Review

Potential role of interferons in treating COVID-19 patients

Mohadeseh Haji Abdolvahab [a], Shima Moradi-kalbolandi [a], Mohammad Zarei [b,c],
Deepanwita Bose [d,e], Keivan Majidzadeh-A [a], Leila Farahmand [a,*]

[a] Recombinant Proteins Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran 1517964311, Iran
[b] Department of Pathology & Laboratory Medicine, Center for Mitochondrial & Epigenomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA
[c] Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[d] Division of Infectious Diseases, Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA
[e] Harvard Medical School, Boston, MA, USA

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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 an 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.

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 envelop 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 replicase 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
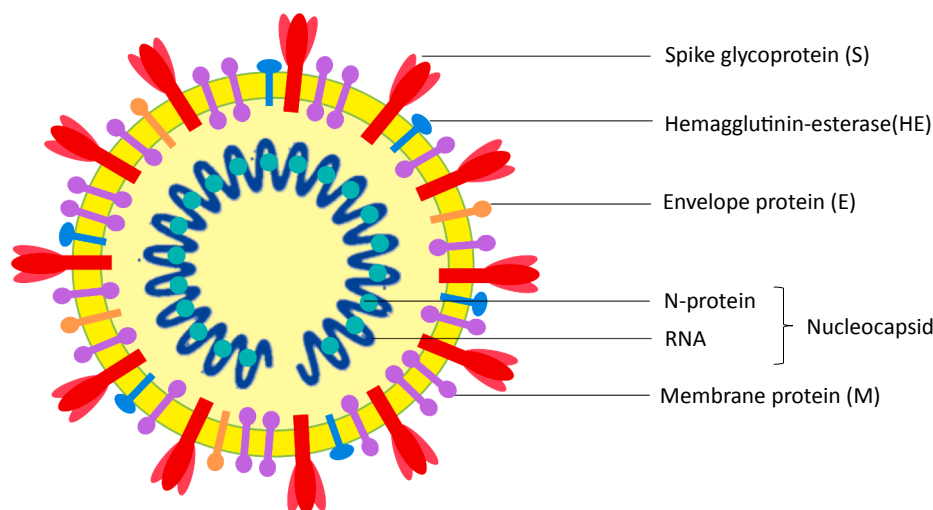

Fig. 1. Schematic representation of a SARS-CoV-2. The viral spike, membrane, hemagglutinin and envelope proteins are integrated in a phospholipid bilayer. The nucleoprotein is coupled with positive-sense single-strand RNA to form a nucleocapsid.
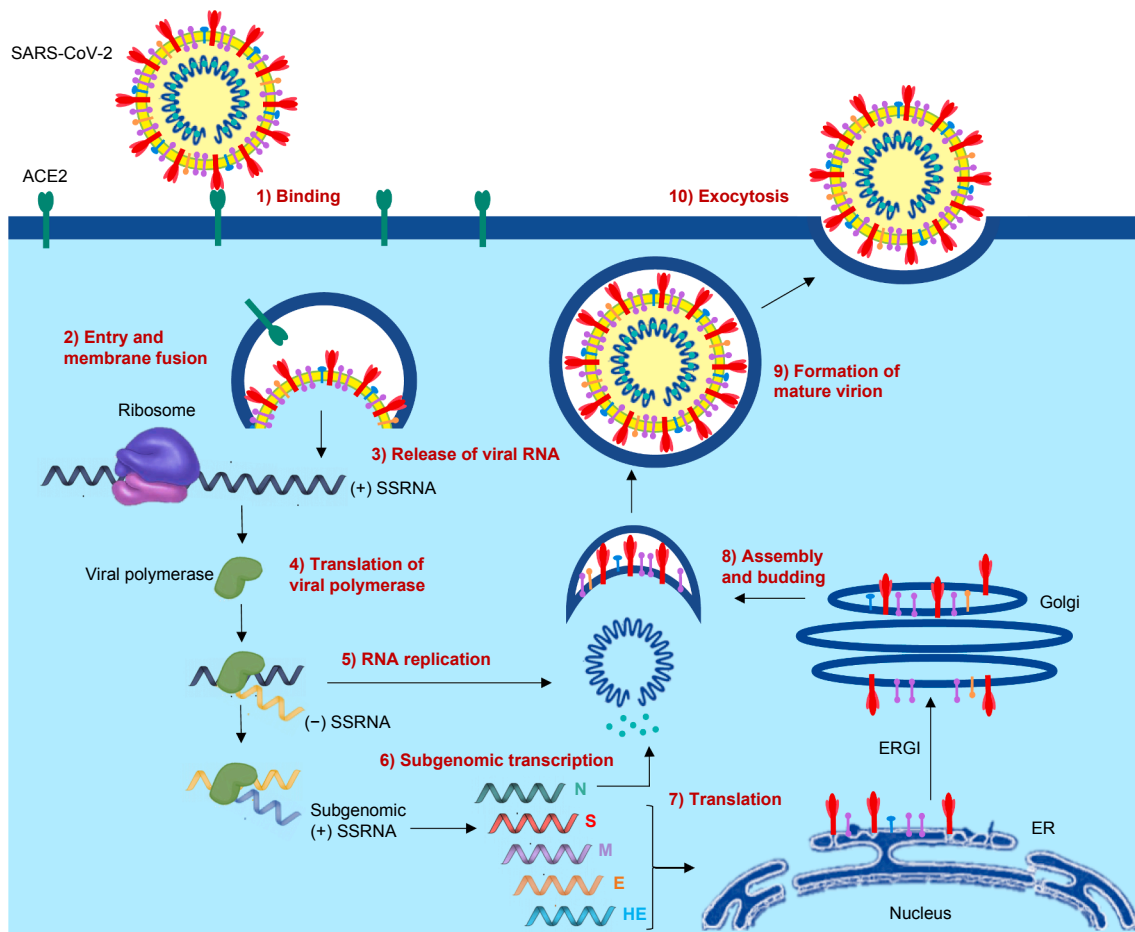
Fig. 2. The life cycle of SARS-CoV-2 from entry and viral replication to viral release in the human cell.

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 antibodis 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 glyco-protein 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 sever 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. TNFα, 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- γ, IL-1β, IL-1ra, MCP-1, MCP-3, and IP-10 were detected in sever COVID-19 infections. Furthermore, IFN- γ, TNF-α, IL-2, and IL-1β 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-α. Type I IFNs stimulating pathway and interferon-stimulated gene (ISGs) were both induced; however, ISGs expression was not observed in PCMBs, 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 defecated 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-α, IL-6, IL-7, CCL-3/MIP-1α, 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-α2, IFN-γ, IL1ra, IL-1α, IP-10, HGF, M-CSF, PDGF-BB, G-CSF, IL2, IL4, IL7, IL10, IL12, and IL17. 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 positive 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 administrated orally, 5–10 mg/kg and 10–15 mg/kg every time, respectively. Sedatives may also be administed 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 (LTVV) 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 therapeutics 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 IFN-stimulated genes (ISGs) including the antiviral enzyme RNase L, and the proinflammatory chemokine CXCL10 [60,129].

Type 1 IFNs are a group of cytokines including α, β, ω, ε and κ subtypes [130]. Type I IFNs are mainly generated by infected cells and immune cells. The single member of the type II IFNs named IFN-γ is also expressed by immune cells. Type III IFNs including 4 sub-members of IFN-λ are produced by restricted immune cells and epithelial cells.

Type I and II IFNs induce proinflammatory immune responses via the stimulation of several genes in immune cells. These activated immune cells either kill infected cells or deactivate viruses with antibodies. Others take up the viruses and parts of dead infected cells.

In contrast, type III IFNs act milder, because they typically decline viral replication in infected cells. Another special characteristic of type III IFNs is that they can support epithelial barrier constancy.

Promotion of the type I IFNs is necessary in restricting the proliferation of viruses within the host cells through the early stage of the disease. Type I IFNs have the antiviral activity which inhibit viral replication and can also orchestrate the innate and adaptive immune systems. Many viruses, including MERS-CoV and SARS-CoV, employ numerous strategies to attack the immune response regulated by type I IFNs [131].

SARS-CoV is a virus that induce intense lung damage, expressess 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 virus 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

Table 1

Current therapeutic agents for the treatment of COVID-19 patients.

