

Novel Coronavirus Disease (COVID-19): Causes, Pathogenesis and Efforts of Treatment

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SUMMARY

At the end of 2019, several pneumonia cases latter known as novel coronavirus disease 2019 (COVID-19) have been reported in Wuhan, China. COVID-19 is caused by a novel virus related to coronavirus family which has been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Due to the rapid spread of the virus worldwide, the World Health Organization (WHO) has announced COVID-19 as a public health emergency of international concern. SARS-CoV-2 is a zoonotic RNA virus believed to be originated in bats and has been transmitted to humans through unknown intermediate. The exact pathogenesis of COVID-19 is not fully well-known, but the virus has the ability to attack the lower respiratory tract through specific receptors called angiotensin converting enzyme 2 (ACE-2) highly expressed on the surface of epithelial cells. The clinical symptoms of COVID-19 are usually mild including respiratory and gastrointestinal symptoms as well as muscle ache. However, some patients display severe symptoms due to the development of acute respiratory disease syndrome (ARDS) and organ damage. To date, there is no specific treatment or vaccine for COVID-19 infection. Scientists have tested the efficacy of several drugs against SARS-CoV-2, and certain preliminary results were promising. Currently, several clinical trials are ongoing to establish the safety and efficacy of some potential drugs in the treatment of COVID-19 infection. This review highlights the characteristics of SARS-CoV-2, the potential pathogenesis of COVID-19 and the proposed agents for treatment of COVID-19 and their preliminary results.

Key Words: Coronavirus, SARS-CoV-2, COVID-19, pathogenesis, cytokine storm, antiviral drugs

Yeni Koronavirüs Hastalığı (COVID-19): Nedenleri, Patogenezi ve Tedavi Çabaları

ÖZ

2019'un sonunda, Çin'in Wuhan şehrinde, yeni koronavirüs hastalığı 2019 (COVID-19) olarak bilinen birkaç pnömöni vakası bildirildi. COVID-19, Ağır Akut Solunum Sendromu Koronavirüs 2 (SARS-CoV-2) olarak adlandırılan koronavirüs ailesiyle ilişkili yeni bir virüsten kaynaklanır. Virüsün dünya çapında hızla yayılması nedeniyle, Dünya Sağlık Örgütü (DSÖ) COVID-19'u uluslararası bir Halk Sağlığı Acil Durumu olarak ilan etti. SARS-CoV-2, yarasalardan kaynaklandığına inanılan ve bilinmeyen bir ara taşıyıcı yoluyla insanlara bulaşan zoonotik bir RNA virüsüdür. COVID-19'un kesin patogenezi tam olarak bilinmemektedir, ancak virüs, konakçı epitelial hücrelerin yüzeyinde yüksek oranda ekspres edilen Anjiyotensin Dönüştürücü Enzim 2 (ACE-2) adı verilen spesifik reseptörler yoluyla alt solunum yoluna saldırma yeteneğine sahiptir. COVID-19'un klinik semptomları, solunum ve gastrointestinal semptomların yanı sıra kas ağrısı dahil olmak üzere genellikle hafiftir. Bununla birlikte, bazı hastalar Akut Solunum Sıkıntısı Sendromu (ASS) ve organ hasarı nedeniyle ciddi semptomlar gösterir. Bugüne kadar, COVID-19 enfeksiyonu için spesifik bir tedavi veya aşı yoktur. Bilim adamları SARS-CoV-2'ye karşı birkaç ilacın etkinliğini test ettiler ve bazı ön sonuçlar umut vericiydi. Halen, COVID-19 enfeksiyonunun tedavisinde bazı potansiyel ilaçların güvenilirliğini ve etkinliğini belirlemek için çeşitli klinik çalışmalar devam etmektedir. Bu derleme SARS-CoV-2'nin özelliklerini, COVID-19'un potansiyel patogenezi ve COVID-19 tedavisi için önerilen ilaçları ve bunların ön sonuçlarını vurgulamaktadır.

