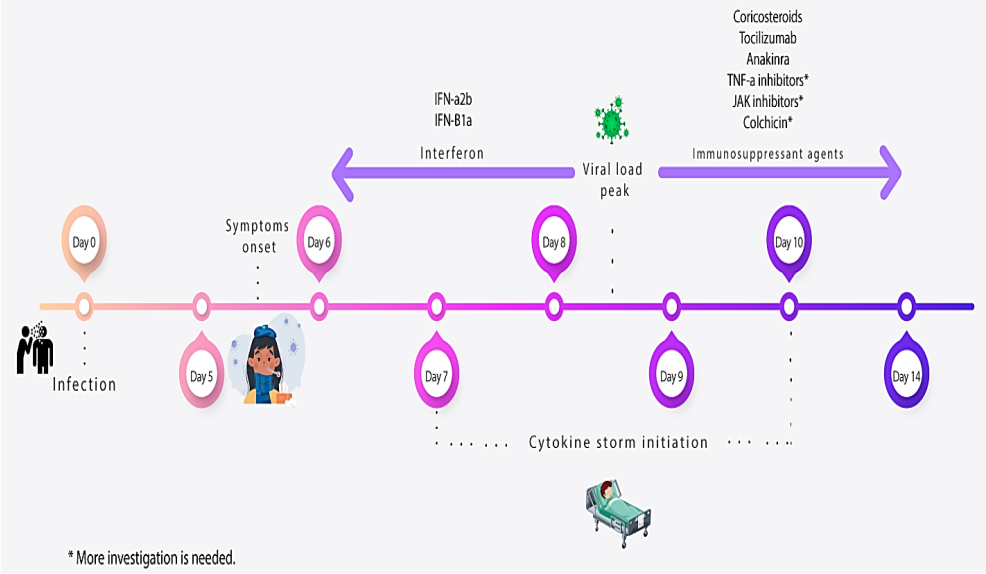

Figure 1. A schematic timeline for COVID-19 infection and the best time for administration of interferons or corticosteroids.

reduced the hospital mortality and the combination of corticosteroids and tocilizumab had a superior survival outcome in comparison with the standard treatment (20).

Moreover, administration of tocilizumab, an IL-6 inhibitor, in a clinical trial on 21 severe or critical patients showed 100% clinical improvement. Another clinical trial on tocilizumab in 30 COVID-19 patients reported significant decrease of ventilator requirement and risk of ICU admission. However, tocilizumab's side effects such as liver damage, neutropenia, and thrombocytopenia should be considered. Additionally, a clinical trial on 21 COVID-19 patients with ARDS using siltuximab showed that 76% of patients experienced clinical improvement or stabilization (16, 17).

Anakinra is also a recombinant IL-1 receptor antagonist that inhibits the binding of both IL-1α and IL-1ß to this receptor. This activity prevents the following inflammatory cascades (21). In a cohort study, it was observed that high dose administration of anakinra showed clinical improvement in 72% of patients (22). Anakinra may be a drug of choice for the treatment of COVID-19 in patients with imminent cytokine storm. Besides, colchicine, an IL-1ß inhibitor, is suggested for this purpose as well, and a clinical trial for defining its role in COVID-19 treatment was performed, but its data has not been published yet (ClinicalTrials.gov- Identifier: NCT04322682) (16).

Among other drugs, Hydroxychloroquine, as one of the first candidate interventions against COVID-19, failed in several clinical trials. As a result, strong recommendation against its administration is mentioned in the latest WHO guidelines (23). A randomized double-blinded placebo-controlled trial of hydroxychloroquine with or without azithromycin reported no benefit in the cure of patients with mild or asymptomatic COVID-19 (24). However, records of positive and synergistic effects of hydroxychloroquine and azithromycin in COVID-19 patients are also found, which raises controversies about this agent (6, 25).

Moreover, some other suggested anti-inflammatory candidates such as TNF-α inhibitors and JAK inhibitors (1) need further investigations in future studies.

5. Conclusion

In this mini-review, two different approaches were analyzed regarding the treatment of COVID-19 patients. Each of these interventions has shown beneficial effects when administered in the optimal timeframe. First of all, interferon therapy should only be considered in the early stages of the disease to prime innate and adaptive immune response against SARS-CoV-2. However, in the late stages of the disease, interferon administration seems to aggravate the patient condition. A main recommendation at this stage of the disease is anti-inflammatory agents, which could support to control the cytokine storm.

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Ethical approval

Not required.

Conflict of Interest

None declared.

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