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 Lassa viruses	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 Japanbased 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	[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	viral RNA polymerase	anti-infulanza 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	[84–87]
Galidesivir	nucleoside analog and inhibits viral RNA-synthesis	viral RNA polymerase	anti-Ebola treatment, 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*, it displayed broad-spectrum antiviral activity against various negative- and positive-sense RNA viruses including coronaviruses, filoviruses, and arenaviruses	[88,89]
Camostat	antiviral entry inhibitors by prohibiting serin protases	trypsin, prostasin, 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 4 is planned	mild adverse effects such as pruritus, increased thirst and appetite, and lightheadedness	*in vitro* study on COVID-19 showed it reduces the infection of Calu-3 lung cells, inhibits COVID-19 infection of lungcells 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 in the	few adverse reactions like diarrhea and dyslipidemia	in mild COVID-19 patients did not increase the proportion of negative conversion	[94]

Table 1 (*continued*)

Therapeutic agent	Main function	Target	Status	Adverse effect	Advantage	References
Lopinavir/ Ritonavir	prohibiting viral protease inhibits cutting of proteins and viral replication by prohibiting viral protease	viral protease	treatment of COVID-19 pneumonia in clinial trial phase 3, approved in China for COVID-19 patients with with pneumonia and severe complications	nausea, vomiting, diarrhea, QTc prolongationhepatotoxicity, its safety and efficacy is questionable	inhibits the 3CLpro 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	in clinical studies phase 4, approved in China for COVID-19 patients with severe complications	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	[100–102]
REGN-COV2	antibody cocktail 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]

Table 1 (*continued*)

Therapeutic agent	Main function	Target	Status	Adverse effect	Advantage	References
Cinanserin	antiserotoninergic	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 proteinase 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	[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	beneficial in patients with ALI 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	[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]

Table 1 (*continued*)

Therapeutic agent	Main function	Target	Status	Adverse effect	Advantage	References
			progressing COVID-19 infection	proximal glaucoma, avascular necrosis of bone	of hospitalization, mortality, lung inflammation absorption	

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	COVID-19 therapy
I	IFN-α	all immune cells/ infected cells [140]	proinflammatory response/ kill infected cells/neutralize the virus [135]	significant systemic side effects including flu-like symptoms/ nausea/fatigue/weight loss/ hematological toxicities/ elevated transaminases/ psychiatric problems (depression and suicidal ideation) [140]	chronic viral infections (e.g. hepatitis) [135,141]	relieve symptoms/shorten disease duration/reduce the period of viral flaking [135]
I	IFN-β	all immune cells/ infected cells [140]	proinflammatory response/ kill infected cells/neutralize the virus [142]	significant systemic side effects including hypersensitivity reaction/neuropsychiatric issues/administration-associated problems [140]	autoimmune diseases (e.g. multiple sclerosis) [141,143]	enhanced ARDS difficulties/ augmented discharge rate/ inhibit viral replication/ upregulate lung antiviral defense/treat LRT illness/ improve recovery/declined mortality rate [143]
II	IFN-γ	all immune cells [132,135]	proinflammatory response/ kill infected cells/neutralize the virus/immune regulator/ induces regulatory T cells and antigen-specific regulatory B cells [142,144]	few side effects including flu-like syndrome/headache/fever/ abdominal pain [144]	a bone disorder/an immune deficiency syndrome/allergic diseases/cancers/infections/ chronic granulomatous disease/osteoporosis/ tuberculosis/hepatitis/ scleroderma [144]	stimulates cytokine expression/ improves immune response/ expands destruction of CTL/ restricting virus replication and distribution [145]
III	IFN-λ	epithelial cells/ limited subset of immune cells like plasmacytoid dendritic cells [140,144]	less inflammatory response/ reduce viral replication and diffusion/stimulate epithelial barrier stability/inhibit the recruitment of neutrophils [135]	few side effects [140]	Infections/autoimmune diseases/hepatitis [140]	modulating immunity/antiviral 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 [146,147]

begun 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 enhanced ARDS difficulties [15]. Using IFN-β-1a significantly augmented the rate of discharge on day 14 and declined 28-day death. There is no published data regarding to the administration of IFN-β-1a in patients with acute COVID-19. However, early use of IFN-β-1a, in severely ill instinctively ventilated patients elevated survival rate. Late administration hardly exhibited any benefits. In this randomized clinical trial efficacy and safety of IFN-β-1a has been evaluated in patients with severe COVID-19 [155].

Notably, IFN-β-1a displayed potent antiviral function at dosages that have been accepted in animals due to its safety profiles [143]. The administration route is another critical aspect in treatment of COVID-19 patients with IFN-β-1a. Both intravenous (i.v.) and subcutaneous (s.c.) administration routes are considered to be suitable in therapy. However, because of various bioavailabilities of IFN-β-1a through i.v. and s.c. administrations this feature requires to be taken in to account more seriously, particularly in critically sick patients [156].

Side effects of IFN-β-1a were hypersensitivity reaction, neuropsychiatric issues, and injection-related problems which all were endurable and recovered through the follow-up medical care [155,157].

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 COVD-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 IFNβ is more effective than IFNα 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 IFNβ 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 histocompatibility 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 noncytolytic 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-λ therapy represented efficacy against different viruses, including MERS-CoV and SARS-CoV-2 [140]. The key activity of IFN-λ 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-λ could hamper recovery procedures of epithelial cells and virus-induced apoptotic cell death [140].

Indeed, IFN-λ can induce an antiviral effect in cells with IFN-λ 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-λs, 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 IFNα 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 solation 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-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 responses 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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References

[1] J. Cui, F. Li, Z.-L. Shi, Origin and evolution of pathogenic coronaviruses, Nat Rev Microbiol 17 (2019) 181–192, https://doi.org/10.1038/s41579-018-0118-9.

[2] P.J. Cherry, James; Demmler-Harrison, Gail J.; Kaplan, Sheldon L.; Steinbach, William J.; Hotez, Feigin and Cherry's Textbook of Pediatric Infectious Diseases., Elsevier Heal. Sci. (2017) PT6615.

[3] P.C.Y. Woo, Y. Huang, S.K.P. Lau, K.-Y. Yuen, Coronavirus genomics and bioinformatics analysis, Viruses. 2 (2010) 1804–1820. doi:10.3390/v2081803.

[4] R.A.M. Fouchier, T. Kuiken, M. Schutten, G. van Amerongen, G.J.J. van Doornum, B.G. van den Hoogen, M. Peiris, W. Lim, K. Stöhr, A.D.M.E. Osterhaus, Aetiology: Koch's postulates fulfilled for SARS virus., Nature. 423 (2003) 240. doi:10.1038/423240a.

[5] B.N. Fields, D.M. Knipe, P.M. Howley, Fields Virology, Fields Virol. (2013) 825–858.

[6] Andrew King Elliot Lefkowitz Michael J. Adams Eric B. Carstens, Virus Taxonomy- Ninth Report of the International Committee on Taxonomy of Viruses, 1st ed., 2011.

[7] N.S. Zhong, B.J. Zheng, Y.M. Li, L.L.M. Poon, Z.H. Xie, K.H. Chan, P.H. Li, S. Y. Tan, Q. Chang, J.P. Xie, X.Q. Liu, J. Xu, D.X. Li, K.Y. Yuen, J.S.M. Peiris, Y. Guan, Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003, The Lancet 362 (2003) 1353–1358, https://doi.org/10.1016/S0140-6736(03)14630-2.

[8] C. Drosten, S. Günther, W. Preiser, S. Van der Werf, H.R. Brodt, S. Becker, H. Rabenau, M. Panning, L. Kolesnikova, R.A.M. Fouchier, A. Berger, A.M. Burguière, J. Cinatl, M. Eickmann, N. Escriou, K. Grywna, S. Kramme, J.C. Manuguerra, S. Müller, V. Rickerts, M. Stürmer, S. Vieth, H.D. Klenk, A.D.M.E. Osterhaus, H. Schmitz, H.W. Doerr, Identification of a novel coronavirus in patients with severe acute respiratory syndrome, N. Engl. J. Med. 348 (2003) 1967–1976. doi:10.1056/NEJMoa030747.

[9] T.G. Ksiazek, D. Erdman, C.S. Goldsmith, S.R. Zaki, T. Peret, S. Emery, S. Tong, C. Urbani, J.A. Comer, W. Lim, P.E. Rollin, S.F. Dowell, A.-E. Ling, C.D. Humphrey, W.-J. Shieh, J. Guarner, C.D. Paddock, P. Rota, B. Fields, J.-Y. Yang, N. Cox, J.M. Hughes, J.W. LeDuc, W.J. Bellini, L.J. Anderson, A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome, N. Engl. J. Med. 348 (2003) 1953–1966. doi:10.1056/NEJMoa030781.

[10] S. Ahmad, A Review of COVID-19 (Coronavirus Disease-2019) Diagnosis, Treatments and Prevention, Eurasian J. Med. Oncol. 4 (2020) 116–125, https://doi.org/10.14744/ejmo.2020.90853.

[11] American Library Association, COVID-19 CORONAVIRUS PANDEMIC, Worldometer. (2020). https://www.worldometers.info/coronavirus/.

[12] T. Singhal, A Review of Coronavirus Disease-2019 (COVID-19), Indian J Pediatr 87 (2020) 281–286, https://doi.org/10.1007/s12098-020-03263-6.

[13] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang, B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (2020) (2019) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[14] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, R. Ren, K.S.M. Leung, E.H.Y. Lau, J.Y. Wong, X. Xing, N. Xiang, Y. Wu, C. Li, Q. Chen, D. Li, T. Liu, J. Zhao, M. Liu, W. Tu, C. Chen, L. Jin, R. Yang, Q. Wang, S. Zhou, R. Wang, H. Liu, Y. Luo, Y. Liu, G. Shao, H. Li, Z. Tao, Y. Yang, Z. Deng, B. Liu, Z. Ma, Y. Zhang, G. Shi, T.T.Y. Lam, J.T. Wu, G.F. Gao, B.J. Cowling, B. Yang, G.M. Leung, Z. Feng, Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, N. Engl. J. Med. 382 (2020) 1199–1207. doi:10.1056/NEJMoa2001316.

