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Review

Potential role of interferons in treating COVID-19 patients

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ABSTRACT

The recently public health crises in the world is emerged by spreading the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also named COVID-19. The virus is originated in bats and transported to humans via undefined intermediate animals. This virus can produce from weak to severe respiratory diseases including acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), pneumonia and even death in patients. The COVID-19 disease is distributed by inhalation via contaminated droplets or contact with infected environment. The incubation time is from 2 to 14 day and the symptoms are typically fever, sore throat, cough, malaise, fatigue, breathlessness among others. It needs to be considered that many infected people are asymptomatic. Developing various immunological and virological methods to diagnose this disease is supported by several laboratories. Treatment is principally supportive; however, there are several agents that are using in treating of COVID-19 patients. Interferons (IFNs) have shown to be crucial in fighting with COVID-19 disease and can be a suitable candidate in treatment of these patients. Combination therapy can be more effective than monotherapy to cure this disease. Prevention necessitates to be performed by isolation of suspected people and home quarantine as well as taking care to infected people with mild or strict disease at hospitals. As the outbreak of SARS-CoV-2 has accelerated, developing effective therapy is an urgent requirement to battle the virus and prevent further pandemic. In this manuscript we reviewed available information about SARS-CoV-2 and probable therapies for COVID-19 patients.

1. Introduction

Coronaviruses exist in the subfamily of Orthocoronavirinae, in the family of Coronaviridae, the order Nidovirales, and realm Riboviria [1]. They are positive-sense single-stranded RNA (+ssRNA) viruses enclosed in a pleomorphic capsid with a helical symmetry [2]. Coronaviruses are one of the largest RNA viruses with the genome consisting of about 26 to 32 kilobases [3]. These viruses called “Corona” means “crown” in Latin, because there are characteristic crown-like spikes on their surfaces [4].

Coronaviruses are shared among birds and mammals, and trigger respiratory as well as intestinal infections in these creatures [5,6]. They were considered to cause mild infections in humans until the epidemic of severe acute respiratory syndrome (SARS) in 2002 in China were appeared [4,7-9]. Coronavirus 2019 (COVID-19) or severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is quickly distributed in December 2019 from its origin in Wuhan City of China throughout the world and created a pandemic [5,10]. Till August 4th 2020 around 18 million cases of coronavirus disease and 0.7 million deaths have been reported [11]. COVID-19 have transmitted to human from bats through unidentified animals [12]. Seven coronaviruses are photogenic in human but generally people get infected with four of them i.e. 229E, OC43, NL63, and HKU1. They commonly produce a respiratory infection vary from the normal common cold to severe diseases like Middle East Respiratory Syndrome (MERS), SARS and the recently revealed COVID-19 [1]. Since knowledge about this virus is promptly growing, readers are advised to be updated frequently [12].

We here review the current data about epidemiology and pathology of this virus till diagnosis and potential treatment options. It is necessary to caution readers that every hour new information about diagnose, clinical trials, and treatment strategies for COVID-19 is updating.

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2. Origin, transmission and pathogenesis of COVID-19

On 31st December 2019, China announced the epidemic to the World Health Organization (WHO) and the Huanan sea food market was sealed. On January 7th, the virus was recognized as a coronavirus with more than 95% similarity to the bat coronavirus and more than 70% homology with the SARS-CoV [12]. It is identified that SARS-CoV-2 originated from bats and transmitted to human by an uncertain intermediate animal. This intermediate animal is suspected to be Pangolins, palm civet or snakes [10,12]. When the virus infected intermediate mammals, it was transferred to the food market and spread there while obtaining further mutations before reached humans [12].

The coronavirus disease increased rapidly and some cases did not in contact with live animal market, indicating sustained human-to-human transmission of coronaviruses [13]. The first death was announced on 11th January 2020. The number of COVID-19 positive people continued to growth rapidly in China and amplified quickly in other countries [14-16]. To date, COVID-19 is spread worldwide and more than 214 countries and territories around the world and 2 international conveyance are infected. By 11th October 2020, 37,508,141 cases had been reported with 1,078,009 deaths and 28,148,081 recovered patients [15].

SARS-CoV-2 evades human respiratory system and enter to the lung mucosa. Then, it distributes among people via inhalation of aerosol particles and droplets formed through talking, sneezing or coughing [10,17]. In addition, people can be infected by contacting with contaminant surfaces and then rubbing the eyes, mouth and nose [12,16].

3. Structure and mechanism of action of SARS-CoV-2

The SARS-CoV-2 is about 100 to 160 nm with the genome of 30,000 nucleotides responsible to encode membrane, nucleocapsid, spike, and envelop proteins as well as several non-structural proteins (nsp) (Fig. 1). The lipid envelope encapsulates the nucleocapsid including nucleoprotein (N) and positive-sense single-strand RNA (+) SSRNA which let the virus to force human cells to produce virus particles. The N-protein binds to (+) SSRNA from its N-terminus and triggers viral transcription and replication. Membrane (M) protein, which is frequent on the surface of virus, has a pivotal role in assembly of SARS-CoV-2. The spike (S) glycoprotein is a transmembrane protein which comes outside the surface and regulate its attachment to the host cell receptors leads to entry of virus into the host cell [18]. The envelope (E) small protein composes the slight part of the virus and plays a crucial role in gathering of virus particles, interaction between virus and host cell, and penetrability of the host membrane [19]. Hemagglutinin-esterase (HE) is a dimer transmembrane glycoprotein that may have a role in virus entry. HE seems to be necessary for infection without having any role in viral replication [20]. Recent studies have been demonstrated that SARS-CoV-2 uses its spikes to attack the pulmonary tract’s cells. These viruses attach to their target cells by angiotensin-converting enzyme 2 (ACE2) and entry into the cells [21].