Anahtar kelimeler: Koronavirüs, SARS-CoV-2, COVID-19, patogenezi, sitokin fırtınası, antiviral ilaçlar

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INTRODUCTION

In December 2019, a striking and rapid outbreak of acute respiratory diseases has been reported in Wuhan, China (Guan et al., 2020; Huang et al., 2020; H. Lu, Stratton, & Tang, 2020). On 7 January 2020, the China Novel Coronavirus Investigating and Research Team succeeded to isolate and identify the 2019 novel coronavirus (2019-nCoV) which was approved as the causative agent of these respiratory diseases (N. Zhu et al., 2020). After that, a new name of the epidemic disease caused by 2019-nCoV was declared by the World Health Organization (WHO) in February 2020: novel coronavirus disease 2019 (COVID-19) (WHO, 2020, February 11). Starting from China, COVID-19 has spread dramatically worldwide (as of 16 July 2020, there are more than 13 378 853 confirmed cases and around 580 045 deaths globally) and consequently, the WHO declared it as a global pandemic on the 7th March 2020 (WHO, 2020, July 16). As the numbers of 2019-nCoV pandemic victims continue to rise rapidly, searching for a vaccine or effective treatment to stop this pandemic and to end this mess has become the greatest concern of the world. Therefore, all attention and support are directed towards the scientists and researchers hoping to develop a vaccine against the killer virus that has infected millions of people, killed thousands, and still threatens the entire world. In this review, we focus on the causative agent of COVID-19 as well as the potential pathogenesis of this disease. In addition, we highlight the findings of studies and clinical trials conducted to evaluate the effectiveness of some drugs against 2019-nCoV.

NOMENCLATURE OF THE NOVEL VIRUS

After numerous cases of severe pneumonia of unknown etiology had been reported in China, beginning in late December 2019, huge efforts have been made to recognize the cause of this illness and to prevent its spread. In January 2020, the Chinese scientists could isolate and identify the virus causing this respiratory illness (R. Lu et al., 2020; Ren et al., 2020; N. Zhu et al., 2020) 2019, patients presenting with viral pneumonia due to an unidentified microbial agent were reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named 2019 novel coronavirus (2019-nCoV). They found that the virus is related to single strand RNA strains and its genetic map was closed to Coronavirus family, where it was more identical to coronavirus strains of bat origin (bat-SL-CoVZC45 and bat-SL-CoVZXC21; about 88% sequence identity), and less similar to both severe acute respiratory syndrome coronavirus (SARS-CoV, about 79% identity) and Middle East respiratory syndrome coronavirus (MERS-CoV, about 50% identity) (R. Lu

et al., 2020; Ren et al., 2020; N. Zhu et al., 2020) 2019, patients presenting with viral pneumonia due to an unidentified microbial agent were reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named 2019 novel coronavirus (2019-nCoV). Moreover, they found that the new virus has similar morphological features to Coronavirus family such as the solar corona appearance, the spherical shape of virus particles (60 to 140 nm diameter) with characteristic spikes (N. Zhu et al., 2020). Based on these findings and the clinical features of patients infected with the virus, it was firstly named 2019-nCoV, and subsequently was renamed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (Gorbalenya et al., 2020; N. Zhu et al., 2020). Coronaviruses are a group of enveloped, single-stranded RNA viruses related to *Coronaviridae* family, and their name is derived from the crown-like or corona-like shape of their virions observed under the electron microscope. These viruses have the ability to infect many birds and mammals causing respiratory and gastrointestinal diseases (Cavanagh, 2007; Erles, Toomey, Brooks, & Brownlie, 2003; Ismail, Tang, & Saif, 2003; Zhou et al., 2018)