[15] Worldometers, Coronavirus Outbreak, (n.d.).

[16] World Health Organization, Coronavirus Disease (COVID-19) Situation Reports, n.d.

[17] Center for disease controle and prevention, coronavirus disease 2019 (COVID-19)., (2020). https://www.cdc.gov/ coronavirus/2019-ncov/symptoms-testing/symptoms.html.

[18] R.N. Kirchdoerfer, C.A. Cottrell, N. Wang, J. Pallesen, H.M. Yassine, H.L. Turner, K.S. Corbett, B.S. Graham, J.S. McLellan, A.B. Ward, Pre-fusion structure of a

human coronavirus spike protein, Nature. 531 (2016) 118–121. doi:10.1038/nature17200.

[19] M.K. Gupta, S. Vemula, R. Donde, G. Gouda, In-silico approaches to detect inhibitors of the human severe acute respiratory syndrome coronavirus envelope protein ion channel, J. Biomol. Struct. Dyn. 0 (2020) 1–11. doi:10.1080/07391102.2020.1751300.

[20] S. Boopathi, A.B. Poma, P. Kolandaivel, Novel 2019 coronavirus structure , mechanism of action , antiviral drug promises and rule out against its treatment, J. Biomol. Struct. Dyn. 0 (2020) 1–10. doi:10.1080/07391102.2020.1758788.

[21] Y. Imai, K. Kuba, J.M. Penninger, The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice, Exp. Physiol. 93 (2008) 543–548. doi:10.1113/expphysiol.2007.040048.

[22] G. Simmons, D.N. Gosalia, A.J. Rennekamp, J.D. Reeves, S.L. Diamond, P. Bates, Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry, Proc. Natl. Acad. Sci. U.S.A. 102 (2005) 11876–11881, https://doi.org/10.1073/pnas.0505577102.

[23] Q. Wang, C. Li, Q. Zhang, T. Wang, J. Li, W. Guan, J. Yu, M. Liang, D. Li, Interactions of SARS Coronavirus Nucleocapsid Protein with the host cell proteasome subunit p42, Virol. J. 7 (2010) 99. doi:10.1186/1743-422X-7-99.

[24] M.J. van Hemert, S.H.E. van den Worm, K. Knoops, A.M. Mommaas, A.E. Gorbalenya, E.J. Snijder, SARS-Coronavirus Replication/Transcription Complexes Are Membrane-Protected and Need a Host Factor for Activity In Vitro, PLOS Pathog. 4 (2008) e1000054. https://doi.org/10.1371/journal.ppat.1000054.

[25] P.S. Masters, The molecular biology of coronaviruses, Adv. Virus Res. 66 (2006) 193–292, https://doi.org/10.1016/S0065-3527(06)66005-3.

[26] S. Zaim, J.H. Chong, V. Sankaranarayanan, A. Harky, COVID-19 and Multiorgan Response, Curr. Probl. Cardiol. 45 (2020) 100618. doi:10.1016/j.cpcardiol.2020.100618.

[27] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, X. Zhang, L. Zhang, Epidemiological and clinical characteristics of 99 cases of novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (2020) (2019) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.

[28] Coronavirus Resource Center, Coronavirus Resource Center, Harvard Medical School, Harvard Health Publishing, n.d.

[29] J. Yu, M. Kang, Y. Song, J. Xia, Q. Guo, T. Song, J. He, H.-L. Yen, M. Peiris, J. Wu, SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients, N. Engl. J. Med. 1–3 (2020).

[30] F. Chen, Z.S. Liu, F.R. Zhang, R.H. Xiong, Y. Chen, X.F. Cheng, W.Y. Wang, J. Ren, [First case of severe childhood novel coronavirus pneumonia in China]., Zhonghua er ke za zhi = Chinese J. Pediatr. 58 (2020) E005. doi:10.3760/cma.j.issn.0578-1310.2020.0005.

[31] L.K. Zeng, X.W. Tao, W.H. Yuan, J. Wang, X. Liu, Z.S. Liu, [First case of neonate infected with novel coronavirus pneumonia in China], Zhonghua Er Ke Za Zhi = Chinese, J. Pediatr. 58 (2020) E009, https://doi.org/10.3760/cma.j.issn.0578-1310.2020.0009.

[32] T.P. Velavan, C.G. Meyer, The COVID-19 epidemic, Trop. Med. Int. Health. 25 (2020) 278–280. doi:10.1111/tmi.13383.

[33] S. Zhang, J. Gan, B.-G. Chen, D. Zheng, J.-G. Zhang, R.-H. Lin, Y.-P. Zhou, W.-Y. Yang, A. Lin, W.-H. Yan, Dynamics of peripheral immune cells and their HLA-G and receptor expressions in a patient suffering from critical COVID-19 pneumonia to convalescence, Clin. Transl. Immunol. 9 (2020) e1128–e1128. doi:10.1002/cti2.1128.

[34] S.N. Han, S.N. Meydani, Antioxidants, cytokines, and influenza infection in aged mice and elderly humans., J. Infect. Dis. 182 Suppl 1 (2000) S74-80. doi:10.1086/315915.

[35] Y. Jiang, J. Xu, C. Zhou, Z. Wu, S. Zhong, J. Liu, W. Luo, T. Chen, Q. Qin, P. Deng, Characterization of cytokine/chemokine profiles of severe acute respiratory syndrome., Am. J. Respir. Crit. Care Med. 171 (2005) 850–857. doi:10.1164/rccm.200407-857OC.

[36] G. Ryzhakov, C.C. Lai, K. Blazek, K. To, T. Hussell, I. Udalova, IL-17 boosts proinflammatory outcome of antiviral response in human cells., J. Immunol. 187 (2011) 5357–5362. doi:10.4049/jimmunol.1100917.

[37] C.R. Crowe, K. Chen, D.A. Pociask, J.F. Alcorn, C. Krivich, R.I. Enelow, T.M. Ross, J.L. Witztum, J.K. Kolls, Critical role of IL-17RA in immunopathology of influenza infection., J. Immunol. 183 (2009) 5301–5310. doi:10.4049/jimmunol.0900995.

[38] L. Josset, V.D. Menachery, L.E. Gralinski, S. Agnihothram, P. Sova, V.S. Carter, B. L. Yount, R.L. Graham, R.S. Baric, M.G. Katze, Cell Host Response to Infection with Novel Human Coronavirus EMC Predicts Potential Antivirals and Important Differences with SARS Coronavirus, MBio. 4 (2013) e00165-13. doi:10.1128/mBio.00165-13.

[39] R. Channappanavar, A.R. Fehr, R. Vijay, M. Mack, J. Zhao, D.K. Meyerholz, S. Perlman, Dysregulated Type I Interferon and Inflammatory Monocyte-Macrophage Responses Cause Lethal Pneumonia in SARS-CoV-Infected Mice., Cell Host Microbe. 19 (2016) 181–193. doi:10.1016/j.chom.2016.01.007.

[40] A.L. Totura, R.S. Baric, SARS coronavirus pathogenesis: host innate immune responses and viral antagonism of interferon., Curr. Opin. Virol. 2 (2012) 264–275. doi:10.1016/j.coviro.2012.04.004.

[41] A. Ichikawa, K. Kuba, M. Morita, S. Chida, H. Tezuka, H. Hara, T. Sasaki, T. Ohteki, V.M. Ranieri, C.C. dos Santos, Y. Kawaoka, S. Akira, A.D. Luster, B. Lu, J. M. Penninger, S. Uhlig, A.S. Slutsky, Y. Imai, CXCL10-CXCR3 enhances the development of neutrophil-mediated fulminant lung injury of viral and nonviral origin., Am. J. Respir. Crit. Care Med. 187 (2013) 65–77. doi:10.1164/rccm.201203-0508OC.

[42] M.B. Frieman, J. Chen, T.E. Morrison, A. Whitmore, W. Funkhouser, J.M. Ward, E.W. Lamirande, A. Roberts, M. Heise, K. Subbarao, R.S. Baric, SARS-CoV

[43] pathogenesis is regulated by a STAT1 dependent but a type I, II and III interferon receptor independent mechanism., PLoS Pathog. 6 (2010) e1000849. doi:10.1371/journal.ppat.1000849.

[43] W. Liu, A. Fontanet, P.-H. Zhang, L. Zhan, Z.-T. Xin, L. Baril, F. Tang, H. Lv, W.-C. Cao, Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome., J. Infect. Dis. 193 (2006) 792–795. doi:10.1086/500469.

[44] N. Lee, P.K.S. Chan, M. Ip, E. Wong, J. Ho, C. Ho, C.S. Cockram, D.S. Hui, Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome., J. Clin. Virol. Off. Publ. Pan Am. Soc. Clin. Virol. 35 (2006) 179–184. doi:10.1016/j.jcv.2005.07.005.