The mechanism of entry and production of SARS-CoV-2 in the host cell is depicted in Fig. 2. The virus binds to ACE2 receptors on the surface of human cell with its S-protein. The S-protein is cleaved by trypsin or furin proteases of the host cell and the mechanism of viral membrane fusion will be stimulated. Naturally, the virus enters into the cytoplasm of human cell by endocytosis and the mechanism of membrane fusion will be activated within endosomes [22]. Once, the virus releases from endosome to the cytoplasm, N-protein is started to degrade by proteasomes [23], and the (+) SSRNA is completely unconfined into the cytoplasm. Translation and replication of (+) SSRNA are arbitrated by the replication-transcription complex (RTC). The RTC encoded in viral (+) SSRNA and composed from nsp is supposed to provoke double membranes throughout the cytoplasm of the infected cell [24]. Following (+) SSRNA is translated to replicate proteins and these replicases apply the (+) SSRNA as a template to produce full-length negative-sense RNAs, which consequently use as templates in creating more genomes. SARS-CoV-2 structural proteins (i.e. S, E, and M) are manufactured in the cytoplasm following by translocation into the endoplasmic reticulum (ER), and then moving to ER-Golgi intermediate compartment (ERGIC) (Fig. 2) [25]. Furthermore, nucleocapsid is shaped in the cytoplasm by sheltering of (+) SSRNA with N-protein. Afterward, they combine inside the ERGIC membrane leads to self-assembly of novel virions. Lastly, these virions are distributed from contaminated cells to other cells by exocytosis. Meanwhile, the infected cell is dead due to the pressure of viral replication on ER. Taking into account that the exact mechanism of action for SARS-CoV-2 is quiet unidentified [20].

4. Symptoms and diagnosis of COVID-19

Generally, patients with COVID-19 disease experience similar symptoms of common cold and flu, whereas some of them never show any symptoms. Symptoms are varied from fever, sneezing, cough, and shortness of breath to throat pain, pneumonia, and acute respiratory distress syndrome (ARDS) [26]. In a group of patients, after a week the disease can lead to pneumonia, ARDS and death; because of the
tremendous increase of inflammatory cytokines such as IL2, IL7, IL10, IP10, GCSF, TNFα, MCP1 and MIP1A [27]. Overall, around 80% of COVID-19 patients represent mild symptoms, around 15% of cases are infected severely, and 5% of them are censoriously ill and may leads to Pneumonia [10,12]. Symptoms could develop in 2 to 14 days after exposure to coronavirus. However, on average, the incubation time is around 5 days [28,29].

Side effects and mortality are generally observed in old patients or patients with comorbid illnesses. Fatality rate in these patients is 50–75%; while this rate in adult patients is 4 to 11%. Overall, the fatality rate in COVID-19 patients is between 2 and 3% [12,15]. Severity of disease in infants, children and young people has also been stated to be considerably slighter than the adult patients. Rarely, multiorgan dysfunction and pneumonia in children as well as mild infection in the neonatal have been reported [30,31].

The standard method to diagnose COVID-19 is reverse transcription polymerase chain reaction (RT-PCR) from a nasopharyngeal or throat swab. Furthermore, chest computed tomography (CT) scan for pneumonia and identification of several symptoms can be applied for diagnosis [32].

5. Immune response to COVID-19

Once the virus enters the host cell, the immune system of the host distinguishes the virus, inducing the innate and adaptive immune responses. Immune cells, particularly Toll-like receptors (TLR) 3, 7, and 8, recognize the virus using pathogen recognition receptors (PRRs) followed by improved interferon (IFN) production. During SARS-CoV and MERS-CoV infection, the activity of host innate immune cells is reduced by their non-structural proteins, leads to change in cytokine production [33–35]. Humoral immune response to SARS-CoV-2 is similar to other coronaviruses, including the IgM and IgG production. B cells prompt immune response against the N-protein at the beginning of COVID-19 infection, where as antibodies against S-protein can be identified after 4 to 8 days from the preliminary symptoms [36,37]. N-protein is smaller and more immunogenic than S-protein, and as it is unglycosylated N-specific neutralizing antibodies are produced at an early phase of acute disease [38]. SARS-CoV-specific antibodies including IgM, IgA, and IgG were identified in patients after the appearance of symptoms at several time points. IgM and IgA were produced after 5 days, and IgG after 14 days of initial symptoms [39]. In addition, IgG was preserved for a longer period than IgM which was started to reduce after 3 months [40,41]. In a study on 16 SARS-CoV-2 patients, IgG against S glycoprotein receptor binding domain (S-RBD) was recognized in all cases, while anti-S-RBD IgM and anti-N-protein IgG were identified in 15 patients and anti-N-protein IgM in 14 patients [42]. A kinetic study on SARS-CoV-2 patients showed that IgM and IgG produced in COVID-19 patients could not cross-react with other coronaviruses except SARS-CoV. Another kinetic study reported the higher IgM and IgG titers in severe COVID-19 patients. Furthermore, it has been observed that patients with feeble IgG responses had upper viral clearance than robust responders. This finding proposes that strong antibody response results in severe disease, where as weak antibody response accompanying the virus removal [43].

Not only neutralizing antibodies are useful in defense against viruses, but also non-neutralizing antibodies can help APCs and other immune cells. Formerly remaining SARS-CoV antibodies may support the viral contagion in Fc receptor (FcR)-expressing cells [44]. The entry of virus
through ACE2-independent pathway does not lead to viral replication; somewhat, viral flaking by macrophages augments tissue damage by myeloid cell stimulation. This viral entry via non-neutralizing antibody followed by abnormal stimulation of immune cells is entitled antibody-dependent enhancement (ADE) [44,45]. ADE has been detected in numerous viral infections, such as MERS and SARS. In the case of MERS, a neutralizing antibody directing RBD to enter into the host cell through dipeptidyl peptidase 4 (DPP4) pathway. While SARS viruses can enter into the FcR-expressing cell via ADE using anti-S antibodies were observed to be involved in ADE to gain entry into FcR-expressing cells [46], while in MERS, a neutralizing monoclonal antibody targeting RBD helped this virus to entry through the DPP4 pathway [47].

Overall, the immunopathology of COVID-19 is almost similar in MERS and SARS infections. Current studies have shown that elevated cytokine levels (e.g. TNF-\(\alpha\), IL-6, and IL-10) and lymphopenia related to the severity of COVID-19 infection [13]. Moreover, along with the diminished number of T cells, the remaining T cells exhibits dysfunction [48]. In severe COVID-19 cases, this dysfunctional immunity can prime a cytokine storm, leading to enhanced respiratory pathology and pulmonary pain as well as a elevated risk of poor clinical results and death. Thus, using antiviral drugs alone might not be enough to inhibit the distressing cytokine storm and respiratory devastation in COVID-19 patients.

Further investigation is required to understand the exact mechanism underlying the viral attack to the host cells and dysregulation of the immune system in COVID-19 patients to be able to develop efficient vaccines and and treatment strategies [49].