HUMAN CORONAVIRUSES

By the emergence of SARS-CoV-2, seven coronaviruses have become able to infect humans divided into two groups: α -human coronaviruses (229E and NL63) and β -human coronaviruses (OC43, HKU1, SARS-CoV, MERS-CoV and SARS-CoV-2) (Hoek et al., 2004; Ksiazek et al., 2003; R. Lu et al., 2020; Perlman & Netland, 2009; Ren et al., 2020; Woo et al., 2005; Zaki, van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012; Zhong et al., 2003; N. Zhu et al., 2020) including severe acute respiratory syndrome (SARS). Usually, human coronaviruses (OC43 and 229E) cause mild upper respiratory tract illness as common cold. However, the image became completely different by the end of 2002 when a new human coronavirus (SARS-CoV) was recognized in China which was responsible for severe acute respiratory syndrome (SARS) and resulted in 8096 infected cases with 774 deaths through July 2003 (Ksiazek et al., 2003; WHO, 2003; Zhong et al., 2003). Following the SARS pandemic, two novel coronaviruses (HKU1 and NL63) were identified in human and were associated with severe respiratory illness (Hoek et al., 2004; Woo et al., 2005) no microbiological cause can be identified in a significant proportion of patients. In the past 3 years, several novel respiratory viruses, including human metapneumovirus, severe acute respiratory syndrome (SARS). In addition, another human respiratory coronavirus (MERS-CoV) was revealed in Saudi

Arabia in the middle of 2012 causing serious respiratory symptoms named later Middle East respiratory syndrome (MERS) (Zaki et al., 2012). On 8 April 2020, the WHO announced that more than 2538 positive cases of MERS were registered including 871 associated deaths globally (WHO, 2020, April 08).

CHARACTERISTICS OF SARS-COV-2

SARS-CoV-2 is an enveloped, single-stranded RNA virus related to β -human coronavirus group. SARS-CoV-2 is a zoonotic virus similar to other human coronaviruses, where bats are considered as a main reservoir of most of them (Corman, Muth, Niemeyer, & Drosten, 2018). Based on the findings of SARS-CoV-2 genetic analysis (88-96% genome sequence identity to bat coronaviruses), it is highly believed that it originated in bats (R. Lu et al., 2020; P. Zhou et al., 2020; N. Zhu et al., 2020) 2019, patients presenting with viral pneumonia due to an unidentified microbial agent were reported in Wuhan, China. A novel coronavirus was subsequently identified as the causative pathogen, provisionally named 2019 novel coronavirus (2019-nCoV). However, its intermediate animal host that transmitted the virus to humans is not yet identified.

Like human coronaviruses, the genetic map of SARS-CoV-2 contains open reading frames (ORFs) in which the ORF1a/b (about two-thirds of viral RNA starting from the 5'-terminus) contain genes encoding the polyproteins required for viral replication, whereas the genes closest to the 3'-terminus encode

the structural proteins and accessory proteins (Perlman & Netland, 2009; P. Zhou et al., 2020) and domestic and companion animals. They are most notorious for causing severe acute respiratory syndrome (SARS). SARS-CoV-2 has the distinctive external structure of coronavirus family which is composed of four structural proteins: spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins, and many accessory proteins that may hinder the host immune responses (Figure 1) (P. Zhou et al., 2020). Morphologically, the S protein forms protrusions of peplomers on the surface of virions which give corona- or crown-like shape of the virus under the electron microscope. Functionally, S protein plays a vital role in viral infection through its two domains: S1 domain which is responsible for binding to the host receptors via its receptor binding domain, and S2 domain which facilitates the membrane fusion (F. Li, 2016). Although the Chinese scientists found a sequence diversity in the receptor binding domain of SARS-CoV-2 and SARS-CoV S-protein, SARS-CoV-2 is able to infect its human target cells by binding to a specific receptor called angiotensin-converting enzyme-2 (ACE-2) receptor, which is the same receptor occupied by S1 domain of SARS-CoV S protein (Hoffmann et al., 2020; W. Li et al., 2003; Wan, Shang, Graham, Baric, & Li, 2020; P. Zhou et al., 2020). SARS-CoV also binds with alternative receptors known as CD209 (DC-SIGN) and CD209L (L-SIGN); however, no studies showed that SARS-CoV-2 can use these receptors to infect its target cells (Jeffers et al., 2004; Marzi et al., 2004).