[45] L. Zhang, F. Zhang, W. Yu, T. He, J. Yu, C.E. Yi, L. Ba, W. Li, M. Farzan, Z. Chen, K. Yuen, D. Ho, Antibody Responses Against SARS Coronavirus Are Correlated With Disease Outcome of Infected Individuals, (n.d.). doi:10.1002/jmv.20499.

[46] L. Liu, Q. Wei, Q. Lin, J. Fang, H. Wang, H. Kwok, H. Tang, K. Nishiura, J. Peng, Z. Tan, T. Wu, K.-W. Cheung, K.-H. Chan, X. Alvarez, C. Qin, A. Lackner, S. Perlman, K.-Y. Yuen, Z. Chen, Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection., JCI Insight. 4 (2019). doi:10.1172/jci.insight.123158.

[47] S.L. Kong, P. Chui, B. Lim, M. Salto-Tellez, Elucidating the molecular physiopathology of acute respiratory distress syndrome in severe acute respiratory syndrome patients., Virus Res. 145 (2009) 260–269. doi:10.1016/j.virusres.2009.07.014.

[48] B. Diao, C. Wang, Y. Tan, X. Chen, Y. Liu, L. Ning, L. Chen, M. Li, Y. Liu, G. Wang, Z. Yuan, Z. Feng, Y. Zhang, Y. Wu, Y. Chen, Reduction and Functional Exhaustion of T Cells in Patients With Coronavirus Disease 2019 (COVID-19), Front. Immunol. 11 (2020) 827, https://doi.org/10.3389/fimmu.2020.00827.

[49] I. Virus, C. Commission, S.- Cov, COVID-19 | Predicted Immune responses | InvivoGen, 33 (2020) 19–20. https://www.invivogen.com/spotlight-covid-19-predicted-immune-responses.

[50] J. Liu, S. Li, J. Liu, B. Liang, X. Wang, H. Wang, W. Li, Q. Tong, J. Yi, L. Zhao, L. Xiong, C. Guo, J. Tian, J. Luo, J. Yao, R. Pang, H. Shen, C. Peng, T. Liu, Q. Zhang, J. Wu, L. Xu, S. Lu, B. Wang, Z. Weng, C. Han, H. Zhu, R. Zhou, H. Zhou, X. Chen, P. Ye, B. Zhu, L. Wang, W. Zhou, S. He, Y. He, S. Jie, P. Wei, J. Zhang, Y. Lu, W. Wang, L. Zhang, L. Li, F. Zhou, J. Wang, U. Dittmer, M. Lu, Y. Hu, D. Yang, X. Zheng, Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients, EBioMedicine. 55 (2020) 102763. doi:10.1016/j.ebiom.2020.102763.

[51] Y. Zhang, B. Li, B. Ning, D. Trabattoni, The Comparative Immunological Characteristics of SARS-CoV, Coronavirus Infect. 11 (2020), https://doi.org/10.3389/fimmu.2020.02033.

[52] L. Wei, S. Ming, B. Zou, Y. Wu, Z. Hong, Viral Invasion and Type I Interferon Response Characterize the Immunophenotypes during Covid-19 Infection, (n.d.).

[53] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the 'Cytokine Storm'' in COVID-19,' J. Infect. 80 (2020) 607–613. doi:10.1016/j.jinf.2020.03.037.

[54] C. Wang, Y. Chen, Aveolar Macrophage Activation and Cytokine Storm in the Pathogenesis of Severe COVID-19 CURRENT STATUS : UNDER REVIEW, (n.d.) 1–18.

[55] S.·bastien N. Margarida Sa Ribero, Nolwenn Jouvenet, Marlène Dreux, Interplay between SARS-CoV-2 and the type I, (2020) 1–22.

[56] H. Chu, J.F.-W. Chan, Y. Wang, T.T.-T. Yuen, Y. Chai, Y. Hou, H. Shuai, D. Yang, B. Hu, X. Huang, X. Zhang, J.-P. Cai, J. Zhou, S. Yuan, K.-H. Kok, K.K.-W. To, I.H.-Y. Chan, A.J. Zhang, K.-Y. Sit, W.-K. Au, K.-Y. Yuen, Comparative Replication and Immune Activation Profiles of SARS-CoV-2 and SARS-CoV in Human Lungs: An Ex Vivo Study With Implications for the Pathogenesis of COVID-19., Clin. Infect. Dis. an Off. Publ. Infect. Dis. Soc. Am. 71 (2020) 1400–1409. doi:10.1093/cid/ciaa410.

[57] B.T. Jerome Hadjadj, Nader Yatim, Laura Barnabei, Aurelien Corneau, Jeremy Boussier, Helene Pere, Bruno Charbit, Vincent Bondet, Camille Chenevier-Gobeaux, Paul Breillat, Nicolas Carlier, Remy Gauzit, Caroline Morbieu, Frederic Pene, Nathalie Marin, Nicolas Ro, Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients, Science (80-.). 6027 (2020). https://doi.org/10.1101/2020.04.19.20068015.

[58] J.F.-W. Chan, K.-H. Kok, Z. Zhu, H. Chu, K.K.-W. To, S. Yuan, K.-Y. Yuen, Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan., Emerg. Microbes Infect. 9 (2020) 221–236. doi:10.1080/22221751.2020.1719902.

[59] M. Spiegel, A. Pichlmair, L. Martínez-Sobrido, J. Cros, A. García-Sastre, O. Haller, F. Weber, Inhibition of Beta interferon induction by severe acute respiratory syndrome coronavirus suggests a two-step model for activation of interferon regulatory factor 3., J. Virol. 79 (2005) 2079–2086. doi:10.1128/JVI.79.4.2079-2086.2005.

[60] C.Y. Cheung, L.L.M. Poon, I.H.Y. Ng, W. Luk, S.-F. Sia, M.H.S. Wu, K.-H. Chan, K.-Y. Yuen, S. Gordon, Y. Guan, J.S.M. Peiris, Cytokine responses in severe acute respiratory syndrome coronavirus-infected macrophages in vitro: possible relevance to pathogenesis., J. Virol. 79 (2005) 7819–7826. doi:10.1128/JVI.79.12.7819-7826.2005.

[61] T. Ziegler, S. Matikainen, E. Rönkkö, P. Osterlund, M. Sillanpää, J. Sirén, R. Fagerlund, M. Immonen, K. Melén, I. Julkunen, Severe acute respiratory syndrome coronavirus fails to activate cytokine-mediated innate immune responses in cultured human monocyte-derived dendritic cells., J. Virol. 79 (2005) 13800–13805. doi:10.1128/JVI.79.21.13800-13805.2005.

[62] R.W.Y. Chan, M.C.W. Chan, S. Agnihothram, L.L.Y. Chan, D.I.T. Kuok, J.H. M. Fong, Y. Guan, L.L.M. Poon, R.S. Baric, J.M. Nicholls, J.S.M. Peiris, Tropism of and Innate Immune Responses to the Novel Human Betacoronavirus Lineage C

Virus in Human Ex Vivo Respiratory Organ Cultures, J. Virol. 87 (2013) 6604–6614, https://doi.org/10.1128/JVI.00009-13.

[63] Q. Zhang, K. Shi, D. Yoo, Suppression of type I interferon production by porcine epidemic diarrhea virus and degradation of CREB-binding protein by nsp1., Virology. 489 (2016) 252–268. doi:10.1016/j.virol.2015.12.010.

[64] J.K. Roth-Cross, L. Martínez-Sobrido, E.P. Scott, A. García-Sastre, S.R. Weiss, Inhibition of the alpha/beta interferon response by mouse hepatitis virus at multiple levels., J. Virol. 81 (2007) 7189–7199. doi:10.1128/JVI.00013-07.

[65] F. Zielecki, M. Weber, M. Eickmann, L. Spiegelberg, A.M. Zaki, M. Matrosovich, S. Becker, F. Weber, Human Cell Tropism and Innate Immune System Interactions of Human Respiratory Coronavirus EMC Compared to Those of Severe Acute Respiratory Syndrome Coronavirus, J. Virol. 87 (2013) 5300–5304, https://doi.org/10.1128/JVI.03496-12.

[66] V.D. Menachery, A.J. Eisfeld, A. Schäfer, L. Josset, A.C. Sims, S. Proll, S. Fan, C. Li, G. Neumann, S.C. Tilton, J. Chang, L.E. Gralinski, C. Long, R. Green, C.M. Williams, J. Weiss, M.M. Matzke, B. Webb-robertson, A.A. Schepmoes, A.K. Shukla, T.O. Metz, R.D. Smith, K.M. Waters, M.G. Katze, Y. Kawaoka, S. Baric, Pathogenic Influenza Viruses and Coronaviruses Utilize Similar and Contrasting Approaches To Control Interferon-Stimulated Gene Responses, 5 (2014) 1–11. doi:10.1128/mBio.01174-14.Editor.