6. Elevated cytokines in COVID-19

In a study performed on cytokine profile of severe COVID-19 patients, meaningful promotion of cytokines such as IFN-\(\gamma\), IL-1\(\beta\), IL-1ra, MCP-1, MCP-3, and IP-10 were detected in severe COVID-19 infections. Furthermore, IFN-\(\gamma\), TNF-\(\alpha\), IL-2, and IL-1\(\beta\) from T helper-1 cells as well as IL-4, IL-10 produced by T helper-2 cells were observed concurrently [13]. The number of CD4 and CD8 molecules and lymphocytes were negatively associated with cytokine secretion, representing a potential correlation between adaptive immunity and cytokine storm. In mild COVID-19 cases, the number of lymphocytes regularly diminished to its normal level till be undetectable. In acute COVID-19 infections, lymphocytes boosting was not accompanied by cytokine storm [50]. This may be because of viral clearance by a cellular immunity at the early stages, and cytokine inhibition by innate immunity leads to disease improvement.

In a study on COVID-19 patients, the insistent production of GM-CSF and IL-6 has been identified represented the pathogenic effect of innate immunity [51]. In another study, the substantial increase was observed for IFN-\(\alpha\). Type I IFNs stimulating pathway and interferon-stimulated gene (ISGs) were both induced; however, ISGs expression was not observed in PMBCs, signifying the pivotal role of pDCs in production of type I IFNs [52]. It has been demonstrated that type I IFNs positively associated with disease harshness, which was not observed in SARS infection, as defeated type I IFN-signalling was negatively related to fatal SARS. All together, these investigations showed that type I IFNs might organize an unbalanced immune reaction leading to COVID-19 worsening [51].

Inflammation is a critical reaction of the immune system to eradicate infections in response to pathogens. The pathogens then regulate the employment of activated immune cells and finally refurbishment of homeostasis and tissue healing. However, SARS-CoV-2 stimulates extreme and sustained cytokine/chemokine responses in several patients called cytokine storm [53].

In a study on acute COVID-19 patients, it has been shown that cytokine storm can consequently dysregulate inflammation leads to disease deterioration [27]. Cytokine storm induces a negative effect rather than having a positive outcome in the host. For instance, cytokine storm causes multiple organ dysfunction syndrome (MODS) or ARDS leads to mortality. Cytokines and chemokines induced by macrophages (i.e., TNF-\(\alpha\), IL-6, IL-7, CCL-3/MIP-1\(\alpha\), CCL-2/MCP-1) in COVID-19 patients were similar to what was detected in cytokine releasing syndromes (CRS) including macrophage activation syndrome (MAS) and hemophagocytic lymphohistocytosis (HLH) [54].

It has been demonstrated that during COVID-19 infection, 38 cytokines were enhanced in plasma of patients. Fifteen cytokines related to lung damage were IFN-\(\alpha\), IFN-\(\gamma\), IL-1ra, IL-1\(\beta\), IP-10, HGF, M-CSF, PDDF-BB, G-CSF, IL-2, IL-4, IL-7, IL-10, IL-12, and IL-17. These cytokines are potential biomarkers to predict the severity of disease. Appropriate management of the cytokine storm at the beginning stage is the main step to achieve success in the treatment of COVID-19 patients and decreasing the death rate [53].

6.1. IFNs secretion and function

Immunological characteristics of MERS-CoV, SARS-CoV, and SARS-CoV-2 infections are different among patients. The IFN expression is various among MARS-CoV, SARS-CoV and SARS-CoV-2 infections. For instance, SARS-CoV-2 is less potent to induce type I IFNs in animal models and in vitro than SARS-CoV and other lung viruses, which may indicate the significant role of IFNs in COVID-19 [55–57]. In COVID-19 patients, despite limited number of immune cells like pDCs produced type I IFNs, it was sufficient to stimulate ISGs. SARS-CoV-2 stimulated lower level of type I IFNs in comparison with SARS-CoV, although it replicated more effective in human respiratory tissues [58–61]. A feeble type I IFN expression might be a sign of other coronavirus diseases such as MERS-CoV [62], the mouse hepatitis virus (MHV) or the porcine epidemic diarrhea virus (PEDV) [63,64]. Certainly, coronaviruses have several strategies to produce type I IFNs and hide or escape from immune system of the host [55].

In MERS-CoV lower IFN active antagonism was observed rather than IFN aggression in SARS-CoV, which may lead to elevated sensitivity to anti-viral effect of IFNs [65]. MERS-CoV similar to SARS-CoV could down-regulate ISG responses [66,67]. Furthermore, delayed and reduced expression of type I IFNs were detected in both infections [68]. However, contrary to MERS infection in SARS atypical IFN effect was observed and the lack of type I IFNs enhanced clinical outcome instead of inducing pulmonary immunopathology [39]. Early injection of type I IFNs in infected mice could rescue them from death despite the down-regulation of cytokine-associated genes. IFN signaling not only modulate anti-inflammatory response during the acute stage of infection, but also regulate adaptive immune activity in severe MERS infection [69].

7. Treatment strategies for COVID-19

As COVID-19 pandemic is escalating every day, finding an effective therapy is urgent. Every day, a new strategy for COVID-19 treatment is introduced. There is no assured treatment for COVID-19 yet. However, treatment emphases on supportive care, symptomatic therapy, oxygen therapy and respiratory support, fluids, antiviral drugs, and boost the immune system of patients. Most of these drugs have represented some benefits in COVID-19 therapies; however, it is not unexpected to observe failure in future (11).

7.1. Supportive treatment

All possible patients for COVID-19 require resting and supportive treatment, confirming sufficient water intake and calorie to diminish the possibility of dehydration. Water, electrolyte and osmotic balance need to sustain in company with the of monitoring oxygen saturation, blood count, urine test, C-reactive protein, myocardial enzyme range, kidney and liver function, and all health warning signs. Chest imaging and arterial blood gas need to be incessantly tested when required [10].
7.2. Symptomatic therapy

Sever cases with high fever need to be controlled continuously. Warm bath and antipyretic medications should be used to decrease the high fever in patients with the temperature more than 38.5°C. Common antipyretic drugs include ibuprofen and paracetamol (acetaminophen) are administered orally, 5–10 mg/kg and 10–15 mg/kg every time, respectively. Sedatives may also be administered in case of a seizure in children [10,70].