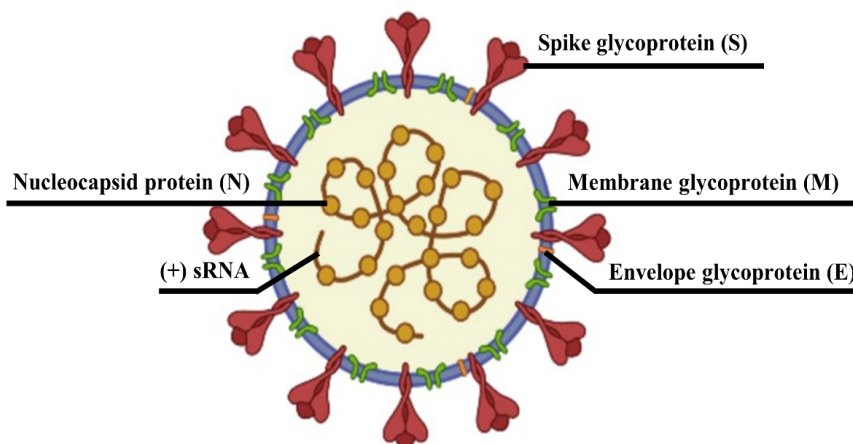


Figure 1: Structure of SARS-CoV-2.

The structure of SARS-CoV-2 consists of four structural proteins. Three transmembrane glycoproteins: spike (S) glycoprotein, envelope (E) glycoprotein and membrane (M) glycoprotein. Inside the virion, the viral positive-sense RNA genome is associated with nucleocapsid (N) glycoprotein.

PATHOGENESIS OF COVID-19

With the continuous spread of COVID-19 and the global increase in the numbers of infected cases and deaths, the scientists work day and night in order to solve the mystery of this killer virus. Until now, the exact pathogenesis of COVID-19 and the mechanism of injury caused by SARS-CoV-2 are not well under-

stood. Owing to the similarity between SARS-CoV and SARS-CoV-2 in their genome as well as the host receptor used to initiate the infection, this could give us an indication that the pathogenesis of both SARS and COVID-19 would be similar.

Virus entry

Besides the prevailing belief that the SARS-CoV-2 is zoonotic virus, it has been proved that SARS-CoV-2 is able to infect humans (Ren et al., 2020; D. Wang et al., 2020; P. Zhou et al., 2020; N. Zhu et al., 2020). Human-to-human transmission was proved between healthcare workers and people who contacted with patients or asymptomatic carriers (Bai et al., 2020; Chan et al., 2020; Guan et al., 2020). Binding between the virus and its host cell plays a critical role in the virus infectivity and transmission. Generally, the enveloped viruses enter into their target cells through two mechanisms: direct fusion of viral envelop with host plasma membrane after binding with specific receptor, and endocytosis process which is pH dependent process and/or can be mediated by specific molecules as clathrin (Sieczkarski & Whittaker, 2002). So far, it is proved that SARS-CoV-2 depends on ACE-2 receptor which binds to S1 domain of S protein to enter its target cells (Hoffmann et al., 2020; W. Li et al., 2003; Wan et al., 2020; Xintian Xu et al., 2020; P. Zhou et al., 2020). Recent studies have shown that the S protein of SARS-CoV-2 has more binding affinity and stronger interaction to ACE-2 receptor than SARS-CoV which may explain the higher transmission rate of SARS-CoV-2 compared with SARS-CoV in humans (Wan et al., 2020; Xintian Xu et al., 2020). Thereafter, the heptad repeat 1 and heptad repeat 2 of S2 domain bind together to facilitate fusion of the virus with target cell membrane (Xia et al., 2020). Human ACE-2 receptor is highly expressed by epithelial cells of the mouth, lower respiratory tissues, and with a lesser extent by the epithelial cells of other organs as kidney and intestines. After SARS-CoV-2 infection, the S protein binds to ACE-2 receptor expressed on the alveolar surface to initiate fusion process and vi-