[67] and A.S. C. Paissoni, D. Spiliotopoulos, G. Musco, GMXPBSA 2.1: A GROMACS tool to perform MM/PBSA and computational alanine scanning., Comput. Phys. Commun. (2015). http://dblp.uni-trier.de/db/journals/cphysics/cphysics186.html#PaissoniSMS15%0ABibTeX key:%0Ajournals/cphysics/PaissoniSMS15.

[68] S.K.P. Lau, C.C.Y. Lau, K.-H. Chan, C.P.Y. Li, H. Chen, D.-Y. Jin, J.F.W. Chan, P.C.Y. Woo, K.-Y. Yuen, Delayed induction of proinflammatory cytokines and suppression of innate antiviral response by the novel Middle East respiratory syndrome coronavirus: implications for pathogenesis and treatment., J. Gen. Virol. 94 (2013) 2679–2690. https://www.unboundmedicine.com/medline/citation/24077366/Delayed_induction_of_proinflammatory_cytokines_and_suppression_of_innate_antiviral_response_by_the_novel_Middle_East_respiratory_syndrome_coronavirus:_implications_for_pathogenesis_and_treatment_.

[69] R. Channappanavar, A.R. Fehr, J. Zheng, C. Wohlford-Lenane, J.E. Abrahante, M. Mack, R. Sompallae, P.B.J. McCray, D.K. Meyerholz, S. Perlman, IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes., J. Clin. Invest. 129 (2019) 3625–3639. doi:10.1172/JCI126363.

[70] C. Guideline, Diagnosis and treatment protocol for novel coronavirus pneumonia (Trial version 7), Chin. Med. J. (Engl) 133 (2020) 1087–1095, https://doi.org/10.1097/CM9.0000000000000819.

[71] NHI, What's New in the Guidelines, June 25, (2020) 1–6. https://www.covid19treatmentguidelines.nih.gov/whats-new/.

[72] C.M. Chu, V.C.C. Cheng, I.F.N. Hung, M.M.L. Wong, K.H. Chan, K.S. Chan, R.Y.T. Kao, L.L.M. Poon, C.L.P. Wong, Y. Guan, J.S.M. Peiris, K.Y. Yuen, Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings, Thorax 59 (2004) 252–256, https://doi.org/10.1136/thorax.2003.012658.

[73] Z.J. Cheng, J. Shan, 2019 Novel coronavirus: where we are and what we know, Infection. 48 (2020) 155–163. doi:10.1007/s15010-020-01401-y.

[74] Z. Zhu, Z. Lu, T. Xu, C. Chen, G. Yang, T. Zha, J. Lu, Y. Xue, Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19, J. Infect. 81 (2020) 21–23. doi:10.1016/j.jinf.2020.03.060.

[75] E.L.C. Tan, E.E. Ooi, C.-Y. Lin, H.C. Tan, A.E. Ling, B. Lim, L.W. Stanton, Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs, Emerg. Infect. Dis. 10 (2004) 581–586. doi:10.3201/eid1004.030458.

[76] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, Remdesivir for the Treatment of Covid-19 — Preliminary Report, N. Engl. J. Med. (2020). doi:10.1056/NEJMoa2007764.

[77] Centers for Disease Control and Prevention (CDC), Severe acute respiratory syndrome (SARS) and coronavirus testing–United States, 2003., MMWR. Morb. Mortal. Wkly. Rep. 52 (2003) 297–302.

[78] S. Coenen, A.W. van der Velden, D. Cianci, H. Goossens, E. Bongard, B.R. Saville, N. Gobat, M. de Paor, M. Ieven, T.J. Verheij, C.C. Butler, Oseltamivir for coronavirus illness: post-hoc exploratory analysis of an open-label, pragmatic, randomised controlled trial in European primary care from to 2018, Br. J. Gen. Pract. 70 (2020) (2016) e444–e449. https://www.unboundmedicine.com/medline/citation/32571773/Oseltamivir_for_coronavirus_illness:_post-hoc_exploratory_analysis_of_an_open-label,_pragmatic,_randomised_controlled_trial_in_European_primary_care_from_2016_to_2018.

[79] N. Vankadari, Arbidol: A potential antiviral drug for the treatment of SARS-CoV-2 by blocking trimerization of the spike glycoprotein, Int. J. Antimicrob. Agents. 56 (2020) 105998. doi:10.1016/j.ijantimicrob.2020.105998.

[80] L. Huang, L. Zhang, Y. Liu, R. Luo, L. Zeng, I. Telegina, V. V Vlassov, Arbidol for preventing and treating influenza in adults and children, Cochrane Database Syst. Rev., 2017, CD011489, doi:10.1002/14651858.CD011489.pub2.

[81] A.J. Wagstaff, H.M. Bryson, Foscarnet A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic use in immunocompromised patients with viral infections, Drugs 48 (1994) 199–226, https://doi.org/10.2165/00003495-199448020-00007.

[82] J.K. Edwards, S.R. Cole, Gains and losses in translation of SDGs at sub-national levels, Lancet. 396 (2020) 953–954, https://doi.org/10.1016/S0140-6736(20)32019-5.

[83] S. Tong, Y. Su, Y. Yu, C. Wu, J. Chen, S. Wang, J. Jiang, Ribavirin therapy for severe COVID-19: a retrospective cohort study, Int. J. Antimicrob. Agents. 56 (2020) 106114. doi:10.1016/j.ijantimicag.2020.106114.

[84] V. Madelain, T.H.T. Nguyen, A. Olivo, X. de Lamballerie, J. Guedj, A.-M. Taburet, F. Mentré, Ebola Virus Infection: Review of the Pharmacokinetic and Pharmacodynamic Properties of Drugs Considered for Testing in Human Efficacy Trials., Clin. Pharmacokinet. 55 (2016) 907–923. doi:10.1007/s40262-015-0364-1.

[85] T. Nagata, A.K. Lefor, M. Hasegawa, M. Ishii, Favipiravir: a new medication for the Ebola virus disease pandemic., Disaster Med. Public Health Prep. 9 (2015) 79–81. doi:10.1017/dmp.2014.151.

[86] K. Rosenke, H. Feldmann, J.B. Westover, P.W. Hanley, C. Martellaro, F. Feldmann, G. Saturday, J. Lovaglio, D.P. Scott, Y. Furuta, T. Komeno, B.B. Gowen, D. Safronetz, Use of Favipiravir to Treat Lassa Virus Infection in Macaques., Emerg. Infect. Dis. 24 (2018) 1696–1699. doi:10.3201/eid2409.180233.

[87] U. Agrawal, R. Raju, Z.F. Udwadia, Favipiravir: A new and emerging antiviral option in COVID-19, Med. J. Armed. Forces India (2020), https://doi.org/10.1016/j.mjafi.2020.08.004.

[88] M. Ataei, H. Hosseinjani, Molecular Mechanisms of Galidesivir as a Potential Antiviral Treatment for, (2020) 2–3.

[89] ClinicalTrials.gov., A study to evaluate the safety, pharmacokinetics and antiviral Effects of Galidesivir in Yellow Fever or COVID-19, n.d.

[90] M.L. Ramsey, J. Nuttall, P.A. Hart, T. Investigative, A phase 1/2 trial to evaluate the pharmacokinetics , safety , and efficacy of NI- 03 in patients with chronic pancreatitis : study protocol for a randomized controlled trial on the assessment of camostat treatment in chronic pancreatitis (TACTIC), (2019) 1–7.

[91] M. Hoffmann, H. Hofmann-winkler, J.C. Smith, N. Krüger, Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity, (2020).

[92] D. Huang, H. Yu, T. Wang, H. Yang, R. Yao, Z. Liang, Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.26256.10.1002/jmv.26256.

[93] I.A. Leneva, R.J. Russell, Y.S. Boriskin, A.J. Hay, Characteristics of arbidol-resistant mutants of influenza virus: Implications for the mechanism of anti-influenza action of arbidol, Antiviral Res. 81 (2009) 132–140, https://doi.org/10.1016/j.antiviral.2008.10.009.

[94] J. Chen, L. Xia, L. Liu, Q. Xu, Y. Ling, D. Huang, W. Huang, S. Song, S. Xu, Y. Shen, H. Lu, Antiviral Activity and Safety of Darunavir/Cobicistat for the Treatment of COVID-19, Open Forum, Infect. Dis. 7 (2020), https://doi.org/10.1093/ofid/ofaa241 ofaa241–ofaa241.

[95] C.-19 T. NIH Guidelines, Lopinavir/Ritonavir and Other HIV Protease Inhibitors, n.d.

[96] Q. Tan, L. Duan, Y. Ma, F. Wu, Q. Huang, K. Mao, W. Xiao, H. Xia, S. Zhang, E. Zhou, P. Ma, S. Song, Y. Li, Z. Zhao, Y. Sun, Z. Li, W. Geng, Bioorganic Chemistry Is oseltamivir suitable for fighting against COVID-19: In silico assessment, in vitro and retrospective study, Bioorg. Chem. 104 (2020), 104257, https://doi.org/10.1016/j.bioorg.2020.104257.