7.3. Oxygen therapy

Inhaling of oxygen is applied in more severe cases. Hypoxia can occur when the virus invading the lungs. Oxygen therapy using oxygen mask and nasal catheter should be rapidly supplied to these patients. In emergency medical conditions, invasive or non-invasive mechanical ventilation (NIV) need to be provided for the patients [71].

7.4. Respiratory and circulation support

Children who cannot endure NIV or can tolerate NIV for around 2 h with no progress, require invasive ventilation (IV) immediately. The IV should acquire low tidal volume ventilation (LTTV) to protect lung and diminish ventilator-associated lung injury (VALI). In addition, lung recruitment, prone-position ventilation, or extracorporeal membrane oxygenation (ECMO) may be required.

In accordance with fluid replacement, monitor hemodynamics, refine microcirculation, and employ vasoactive agents if necessary [70].

7.5. Therapeutics

Several therapies are applied in COVID-19 patients, despite the safety and efficacy of some of them are questionable [72]. The function, positive and negative effects of antiviral agents including Arbidol, Foscarnet, Remdesivir, Ribavirin, Favipiravir, Galidesivir, Camostat, Umifenovir, Darunavir, Lopinavir/ritonavir, and Oseltamivir, antibody and stem cell therapies as well as other medicines are depicted in Table 1.

8. Interferons as a potential treatment for COVID-19

IFNs are natural broad-spectrum antiviral and anti-inflammatory proteins which bind to their receptors on the surface of different cells and induce JAK-STAT signaling pathway, followed by transcription of several proteins to hinder type I IFNs signaling cascades. However, current studies have confirmed that IFNs are expressed during SARS-CoV-2 infection. Moreover, STAT1 translocation following by ISGs activation could be determined in the infected lungs by SARS-CoV. In parallel with these investigation, plasmacytoid dendritic cells (pDCs) produce IFNs during SARS-CoV infection in vitro. These observations approve the essential role of IFNs throughout viral infections [132]. A study on SARS-CoV showed a successful type I IFN therapy [133], where as another research on larger group hardly revealed any positive effect [134].

Studies in mouse models represented less tissue destruction if the type III IFN response included in the immune response against respiratory infection.

As the receptors of type I IFN (IFNAR) are expressed on the surface of all cells, the injection of type I IFNs may have intense systemic adverse effects. Contrary, the receptor complex of type III IFNs (IFN-λ), which contains IFNLR1 and IL10R2 subunits, is expressed only on epithelial cells and a limited subset of immune cells such as neutrophils. Thus, administration of type III IFNs at an early phase of COVID-19 disease would leads to localized antiviral reactivities with fewer inflammation and adverse effects compare to the systemic immune response of type I IFNs [135].

Early implementation of IFNs has special benefits in lessening virus counts and clinical symptoms of COVID-19. However, it rarely reduces fatality rates [136,137]. It has also been proposed that IFNs were effective in some patients [138,139]. Subtype variety could be one of the reason of contradictions among studies. Further details about each type of IFNs are described is separate sections below. Table 2 depicted some principal information about IFNs.

8.1. Interferon α (IFN-α)

IFN-α can decrease the number of viruses in the early phase of COVID-19 leads to relieve symptoms and shorten disease duration. Clinical studies with IFN-α in treatment of patients with SARS, pneumonia, bronchiolitis, sever URTI, hand foot mouth disease (HFMD), and other viral diseases in children, represented the positive effect of this product.

It is proposed that IFN-α nebulization needs to be administrated 200,000–400,000 IU/kg or 2–4 μg/kg in 2 mL sterile water, 2 times a day for 5–7 days. The high-risk peoples who are in contact with infected COVID-19 patients or patients in the early stage with only URTI require to use IFN-α2b spray. IFN-α2b should sprays 1–2 times on each side of the nose, 8–10 times on the throat, with a dosage of 8000 IU per injection, every 1–2 h, for a period of 5–7 days [70,139]. Interestingly, IFN-α2b therapy could reduce the period of viral flaking. Declining markers of intense inflammation including IL-6 and CRP related to this reduced viral flaking. This finding representing the probability of IFN-α2b in treating COVID-19 disease [148].

In a clinical trial on 446 patients with SARS-CoV-2 infection in Hubei, China has been represented that early usage of IFN-α2b could diminish in-hospital death compare to patients who didn’t received IFN-α2b. However, IFN-α2b administrated in late stage raised mortality. Among survived patients, early administration of IFN-α2b could not improve CT scan or hospital release, while late IFN-α2b causes postponed recovery. Therefore, IFN-α2b administrated throughout the early phase of COVID-19 disease is associated with promising clinical outcomes [149].