rus entry (Perico, Benigni, & Remuzzi, 2020). Up to the date of preparing this review, it is not clear whether SARS-CoV-2 can use other mechanisms to enter the host cells like SARS-CoV which has the ability to enter the cells via pH-dependent endocytosis, and clathrin- and caveolae-independent endocytosis (Wang et al., 2008). However, it is believed that low pH enhances SARS-CoV-2 to enter into endosomes and lysosomes to start its replication cycle and to spread through the whole lungs and other organs (Perico et al., 2020). SARS-CoV-2 has a unique replicative cycle similar to other human coronaviruses which begins by translation of the replicase gene encoding two polyproteins: pp1a and pp1ab (Figure 2) (Fehr & Perlman, 2015; Wit, Doremalen, Falzarano, & Munster, 2016). The pp1a and pp1ab polyproteins are separated by proteases into non-structural proteins (nsp1-nsp16) (Fehr & Perlman, 2015). Some nsps gather to form viral replicase-transcriptase complex which is necessary for viral RNA replication, and transcription of the sub-genomic RNA into mRNAs of the structural and accessory proteins (Fehr & Perlman, 2015). Importantly, other nsps play a role in blocking host cell innate immune responses (Fehr & Perlman, 2015). Once the mRNAs of structural and accessory proteins are translated, the new viral RNAs encapsulated by N protein and other viral structural proteins enter into the endoplasmic reticulum and move into the endoplasmic reticulum-Golgi intermediate compartment where the new virions buds are generated inside double-membrane vesicles (Fehr & Perlman, 2015). Finally, the virion-containing vesicles move and fuse with the plasma membrane to release the newly formed viruses in order to infect new target cells (Fehr & Perlman, 2015). In severe cases, most of the ciliated cells in the alveoli are damaged. Consequently, these cells are not able to perform their normal activity, which leads to gradual accumulation of fluids in the lungs and finally development of acute respiratory distress syndrome (ARDS) (Perico et al., 2020).