[97] R. Wu, L. Wang, H.-C.D. Kuo, A. Shannar, R. Peter, P.J. Chou, S. Li, R. Hudlikar, X. Liu, Z. Liu, G.J. Poiani, L. Amorosa, L. Brunetti, A.-N. Kong, An Update on Current Therapeutic Drugs Treating COVID-19, Curr. Pharmacol. Reports. 6 (2020) 56–70. doi:10.1007/s40495-020-00216-7.

[98] NIH. ClinicalTrials.gov Identifier: NCT04327388, Sarilumab COVID-19, n.d.

[99] V. Strand, M. Reaney, C. Chen, C.W.J. Proudfoot, S. Guillonneau, D. Bauer, E. Mangan, N.M.H. Graham, H. Van Hoogstraten, Y. Lin, C. Pacheco-tena, R. Fleischmann, Sarilumab improves patient-reported outcomes in rheumatoid arthritis patients with inadequate response/intolerance to tumour necrosis factor inhibitors, (2017) 1–10. doi:10.1136/rmdopen-2016-000416.

[100] [guidline] NIH, Interleukin-6 Inhibitors. COVID-19 Treatment Guidelines., n.d.

[101] G. Guaraldi, M. Meschiari, A. Cozzi-lepri, J. Milic, R. Tonelli, M. Menozzi, E. Franceschini, R. Pascale, G. Dolci, L. Brugioni, A. Pietrangelo, A. Cossarizza, F. Pea, E. Clini, C. Salvarani, M. Massari, P.L. Viale, C. Mussini, Tocilizumab in patients with severe COVID-19 : a retrospective cohort study, 2 (2020). doi:10.1016/S2665-9913(20)30173-9.

[102] N. Biran, A. Ip, J. Ahn, R.C. Go, S. Wang, S. Mathura, B.A. Sinclaire, U. Bednarz, M. Marafelias, E. Hansen, D.S. Siegel, A.H. Goy, A.L. Pecora, I.S. Sawczuk, L.S. Koniaris, M. Simwenyi, D.W. Varga, L.K. Tank, A.A. Stein, V. Allusson, G.S. Lin, W.F. Oser, R.A. Tuma, J. Reichman, L.B. Jr, K.L. Carpenter, E.J. Costanzo, V. Vivona, S.L. Goldberg, Tocilizumab among patients with COVID-19 in the intensive care unit : a multicentre observational study, Lancet Rheumatol. 2 (n.d.) e603–e612. doi:10.1016/S2665-9913(20)30277-0.

[103] Siladitya Ray, Regeneron Antibody Therapy For Covid-19 Enters Late-Stage Trials, Forbes. (2020). https://www.forbes.com/sites/siladityaray/2020/07/06/regeneron-antibody-therapy-for-covid-19-enters-late-stage-trials/#de28382117cd.

[104] Regeneron, REGN-COV2 ANTIBODY COCKTAIL PROGRAM UPDATE NOTE REGARDING FORWARD-LOOKING STATEMENTS, (2020).

[105] J.W. Lee, X. Fang, A. Krasnodembskaya, J.P. Howard, M.A. Matthay, Concise review: Mesenchymal stem cells for acute lung injury: role of paracrine soluble factors., Stem Cells. 29 (2011) 913–919. doi:10.1002/stem.643.

[106] K. Xiao, F. Hou, X. Huang, B. Li, Z.R. Qian, L. Xie, Mesenchymal stem cells: current clinical progress in ARDS and COVID-19, (2020) 1–7.

[107] S. Atluri, L. Manchikanti, J.A. Hirsch, Expanded Umbilical Cord Mesenchymal Stem Cells (UC-MSCs) as a Therapeutic Strategy in Managing Critically Ill COVID-19 Patients: The Case for Compassionate Use, Pain Phys. 23 (2020) E71–E83.

[108] A. Uccelli, N.K. de Rosbo, The immunomodulatory function of mesenchymal stem cells: mode of action and pathways, Ann. N. Y. Acad. Sci. 1351 (2015) 114–126. doi:doi:10.1111/nyas.12815.

[109] T. Ben-Mordechai, D. Palevski, Y. Glucksam-Galnoy, I. Elron-Gross, R. Margalit, J. Leor, Targeting macrophage subsets for infarct repair., J. Cardiovasc. Pharmacol. Ther. 20 (2015) 36–51. doi:10.1177/1074248414534916.

[110] K. Ibrahim, Flavonoids (2001).

[111] M. Russo, S. Moccia, C. Spagnuolo, I. Tedesco, G.L. Russo, Roles of flavonoids against coronavirus infection, Chem. Biol. Interact. 328 (2020) 109211. doi: 10.1016/j.cbi.2020.109211.

[112] W. Ngwa, R. Kumar, D. Thompson, W. Lyerly, R. Moore, T.-E. Reid, H. Lowe, N. Toyang, Potential of Flavonoid-Inspired Phytomedicines against COVID-19, Molecules. 25 (2020) 2707. doi:10.3390/molecules25112707.

[113] L. Chen, C. Gui, X. Luo, Q. Yang, S. Günther, E. Scandella, C. Drosten, D. Bai, X. He, B. Ludewig, J. Chen, H. Luo, Y. Yang, Y. Yang, J. Zou, V. Thiel, K. Chen, J. Shen, X. Shen, H. Jiang, Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication in vitro, J. Virol. 79 (2005) 7095–7103. doi:10.1128/JVI.79.11.7095-7103.2005.

[114] L. Gozzo, P. Viale, L. Longo, D.C. Vitale, F. Drago, The Potential Role of Heparin in Patients With COVID-19: Beyond the Anticoagulant Effect. A Review, Front. Pharmacol. 11 (2020) 1307, https://doi.org/10.3389/fphar.2020.01307.

[115] P. Di Micco, G. Di Micco, M.R. Poggiano, C. Salzano, M. Imparato, L. Fontanella, A. Fontanella, Blood Targets of Adjuvant Therapy Against COVID19, (2020).

[116] M. Kotowski, A. Bogacz, K. Lechowicz, J. Rosik, M. Sietnicki, COVID-19 : The In fl uence of ACE Genotype and ACE-I and ARBs on the Course of SARS-CoV-2 Infection in Elderly Patients, (2020) 1231–1240.

[117] J.S. Rico-Mesa, A. White, A.S. Anderson, Outcomes in Patients with COVID-19 Infection Taking ACEI/ARB, Curr. Cardiol. Rep. 22 (2020) 31. doi:10.1007/s11886-020-01291-4.

[118] WHO, COVID-19 and the use of angiotensin-converting enzyme inhibitors and receptor blockers, n.d. https://www.who.int/news-room/commentaries/detail/covid-19-and-the-use-of-angiotensin-converting-enzyme-inhibitors-and-receptor-blockers.

[119] G.M. Kuster, O. Pfister, T. Burkard, Q. Zhou, R. Twerenbold, P. Haaf, A.F. Widmer, S. Osswald, SARS-CoV2: should inhibitors of the renin–angiotensin system be withdrawn in patients with COVID-19?, Eur. Heart J. 41 (2020) 1801–1803. doi:10.1093/eurheartj/ehaa235.

[120] J. Watkins, Preventing a covid-19 pandemic, (2020). doi:10.1136/bmj.m810.

[121] D. Acanfora, M.M. Ciccone, P. Scicchitano, C. Acanfora, G. Casucci, Sacubitril/valsartan in COVID-19 patients: the need for trials, Eur. Hear. J. - Cardiovasc. Pharmacother. 6 (2020) 253–254. doi:10.1093/ehjcvp/pvaa044.

[122] A. Vitiello, R. La Porta, F. Ferrara, Sacubitril, valsartan and SARS-CoV-2, BMJ Evidence-Based Med. (2020) bmjebm-2020-111497. doi:10.1136/bmjebm-2020-111497.

[123] C.-19 T. NIH Guidelines, Interleukin-1 Inhibitors, n.d.

[124] E. Nasonov, M. Samsonov, The role of Interleukin 6 inhibitors in therapy of severe COVID-19, Biomed. Pharmacother. 131 (2020), https://doi.org/10.1016/j.biopha.2020.110698.

[125] S. Scherger, A. Henao-Martínez, C. Franco-Paredes, L. Shapiro, Rethinking interleukin-6 blockade for treatment of COVID-19, Med. Hypotheses 144 (2020), https://doi.org/10.1016/j.mehy.2020.110053.

[126] S. Lu, Q. Zhou, L. Huang, Q. Shi, S. Zhao, Z. Wang, W. Li, Y. Tang, Y. Ma, X. Luo, T. Fukuoka, H.S. Ahn, M.S. Lee, Z. Luo, E. Liu, Y. Chen, C. Zhou, D. Peng, Effectiveness and safety of glucocorticoids to treat COVID-19: a rapid review and meta-analysis, Ann. Transl. Med. 8 (2020) 627. doi:10.21037/atm-20-3307.

[127] J.K.A. Robin E Ferner, Nicholas DeVito, Dexamethasone, n.d.

[128] S. Timmermans, J. Souffriau, C. Libert, A General Introduction to Glucocorticoid Biology, Front. Immunol. 10 (2019) 1545, https://doi.org/10.3389/fimmu.2019.01545.