8.2. Interferon beta (IFN-β)

8.2.1. Interferon beta-1a (IFN-β-1a)

IFN-β-1a has been demonstrated to be beneficial in treating viral diseases such as hepatitis [150] and SARS-CoV [131,151–153]. Because of the high similarity of SARS-CoV with SARS-CoV-2, IFN-β-1a was added to the antiviral drugs using in COVID-19 patients. SARS-CoV-2 enters the cell by binding to ACE2 receptor, and its expression is
| Therapeutic agent | Main function | Target | Status | Adverse effect | Advantage | References |
|-------------------|---------------|--------|--------|---------------|-----------|------------|
| **Antiviral drugs** | | | | | | |
| Arbidol | blocks trimerization of the spike glycoprotein | spike glycoprotein | approved in Russia and China for treatment of SARS, influenza, and Zika virus | nausea, diarrhoea, dizziness and elevated serum transaminase | few COVID-19 patients showed efficient recovery after receiving arbidol treatment | [72,74,79,80] |
| Foscarnet | acts like the pyrophosphate molecule by binding to the viral DNA polymerase and prohibiting the elongation of DNA chain | viral DNA polymerase | approved for the treatment of HIV/AIDS-related cytomegalovirus (CMV) infections and herpes | anaemia, nausea, vomiting, genital, ulceration electrolyte derangements, reduced renal function, kidney injury | used to treat infected patients with Herpesviridae family, prevents certain viruses from multiplying and inhibit coronavirus infection | [75,81] |
| Remdesivir | nucleoside analog and inhibits viral RNA-synthesis | viral RNA polymerase | experimental Ebola treatment, limited efficacy against SARS | it was authorised in USA and Japan based on phase 3 trial results, but no benefits in severe COVID-19 patients in Chinese clinical trial were observed, no clinical trials have been submitted in outpatients | moderate success in adult hospitalized Covid-19 patients and indicated reduction of respiratory infection, improved recovery and death rate in patients with severe COVID-19 | [76,82] |
| Ribavirin | nucleoside analog and inhibits viral RNA-synthesis | viral RNA polymerase | limited efficacy against SARS | no significant adverse effects, but further studies is required about efficacy and safety | in patients with severe COVID-19 it can not avoid coronavirus replication or cell-to-cell transmission, neither associated with an improved death rate, nor with enhanced negative conversion time for SARS-CoV-2 test | [77,83] |
| Favipiravir | nucleoside analog and inhibits viral RNA polymerase | anti-influenza treatment | good safety profile, minor adverse effects including hyperuricemia, teratogenicity diarrhea, reduced neutrophil count and transaminitis | inhibits replication of influenza A and B, and other life-threatening pathogens such as Ebola virus, Lassa virus, approved for emergency use for the treatment of mild to moderate COVID-19 disease, shortening viral shedding and reduces viral transmission in vitro, it displayed broad-spectrum antiviral activity against various negative- and positive-sense RNA viruses including coronaviruses, filoviruses, and arenaviruses | test | [84-87] |
| Galidesivir | nucleoside analog and inhibits viral RNA-synthesis | viral RNA polymerase | ongoing phase 1 clinical trial to evaluate its pharmacokinetics, safety, and antiviral activity in hospitalized adult patients with either yellow fever or COVID-19 | not available, primary outcomes with echocardiogram changes, emergent and serious adverse effects | in vitro study on COVID-19 showed it reduces the infection of Calu-3 lung cells, inhibits COVID-19 infection of lung cells by blocking the virus-activating host cell protease TMPRSS2 | [88,89] |
| Camostat | antiviral entry inhibitors by inhibiting serine proteases | trypsin, prostatin, matriptase and plasma kallikrein of the host cells | approved for the treatment of chronic pancreatitis, postoperative reflux esophagitis, cancer, viral infections, fibrosis in liver or kidney disease, for COVID-19 clinical trials | mild adverse effects such as pruritus, increased thirst and appetite, and lightheadedness | it reduces the infection of Calu-3 lung cells, inhibits COVID-19 infection of lung cells by blocking the virus-activating host cell protease TMPRSS2 | [90,91] |
| Umifenovir | inhibits the fusion of virus with host cells, virus entry and synthesis of viral RNA, stimulate host immunity | prevents contact between the virus and target host cells | licensed for prophylaxis and treatment of influenza, for COVID-19 clinical trials 4 is planned | safe in COVID-19 patients | in vitro with antiviral effects in early stage of viral replication, in vivo without improving patient-important outcomes in COVID-19 patients | [92,93] |
| Darunavir | inhibits cutting of proteins and viral replication by | viral protease | clinical trials phase 3 is ongoing to evaluate its efficacy and safety | few adverse reactions like diarrhea and dyslipidemia | in mild COVID-19 patients did not increase the proportion of negative conversion | [94] |

(continued on next page)
| Therapeutic agent | Main function | Target | Status | Adverse effect | Advantage | References |
|-------------------|---------------|--------|--------|----------------|-----------|------------|
| Lopinavir/ Ritonavir | inhibits cutting of viral protease and viral replication by prohibiting viral protease | viral protease | treatment of COVID-19 pneumonia in clinical trial phase 3, approved in China for COVID-19 patients with pneumonia and severe complications | nausea, vomiting, diarrhea, QTc prolongation, hepatotoxicity, its safety and efficacy is questionable | inhibits the 3Cpro and the Plpro enzymes of SARS-CoV-2 in vitro, successes in recovery of a low number of COVID-19 patients | [70,72,95] |
| Oseltamivir | antiviral exit inhibitor, inhibits the spread of the virus in the human body | neuraminidase on the surface of the virus | approved for the treatment of influenza A, B, and HIV patients, without antiviral effect on coronavirus, but may be used in combination therapy | nausea, vomiting, epilepsy, elevated liver enzymes, and arrhythmias | its clinical use neither improves the patients’ symptoms nor reduces disease progression, so it is not effective for COVID-19 patients | [78,96,97] |
| Antibody therapy Sarilumab (Kevzara) | inflammatory signal blockers | anti-IL6 receptor | approved for the treatment of adults with moderately to severely active rheumatoid arthritis, in clinical studies phase 4 for critically ill patients with COVID-19 | serious adverse events in 26-29% of Kevzara patients, leading to death was approximately 10% | no benefit for critical or ventilated COVID-19 Patients | [98,99] |
| Tocilizumab (Actemra) | inflammatory signal blockers | anti-IL6 ligand | higher prevalence of infection, data from ongoing randomised clinical trials are required to know the side effects | decreases the cytokine storm syndrome associated with severe COVID-19, reduces invasive mechanical ventilation or mortality rate in patients with severe COVID-19 pneumonia | reduces viral load and improve symptoms in non-hospitalized COVID-19 patients | [100-102] |
| REGN-COV2 | hindered infectivity, and prevented emergence of viral resistant mutants | viral spike protein | ongoing clinical trials phase 4 for the treatment of hospitalized and non-hospitalized COVID-19 patients | no unexpected safety findings and no deaths in the trials | reduces viral load and improve symptoms in non-hospitalized COVID-19 patients | [103,104] |
| Stem cell therapy Mesenchymal stem cells (MSC) therapy | immune regulatory, anti-inflammatory, antiapoptotic | host tissue, through mitochondrial transfer and direct interactions between cells | approved for the treatment of ARDS, in China used to treat severe COVID-19 pneumonia-induced ALI or ARDS, few clinical data have shown MSCs can considerably improve lung injury in COVID-19 patients | no serious adverse events | fights fibrosis, inhibits overactivation of the immune system and the production of pro-inflammatory cytokines including IFN-γ, IL-1, IL-6, IL-12, and TNF-α, decreases cytokine storms, induces the production of keratinocyte growth factor (KGF), IL-10, and vascular endothelial growth (VEGF), clears the fluid and microorganisms of pulmonary alveolus, inhibits ARDS and organ failure, promotes endogenous repair, impairs lung tissues in COVID-19 patients | [105-109] |
| Other medicines Flavonoids | antioxidant, anti-inflammatory and antiviral agent | SARS 3CL protease | use in liver diseases and those associated with vascular permeability and capillary fragility, one clinical trial showed its effectiveness in improving anti-coronavirus prophylaxis and treating COVID-19 patients | lack of systemic toxicity and no significant adverse reactions | reduce viral protein and RNA synthesis, prevent the virally induced shut-down of the host protein synthesis, reduce inflammation, inhibit the proteolytic activity of SARS-CoV 3CL, inhibit both TMPRSS2 and Furin which cleave | [110-112] |
| Therapeutic agent | Main function | Target | Status | Adverse effect | Advantage | References |
|-------------------|---------------|--------|--------|----------------|-----------|------------|
| Cinanserin | antiserotonergic | SARS 3CL protease | inhibitor of the 3C-like protease of SARS-CoV and HCoV-229E, reduces viral replication | in dogs hepatotoxicity, in humans no remarkable adverse effects | the SARS-CoV-2 spike protein facilitating SARS-CoV-2 infectivity prevents SARS-CoV replication by binding and inhibiting 3CL protease with lowered antiserotonin activity and toxicity | [86,113] |
| Heparinoids | anticoagulant, anti-inflammatory, immunomodulatory, anti-viral, anti-complement activity | viral binding protein | reduces swelling and healing, approved for the treatment of heparinoid, bruises, phlebitis, haematomas, varicose veins, piles, itchy bottom, ongoing clinical trials for COVID-19 hospitalized cases | rarely rash, a serious allergic reaction (anaphylaxis) to heparinoid | heparin binding proteins with pleiotropic role and anticoagulant effect in COVID-19 patients, exerts ancillary effects during COVID19 and develops the outcome of the infection beneficial in patients with ALL or ARDS as a complication after COVID-19, disables viral entry into the heart and lungs, ACE2 receptor blockade, decreases inflammation, no improvement in morbidity or mortality rate | [114,115] |
| ACE-I | anti-hypertensives | viral proteases | approved for the treatment of high blood pressure, heart failure, heart attacks, coronary artery disease, diabetes, certain chronic kidney diseases, scleroderma, may help against the coronavirus | not harmful, retrograde feedback mechanism, by which ACE2 receptors are upregulated | increases susceptibility to SARS CoV-2 and the likelihood of severe COVID-19 illness, potential benefits on patients with other viral lung infections | [116,117] |
| Angiotensin receptor blockers (ARBs) | anti-hypertensives | viral proteases | approved for the treatment of heart failure, hypertension coronary, kidney disease, artery disease, long-term therapy with ARBs reduces the risk of poor outcomes from COVID-19 | headache, fainting,dizziness, fatigue,respiratory symptoms, leg swelling, vomiting, diarrhea, back pain | increases susceptibility to SARS CoV-2 and the likelihood of severe COVID-19 illness, potential benefits on patients with other viral lung infections | [118-120] |
| Sacubitril/valsartan | anti-hypertensives | viral proteases | approved for the treatment of heart failure, have therapeutic efficacy with antifibrotic and anti-inflammatory effects in severe stages of COVID-19, clinical trials are required to be able to validate its positive effect in COVID-19 patients | hypotension, hyperkalemia, increased serum creatinine, renal failure, acute kidney injury, syndrome | maximize the anti-inflammatory effects of an augmented natriuretic peptide system, covers the effects of angiotensin II, decreases profibrotic and proinflammatory activities, increases N-terminal pro hormone BNP (NT-proBNP) in patients with COVID-19 | [70,121,122] |
| Interleukins (ILs) antagonists | anti-inflammatory, | viral diffusion | approved to treat rheumatoid arthritis, cryopyrin-associated periodic syndromes, neonatal-onset multisystem inflammatory disease, for COVID-19 patients IL-1 inhibitors (anakinra) showed improvement outcomes, IL-6 inhibitor is in ongoing clinical trials, but it is used in China and Italy as a potential therapy | not associated with any significant safety concerns, no pulmonary adverse events, organ damage or other serious adverse effects | anti-inflammatory properties, improves COVID-19 patient’s conditions | [123-125] |
| Glucocorticoids (GCs) | anti-inflammatory, regulatory of gene transcription | binds to the GC receptor (GR) of cells | approved for the treatment of various pulmonary inflammatory diseases, autoimmune diseases, cancer, considered for patients with rapidly | adverse reactions such as diabetes, coinfections, susceptibility to infection, adrenal suppression, covering clinical signs, disturbed carbohydrate metabolism, heart failure, muscle weakness, cataract, hypertension, | modulates genes controlling the metabolism, development, and immune response, reduces the duration of fever, but not duration | [126-128] |

(continued on next page)
began leads to induction of innate immune system [60,131,154]. Generally, IFNs are produced after viral infection to hinder the infection. However, several studies have shown that despite its effectiveness in restraining the SARS-CoV replication, IFNs expression was reduced during infection with SARS-CoV [60]. Recent studies represented that IFN-β-1a augmented the rate of discharge on day 14 and declined 28-day death.

Table 2
Summary of the positive and negative effects of different IFN in treatment of several diseases.

| Type | Name | Cell producer | Function | Side effects | Treatment | Advantage | References |
|------|------|---------------|----------|--------------|-----------|-----------|------------|
| I    | IFN-α | all immune cells | proinflammatory response/kill infected cells/neutralize the virus | significant systemic side effects including flu-like symptoms/nausea/fatigue/weight loss/hematological toxicities/ elevated transaminases/psychiatric problems (depression and suicidal ideation) | chronic viral infections (e.g. hepatitis) | COVID-19 therapy relieve symptoms/shorten disease duration/reduce the period of viral flaking |
| I    | IFN-β | all immune cells | proinflammatory response/kill infected cells/neutralize the virus | significant systemic side effects including hypersensitivity reaction/neuropsychiatric issues/administration-associated problems | autoimmune diseases (e.g. multiple sclerosis) | enhanced ARDS difficulties/augmented discharge rate/inhibit viral replication/upregulate lung antiviral defense/treat LRTI illness/improve recovery/declined mortality rate |
| II   | IFN-γ | all immune cells | proinflammatory response/kill infected cells/neutralize the virus/immune regulator/induces regulatory T cells and antigen-specific regulatory B cells | few side effects including flu-like syndrome/headache/fever/abdominal pain | a bone disorder/an immune deficiency syndrome/allergic diseases/cancers/infections/chronic granulomatous disease/osteoporosis/tuberculosis/hepatitis/scleroderma | modulating immunity/anti-viral immunity in the respiratory tract/induces several antiviral genes in epithelial cells/control of viral infections in epithelial cells of both respiratory and gastrointestinal tracts/proinflammatory activity in the lungs |
| III  | IFN-λ | epithelial cells/limited subset of immune cells like plasmacytoid dendritic cells | less inflammatory response/reduce viral replication and diffusion/stimulate epithelial barrier stability/inhibit the recruitment of neutrophils | few side effects | Infections/autoimmune diseases/hepatitis | |