[129] W.M. Schneider, M.D. Chevillotte, C.M. Rice, Interferon-stimulated genes: a complex web of host defenses., Annu. Rev. Immunol. 32 (2014) 513–545. doi:10.1146/annurev-immunol-032713-120231.

[130] C.E. Samuel, Antiviral Actions of Interferons, Clin. Microbiol. Rev. 14 (2001) 778–809, https://doi.org/10.1128/CMR.14.4.778-809.2001.

[131] E. Kindler, V. Thiel, F. Weber, Interaction of SARS and MERS Coronaviruses with the Antiviral Interferon Response, Adv. Virus Res. 96 (2016) 219–243, https://doi.org/10.1016/bs.aivir.2016.08.006.

[132] A. de Lang, T. Baas, S.L. Smits, M.G. Katze, A.D.M.E. Osterhaus, B.L. Haagmans, Unraveling the complexities of the interferon response during SARS-CoV infection, Future Virol. 4 (2009) 71–78. doi:10.2217/17460794.4.1.71.

[133] M.R. Loutfy, L.M. Blatt, K.A. Siminovitch, S. Ward, B. Wolff, H. Lho, D.H. Pham, H. Deif, E.A. LaMere, M. Chang, K.C. Kain, G.A. Farcas, P. Ferguson, M. Latchford, G. Levy, J.W. Dennis, E.K.Y. Lai, E.N. Fish, Interferon Alfacon-1 Plus Corticosteroids in Severe Acute Respiratory SyndromeA Preliminary Study, JAMA. 290 (2003) 3222–3228. doi:10.1001/jama.290.24.3222.

[134] Z. Zhao, F. Zhang, M. Xu, K. Huang, W. Zhong, W. Cai, Z. Yin, S. Huang, Z. Deng, M. Wei, J. Xiong, P.M. Hawkey, Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China, J. Med. Microbiol. 52 (2003) 715–720, https://doi.org/10.1099/jmm.0.05320-0.

[135] Nancy R. Gough, Interferon Responses Could Explain Susceptibility to Severe COVID-19. Impaired or delayed antiviral signaling could be a treatable cause of serious COVID-19., 2020.

[136] A.S. Omrani, M.M. Saad, K. Baig, A. Bahloul, M. Abdul-Matin, A.Y. Alaidaroos, G. A. Almakhlafi, M.M. Albarrak, Z.A. Memish, A.M. Albarrak, Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: A retrospective cohort study, Lancet Infect. Dis. 14 (2014) 1090–1095. doi:10.1016/S1473-3099(14)70920-X.

[137] A. Zumla, J.F.W. Chan, E.I. Azhar, D.S.C. Hui, K.-Y. Yuen, Coronaviruses — drug discovery and therapeutic options, Nat. Rev. Drug Discov. 15 (2016) 327–347. doi:10.1038/nrd.2015.37.

[138] Sarah Shalhoub, Interferon beta-1b for COVID-19, The Lancet 395 (2020) 1670–1671, https://doi.org/10.1016/S0140-6736(20)31101-6.

[139] J.A. Al-Tawfiq, H. Momattin, J. Dib, Z.A. Memish, Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: An observational study, Int. J. Infect. Dis. 20 (2014) 42–46. doi:10.1016/j.ijid.2013.12.003.

[140] L. Prokunina-Olsson, N. Alphonse, R.E. Dickenson, J.E. Durbin, J.S. Glenn, R. Hartmann, S.V. Kotenko, H.M. Lazear, T.R. O'Brien, C. Odendall, O. O. Onabajo, H. Piontkivska, D.M. Santer, N.C. Reich, A. Wack, I. Zanoni, COVID-19 and emerging viral infections: The case for interferon lambda, J. Exp. Med. 217 (2020) 5–8, https://doi.org/10.1084/jem.20200653.

[141] E. Sallard, F.X. Lescure, Y. Yazdanpanah, F. Mentre, N. Peiffer-Smadja, Type 1 interferons as a potential treatment against COVID-19, Antiviral Res. 178 (2020). doi:10.1016/j.antiviral.2020.104791.

[142] B. Sainz, E.C. Mossel, C.J. Peters, R.F. Garry, Interferon-beta and interferon-gamma synergistically inhibit the replication of severe acute respiratory syndrome-associated coronavirus (SARS-CoV), Virology. 329 (2004) 11–17. doi:10.1016/j.virol.2004.08.011.

[143] L.E. Hensley, E.A. Fritz, P.B. Jahrling, C.L. Karp, J.W. Huggins, T.W. Geisbert, Interferon-β 1a and SARS Coronavirus Replication, Emerg. Infect. Dis. 10 (2004) 317–319. doi:10.3201/eid1002.030482.

[144] G. Noh, C. Halla, G. Hospital, IFN- γ as a Major Antiviral Therapeutic for Viral Epidemics , Including Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Clinically Forgotten but Potential Antiviral Cytokine and Non-Virus-Specific Antiviral as a New Antiviral Strategy, 2 (2020).

[145] J.J. Hooks, Y. Wang, B. Detrick, The Critical Role of IFN-γ in Experimental Coronavirus Retinopathy, Invest. Ophthalmol. Vis. Sci. 44 (8) (2003) 3402, https://doi.org/10.1167/iovs.02-1106.

[146] M. Mordstein, E. Neugebauer, V. Ditt, B. Jessen, T. Rieger, V. Falcone, F. Sorgeloos, S. Ehl, D. Mayer, G. Kochs, M. Schwemmle, S. Günther, C. Drosten, T. Michiels, P. Staeheli, Lambda Interferon Renders Epithelial Cells of the Respiratory and Gastrointestinal Tracts Resistant to Viral Infections, J. Virol. 84 (2010) 5670–5677. doi:10.1128/jvi.00272-10.

[147] E. Andreakos, S. Tsiodras, COVID -19: lambda interferon against viral load and hyperinflammation, EMBO Mol. Med. 12 (2020) 10–13, https://doi.org/10.15252/emmm.202012465.

[148] Q. Zhou, V. Chen, C.P. Shannon, X.S. Wei, X. Xiang, X. Wang, Z.H. Wang, S. J. Tebbutt, T.R. Kollmann, E.N. Fish, Interferon-α2b Treatment for COVID-19, Front. Immunol. 11 (2020) 1–6, https://doi.org/10.3389/fimmu.2020.01061.

[149] N. Wang, Y. Zhan, L. Zhu, Z. Zheng, Y. Lu, P. Hong, Clinical and Translational Report Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients Clinical and Translational Report Retrospective Multicenter Cohort Study Shows Early Interferon Therapy Is Associated with Favorable Clinical Responses in COVID-19 Patients, Cell Host Microbe. (2020) 1–10. doi:10.1016/j.chom.2020.07.005.

[150] P.-N. Cheng, P. Marcellin, B. Bacon, G. Farrell, I. Parsons, T. Wee, T.-T. Chang, Racial differences in responses to interferon-beta-1a in chronic hepatitis C unresponsive to interferon-alpha: a better response in Chinese patients, J. Viral Hepat. 11 (5) (2004) 418–426, https://doi.org/10.1111/j.1365-2893.2004.00514.x.

[151] J. Cinatl, B. Morgenstern, G. Bauer, P. Chandra, H. Rabenau, H.W. Doerr, Treatment of SARS with human interferons, The Lancet 362 (2003) 293–294, https://doi.org/10.1016/S0140-6736(03)13973-6.

[152] X. Luo, Y. Guo, J. Bao, Y. Liu, D. An, B. Ma, M. Gao, J. Wang, Characterization and antivirus activities of a novel bovine, 66 (2015) 357–363. doi:10.1016/j.molimm.2015.04.009.

[153] B. Morgenstern, M. Michaelis, P.C. Baer, H.W. Doerr, J. Cinatl Jr, Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines, Biochem. Biophys. Res. Commun. 326 (2005) 905–908, https://doi.org/10.1016/j.bbrc.2004.11.128.

[154] A. Bernheim, X. Mei, M.S.M. Huang, Y. Yang, Z.A. Fayad, Chest CT Findings in Coronavirus Disease 2019 (COVID-19): Relationship to Duration of Infection, 2019 (2020).

[155] E. Davoudi-Monfared, H. Rahmani, H. Khalili, M. Hajiabdolbaghi, M. Salehi, L. Abbasian, H. Kazemzadeh, M.S. Yekaninejad, Efficacy and safety of interferon β-1a in treatment of severe COVID-19: A randomized clinical trial, Antimicrob. Agents Chemother. (2020) AAC.01061-20. doi:10.1128/AAC.01061-20.

[156] J. Jalkanen, M. Hollmén, S. Jalkanen, Interferon beta-1a for COVID-19: critical importance of the administration route, Crit. Care. 24 (2020) 10–12, https://doi.org/10.1186/s13054-020-03048-5.