On 20th July 2020, Synairgen PLC announced positive results of phase II trial on the novel formulation of IFN-β-1a, called SNG001, in hospitalized 220 COVID-19 patients. SNG001 is a spray to deliver IFN-β-1a to the lungs via nebulization to treat LRTI caused by SARS-CoV-2 viruses. The patients with chronic obstructive pulmonary disease (COPD) or asthma inhaled SNG001 tolerated the drug very well and exhibited improved lung function and recovery rate as well as reduced breathlessness and mortality rate [158].

8.2.2. Interferon beta-1b (IFN-β-1b)

Recent study on IFN-β-1b depicted its potential in vitro to inhibit SARS-CoV and MERS-CoV. In another study, it also hindered SARS-CoV-2 virus effectively. Therefore, some guidelines suggest the subcutaneous administration of IFN-β-1b accompanied by other antiviral drugs. Recently, the efficacy of IFN-β-1b in COVID-19 patients with moderate to severe pneumonia who hospitalized between 23th February to 4th April 2020 was explored. Patients received 3 to 5 dosages of IFN-β-1b subcutaneously and endpoint of the study was in-hospital fatality. Patients who received IFN-β-1b were also receive lopinavir/ritonavir and hydroxychloroquine.

The total mortality rate was about 20% in patients who received IFN-β-1b compared to 27% of counterparts who did not use this drug. IFN-β-1b administration time in viral disease has been displayed its significance in successful therapy in mouse models. Although IFN-β-1b therapy reduced in-hospital mortality in patients because of the combination therapy in many patients, it is hard to assign effectiveness to any one drug [159]. In a recent retrospective study on COVID-19 patients with mild or moderate disease treated with IFN-β-1b,
despite small number of patients meaningful efficiency and no mortality were observed. Thus, this result confirms that IFN-β-1b is a potential therapeutic agents for SARS-CoV-2 [138].

Early enrolment to organize doses of IFN-β-1b is crucial; however it might be unrealistic as patients hardly present in hospital sooner than 7 days, when disease features usually worsen [160]. It was regularly displayed that IFNγ is more effective than IFNβ to hinder COVID-19 [161]. Among IFN-I subtypes, IFNβ-1a and –1b were the greatest effectiveness subtype in preventing COVID-19 patients [143]. This reality can be associated to the defensive function of IFNγ in the lung, preservation of endothelial barrier activity and increasing anti-inflammatory adenosine [141].

8.3. Interferon gamma (IFN-γ)

IFN-γ is an immunoregulatory protein with a broad-spectrum antiviral and antimicrobial functions which has influence on multiple cells and cellular activities [162,163]. It has been demonstrated that IFN-γ initiates its antiviral activity using cellular function at multiple stages [145]. At the beginning, IFN-γ binds to its receptor and subsequently induces several genes resulted in declining virus replication [164]. Otherwise, IFN-γ stimulates cytokine expression by activation of monocytes, macrophages, and T cells. Furthermore, it expands destruction of cytotoxic T lymphocyte (CTL) by inducing major histo-compatibility complex (MHC) class I, or granzyme B. In addition, it improves immune response by stimulation of MHC class II receptors [165]. Recent studies on treatment of coronavirus infection with IFN-γ represented its pivotal role in restricting virus replication and distribution inside the retina and protecting host cells throughout a retinal infection [145].

Current experimental studies demonstrate that IFN-γ production by retinal cellular infiltration is a critical function of an immune response accountable for noncytotoxic virus clearance from the retina [145]. There are some clinical protocols about dosage and treatment duration of IFN-γ. Hopefully, few adverse effects are detected for this available and cheap therapeutic. The safety of IFN-γ has already been approved but its efficacy needs to be confirmed. IFN-γ is recently suggested to be used in virus pandemics, particularly for endangered patients when exact therapeutics are not obtainable [144].

8.4. Interferon lambda (IFN-λ)

IFN-λ mainly stimulates epithelial cells and decreases the macrophage-mediated activity of IFN-α and β [166]. Furthermore, IFN-λ prohibit the employment of neutrophils to the location of inflammation [167]. MERS-CoV and SARS-CoV principally invade to alveolar epithelial cells (AEC). As IFN-λ induces several antiviral genes in epithelial cells, leading to antiviral activities, it can be a proper candidate for an effective treatment.

To date, the only available therapeutic IFN-λ in the market is pegylated IFN-λ1 (peg-IFN-λ1). In vitro, IFN-λ1 therapy represented efficacy against different viruses, including MERS-CoV and SARS-CoV-2 [140]. The key activity of IFN-λ1 is to hinder viral infection by inducing an antiviral response and, if infected, to reduce viral production and diffusion. In treatment of COVID-19, the lack of proinflammatory activity in the lungs is one of the significant benefits of IFN-λ compare to type I IFNs [140,166]. However, it needs to be determined if immune system is reactive to IFN-λ in COVID-19, as the immune cells impair inflammation. Additionally, it needs to be investigated that if antiproliferative effect of IFN-λ1 could hamper recovery procedures of epithelial cells and virus-induced apoptotic cell death [140].

Indeed, IFN-λ1 can induce an antiviral effect in cells with IFNλ-1 receptor 1 (IFNLR1). For COVID-19, it is uncertain whether alveolar endothelial cells or macrophages are effectively infected and supported viruses to not be available to IFN-λ antiviral function for absence of IFNLR1. Although IFN-λ may be more suitable than type I IFNs in anti-COVID-19 therapy, more studies are required to analyze probable negative effects of IFN-λ.