[157] Y.M. Arabi, A. Alothman, H.H. Balkhy, A. Al-Dawood, S. AlJohani, S. Al Harbi, S. Kojan, M. Al Jeraisy, A.M. Deeb, A.M. Assiri, F. Al-Hameed, A. AlSaedi, Y. Mandourah, G.A. Almekhlafi, N.M. Sherbeeni, F.E. Elzein, J. Memon, Y. Taha, A. Almotairi, K.A. Maghrabi, I. Qushmaq, A. Al Bshabshe, A. Kharaba, S. Shalhoub, J. Jose, R.A. Fowler, F.G. Hayden, M.A. Hussein, Y.M. Arabi, A. Alothman, H.H. Balkhy, A. Al-Dawood, S. AlJohani, S. Al Harbi, S. Kojan, M. Al Jeraisy, A.M. Deeb, J. Jose, M.A. Hussein, M. Al Muhaidib, M. Sadat, H. Al Anizi, R. Dael, A.M. Assiri, M. AlMazroa, A. Asiri, Z.A. Memish, S.S. Ghazal, S.H. Alfaraj, F. Bafaqeeh,

A. Al Harthy, M. Al Sulaiman, A. Mady, Y. Mandourah, G.A. AlMekhlafi, N.M. Sherbeeni, F.E. Elzein, R. Muhammed, S. Al Samirrai, S. Awad, R.C. Cabal, A.A. Malibary, B. Al Onazi, M. Aljuhani, M. Vince, A. Almotairi, M. Al Enani, A. Alqurashi, F. Alenezi, N. Alkhani, K.A. Maghrabi, F. Al-Hameed, A. AlSaedi, A. Thaqafi, O. Al Oraabi, J. Rifai, P. Elsamadisi, M.S. Hendy, S.A. Basher, M. Abduldhaher, W. Bajhamoum, I. Qushmaq, S. Shalhoub, Y. Taha, J. Memon, S. Bashir, I. Al-Dossary, S. Al Mekhloof, B. Al-Muhainy, S. Suliman, M.S. Alshahrani, A. Al Bshabshe, A. Kharaba, A. Al Jabri, M. Farid, A. Alaidarous, W. Alseraihi, H. Shahada, J. Shimi, S. Riaz, B. Alharthi, O. Yasin, M. Khathlan, R.A. Fowler, F.G. Hayden, A. the M. trial group, Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon-β1b (MIRACLE trial): study protocol for a randomized controlled trial, Trials. 19 (2018) 81. doi: 10.1186/s13063-017-2427-0.

[158] Synairgen plc, COVID-19 – SG016 Clinical Trial Data Readout, England, n.d. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwib4P75rP7qAhVR8OAKHZ1XAOUQFjABegQIAhAB&url=https%3A%2F%2Fwww.synairgen.com%2Fcovid-19%2F&usg=AOvVaw1yesWdAIorvqHpKaL1Ur1-.

[159] L. Thomas, Study evaluates the effectiveness of interferon beta 1b in COVID - 19 pneumonia, (2020) 1–6.

[160] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study., Lancet (London, England), 395 (2020), p. 1054–1062. doi:10.1016/S0140-6736(20)30566-3.

[161] L.J. Stockman, R. Bellamy, P. Garner, SARS: Systematic review of treatment effects, PLoS Med. 3 (2006) 1525–1531. doi:10.1371/journal.pmed.0030343.L.J. Stockman, R. Bellamy, P. Garner, SARS: Systematic review of treatment effects, PLoS Med. 3 (2006) 1525–1531. doi:10.1371/journal.pmed.0030343.

[162] S. Kang, H.M. Brown, S. Hwang, Direct Antiviral Mechanisms of Interferon-Gamma, Immune Netw. 18 (2018), e33, https://doi.org/10.4110/in.2018.18.e33.

[163] A. Billiau, P. Matthys, Interferon-gamma: a historical perspective, Cytokine Growth Factor Rev. 20 (2009) 97–113, https://doi.org/10.1016/j.cytogfr.2009.02.004.

[164] D.E. Levy, A. García-Sastre, The virus battles: IFN induction of the antiviral state and mechanisms of viral evasion, Cytokine Growth Factor Rev. 12 (2001) 143–156, https://doi.org/10.1016/s1359-6101(00)00027-7.

[165] L.G. Guidotti, F.V. Chisari, Cytokine-Mediated Control of Viral Infections, Virology 273 (2000) 221–227, https://doi.org/10.1006/viro.2000.0442.

[166] S. Davidson, T.M. McCabe, S. Crotta, H.H. Gad, E.M. Hessel, S. Beinke, R. Hartmann, A. Wack, IFN λ is a potent anti-influenza therapeutic without the inflammatory side effects of IFN α treatment, EMBO Mol. Med. 8 (2016) 1099–1112, https://doi.org/10.15252/emmm.201606413.

[167] K. Blazek, H.L. Eames, M. Weiss, A.J. Byrne, D. Perocheau, J.E. Pease, S. Doyle, F. McCann, R.O. Williams, I.A. Udalova, IFN-λ resolves inflammation via suppression of neutrophil infiltration and IL-1β production, J. Exp. Med. 212 (2015) 845–853. doi:10.1084/jem.20140995.

[168] T.P. Sheahan, A.C. Sims, S.R. Leist, A. Schäfer, J. Won, A.J. Brown, S.A. Montgomery, A. Hogg, D. Babusis, M.O. Clarke, J.E. Spahn, L. Bauer, S. Sellers, D. Porter, J.Y. Feng, T. Cihlar, R. Jordan, M.R. Denison, R.S. Baric, Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV, Nat. Commun. 11 (2020) 222. doi:10.1038/s41467-019-13940-6.

[169] K.G. Lokugamage, A. Hage, M. de Vries, A.M. Valero-Jimenez, C. Schindewolf, M. Dittmann, R. Rajsbaum, V.D. Menachery, Type I interferon susceptibility distinguishes SARS-CoV-2 from SARS-CoV, BioRxiv. 2020 3 (2020), https://doi.org/10.1101/2020.03.07.982264.

[170] J. Jacques, V. Eynde, COVID-19 : An Update About the Discovery Clinical Trial, (2020). doi:10.3390/ph13050098.

[171] I.F.N. Hung, K.C. Lung, E.Y.K. Tso, R. Liu, T.W.H. Chung, M.Y. Chu, Y.Y. Ng, J. Lo, J. Chan, A.R. Tam, H.P. Shum, V. Chan, A.K.L. Wu, K.M. Sin, W.S. Leung, W.L. Law, D.C. Lung, S. Sin, P. Yeung, C.C.Y. Yip, R.R. Zhang, A.Y.F. Fung, E.Y.W. Yan, K.H. Leung, J.D. Ip, A.W.H. Chu, W.M. Chan, A.C.K. Ng, R. Lee, K. Fung, A. Yeung, T.C. Wu, J.W.M. Chan, W.W. Yan, W.M. Chan, J.F.W. Chan, A.K.W. Lie, O. T.Y. Tsang, V.C.C. Cheng, T.L. Que, C.S. Lau, K.H. Chan, K.K.W. To, K.Y. Yuen, Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial, Lancet. 395 (2020) 1695–1704. doi:10.1016/S0140-6736(20)31042-4.

[172] S.G.V. Rosa, W.C. Santos, Clinical trials on drug repositioning for COVID-19 treatment, Rev. Panam. Salud Pública. 44 (2020) 1, https://doi.org/10.26633/rpsp.2020.40.

[173] Y.-H. Jin, L. Cai, Z.-S. Cheng, H. Cheng, T. Deng, Y.-P. Fan, C. Fang, D. Huang, L.-Q. Huang, Q. Huang, Y. Han, B. Hu, F. Hu, B.-H. Li, Y.-R. Li, K. Liang, L.-K. Lin, L.-S. Luo, J. Ma, L.-L. Ma, Z.-Y. Peng, Y.-B. Pan, Z.-Y. Pan, X.-Q. Ren, H.-M. Sun, Y. Wang, Y.-Y. Wang, H. Weng, C.-J. Wei, D.-F. Wu, J. Xia, Y. Xiong, H.-B. Xu, X.-M. Yao, Y.-F. Yuan, T.-S. Ye, X.-C. Zhang, Y.-W. Zhang, Y.-G. Zhang, H.-M. Zhang, Y. Zhao, M.-J. Zhao, H. Zi, X.-T. Zeng, Y.-Y. Wang, X.-H. Wang, for the Z.H. of W.U. N.C.M. and R.T. Evidence-Based Medicine Chapter of China International Exchange and Promotive Association for Medical and Health Care (CPAM), A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version), Mil. Med. Res. 7 (2020) 4. doi:10.1186/s40779-020-0233-6.

[174] D. Chang, H. Xu, A. Rebaza, L. Sharma, C.S. Dela Cruz, Correspondence workers from subclinical coronavirus infection, Lancet Respir. 8 (2020), e13, https://doi.org/10.1016/S2213-2600(20)30066-7.

[175] World Health Organization, Coronavirus disease [COVID-19] Technical Guidance: Infection Prevention and Control., n.d.

[176] J. Li, J.J. Li, X. Xie, X. Cai, J. Huang, X. Tian, H. Zhu, Game consumption and the 2019 novel coronavirus, Lancet. Infect. Dis. 20 (2020) 275–276. doi:10.1016/S1473-3099(20)30063-3.