Even though not yet administrated in active COVID-19 infection, no improved lung infections have appeared in 3,000 patients who were preserved for 48 weeks with peg-IFN-λ1. Probable side effects might also be diminished by shorter treatment period [140].

There are many outstanding questions in relation to COVID-19 and IFN-λ, however it could be beneficial in this pandemic outbreak.

9. Potential combination therapy and clinical trials for COVID-19

A combination of IFN-α-2a with ribavirin postponed mortality rate [136] and displayed efficient outcomes in the rhesus macaque, but was questionable in human [141]. In China, the administration of 5 million U of IFNs twice a day accompanied with ribavirin in COVID-19 patients is recommended [141]. Administration of IFNβ with lopinavir/ritonavir enhanced pulmonary function without declining virus production or lung injury in COVID-19 infection [168]. In general, the combination of type I IFN with remdesivir, ribavirin, or lopinavir/ritonavir could elevate its efficacy in COVID-19 [168]. It might also be applicable to treat COVID-19 patients with type III IFN due to its shielding property in the pulmonary tract [169].

In clinical trials performed on 4th May 2020 on COVID-19 patients, treating with the combination of opinavir/ritonavir, chloroquine/ hydroxychloroquine, and plasma therapy were evaluated. Although protein and cell therapies have been shown promising results in different diseases, were not effective in COVID-19. The antiviral medications like remdesivir applies in moderate level in the therapeutic community. Outcomes of the effectiveness of remdesivir are discontinued by the manufacturer. Treatment with lopinavir/ritonavir hardly showed promising remedial effects. More investigations are still required to be able to clarify inconsistent data about the merits of using chloroquine and hydroxychloroquine in COVID-19 [170]. IFN-β-1 may consider as a safe and effective treatment against SARS-CoV-2 in the early phases of the disease [141]. Furthermore, combination therapy with IFN-γ and a type I IFN might stimulate synergistic effects. However, more comprehensive studies are required to demonstrate the ideal timing and dosage to avoid undesired outcomes. The azithromycin-hydroxychloroquine combination was also exhibited positive results in clinical trials against COVID-19; however further studies with more patients may be needed to approve these results.

In a randomised phase 2 clinical trial in COVID-19 patients, a triple combination of an injectable IFN-β-1b, with an oral nucleoside (ribavirin) and protease suppressor (lopinavir/ritonavir), administrated in 7 days of symptom beginning, was inhibited the flaking of SARS-CoV-2 [171].

Overall SARS-CoV-2 is more delicate to type I IFNs than other therapeutics. The data of IFN therapy against COVID-19 executed in China will be published in a near future. This data should reveal more accurate information about this therapy [141].

In conclusion, combination therapy with various drugs in different stages of this pandemic could be more efficient than monotherapy [172]. We hope the ongoing clinical trials scheduled to be finished in 2020, may assist us to find the most effective therapeutics to treat COVID-19 in this year.

10. Prevention

To date, there is no particular medicine or vaccine to abort symptoms efficiently and treat patients. Therefore, prevention is the only way to protect yourself from this virus by staying at home, covering your mouth when coughing, washing your hands often, keeping a safe distance from others and self-isolating for 14 days when you suspect to be infected [17].

Some virus characteristics make prevention problematic...
particularly, spreading from asymptomatic and even recovered people, various features of this disease, prolonged incubation time, the contamination even before initiation of symptoms, and extensive disease period. Not only infected cases, but also suspected people need to be quarantined at home. Indoor ventilation with sunlight is recommended to destruct the viruses [12,173].

Having strong immune system is the most vital defense against different diseases. People with healthy body and immune system could better fight with disease. When the immune system is droning, people need to strengthen their body potency. People should focus on their health with daily sport activities and nutrients that support and improve the length of their life in health. During COVID-19 pandemic, get sufficient sleep, sunlight and fresh air everyday [10]. In addition, people should escape from crowded and closed areas, postpone their trip to other places, wear a mask, and follow all hygiene rules. Especially older adults and people with any comorbidities should be more careful about these guidelines. There is a high risk of transmission of SARS-CoV-2 to healthcare workers which was happened in 21% of healthcare workers in 2002 [174]. Therefore, all interactions particularly healthcare workers need to be checked for progress of any COVID-19 symptoms. COVID-19 patients have to wear surgical masks and should be isolated and maintained in separate rooms. In hospital sometimes negative pressure rooms are used. Patients can leave the solution room when they have no fever for more than 3 days and have no positive molecular test from 1 sample in two repeated measurements [12,175]. In China, new regulations about trading of animals are introduced to inhibit viral transmission form animal to human or vice versa [32].

Furthermore, travel restrictions are extended from China to all over the world to test and isolate suspected passengers for COVID-19. Whether these regulations could slow down the viral distribution is not known [176].

11. Conclusions and future perspectives

COVID-19 outbreak has challenged the public health, medical and economic infrastructure of the world. This viral infection can reveal by fever or pneumonia. In passing time, we will know how this virus will influence our lives. The current mortality rate of COVID-19 infection based on the approved cases and fatalities is about 2%. There are several pulmonary supportive therapies besides antiviral drugs, these are mainly used in sever COVID-19 cases. However, the pathogenesis of the virus as well as immune deficiency of the host in acute patients need to be considered to balance the advantage and risk ratio before beginning therapy. The higher fatality rates in elder could be described by the developed IFN activities threshold. Varied IFN replications triggered by innate immune system in different ages could describe various mortality rates in children, adult and elderly. Although there are evidences about the effectiveness of IFN therapy in COVID-19 infections, the suitable doses and treatment duration is required to be evaluated in clinical trials. Furthermore, to hinder side effects due to IFN therapy, the signaling pathway and kinetics of different IFNs secreted in mild and severe COVID-19 infections need to be defined. Last but not least, understanding cellular objectives that can restrict or prohibit IFN-α associated inflammation is required to identify the probable application of IFN therapy. Investigation of the natural biology of IFNs response can lead to effective and safe antiviral therapies.

Combination therapy can support inequity of the immune reactions which may happen at the advanced phases of SARS-CoV-2 infection. As the disease progresses, the immune reactivities would lead to immunopathogenic responses due to cytokine storm in acute respiratory syndrome, signifying a necessity for moderating the immune function. Considering that this proposal needs additional further clinical evidences to be confirmed before a complete understanding. There are still several open questions that are uncertain about COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

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