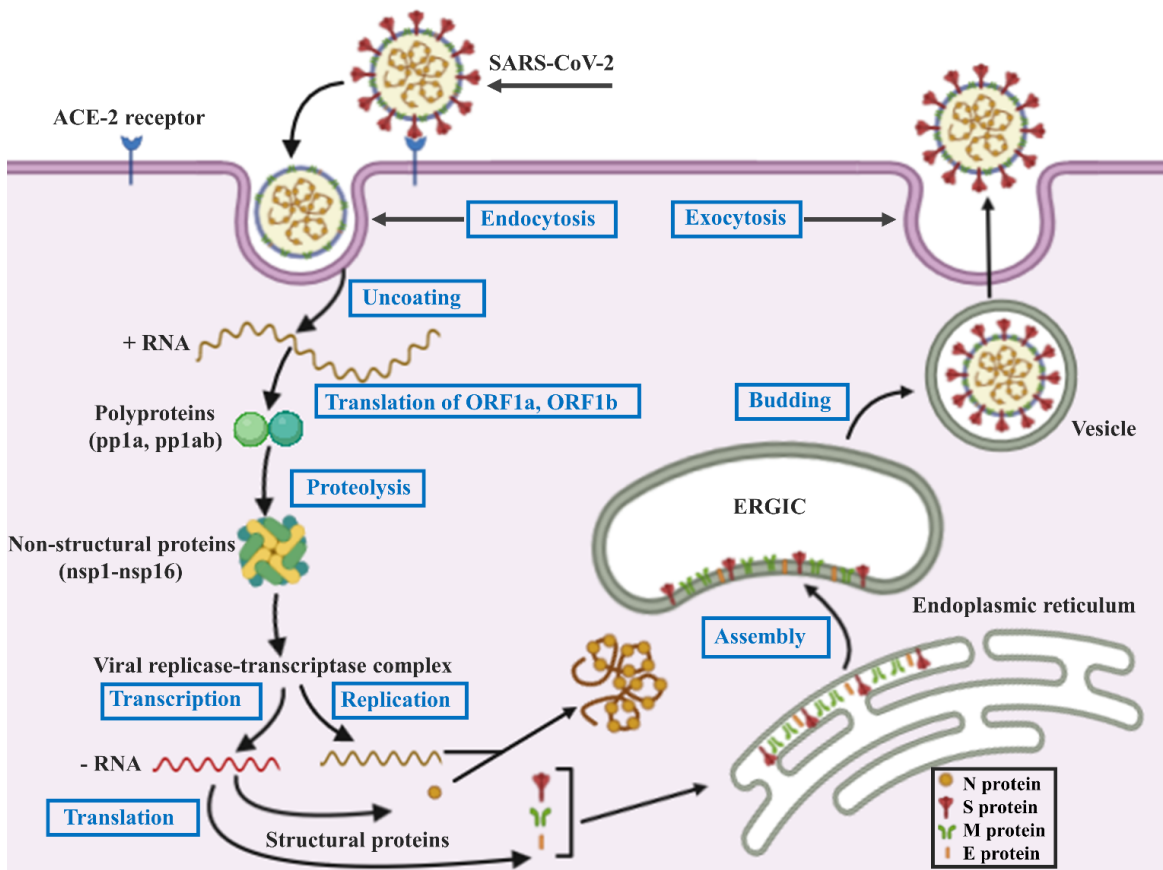


Figure 2: Replication cycle of SARS-CoV-2.

Firstly, the viral S glycoprotein binds to specific receptors called angiotensin-converting enzyme 2 (ACE-2), expressed on the surface of target cell. This binding facilitates the fusion of the virus membrane with the target plasma membrane, which results in virus entry through endocytosis process. Then the viral RNA is released in the cytoplasm, and ORF1a and ORF1ab are translated into polyproteins pp1a and 1ab. which are then cleaved into small products by viral proteinases. After that, pp1a and pp1ab undergo proteolysis process via proteases to produce 16 non-structural proteins (nsps) which form the RNA replicase-transcriptase complex. This complex is responsible for replication process to generate new copies of (+) RNA genome as well as transcription process for the sub-genomic RNA to produce (-) RNA and mRNA encoding all structural proteins, which then is translated into S, M, E and N glycoproteins. The new genomic RNAs bind to N glycoprotein in the cytoplasm forming viral nucleocapsids, then the viral nucleocapsids are assembled with S, M, and glycoproteins at the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). Following assembly process, the vesicles including virion particles are released from the ERGIC, and finally the virions are

released from the infected cell through exocytosis process.

Host immune response and immunopathology

Understanding the host immune response against SARS-CoV-2 can greatly contribute to avoid the major complications of COVID-19 such as ARDS. However, the responses underlying the role of the immune system against SARS-CoV-2 infection is still poorly understood. It is thought that the immune response against coronaviruses and SARS-CoV-2 could be similar due to structural similarity, genomic similarity mainly with SARS-CoV and MERS-CoV, and the fact that both SARS-CoV and SARS-CoV-2 use ACE-2 receptors to enter the host cells (Hoffmann et al., 2020; W. Li et al., 2003; Liang et al., 2020; R. Lu et al., 2020; Perlman & Netland, 2009; Ren et al., 2020; Wan et al., 2020; P. Zhou et al., 2020). In overall, both innate and adaptive branches of the immune system play a critical role in protecting the body from coronaviruses. Firstly, the innate immune system can identify RNAs of coronaviruses via pattern recognition receptors (PRRs) as retinoic acid-inducible gene 1 (RIG-I), melanoma differentiation-associated protein 5 (MDA-5) and toll-like re-

ceptor 3 (TLR3) which are expressed on the cell surface of innate immune cells such as monocytes, macrophages and neutrophils (Dandekar & Perlman, 2005; de Wilde, Snijder, Kikkert, & van Hemert, 2018). In addition, Wang and Liu (2016) demonstrated that M protein of SARS-CoV can function as a pathogen-associated molecular pattern (PAMP) through Toll-like pathway. In general, stimulation of these receptors triggers different signaling cascades such as NF- κ B and IRF3 which are responsible for the production of type 1 interferon (IFN) and pro-inflammatory cytokines which have antiviral activity at an early stage as well as attracting other immune cells to the infection site (Dandekar & Perlman, 2005; de Wilde et al., 2018; Prompetchara, Ketloy, & Palaga, 2020). Innate immune system also plays an essential role in activation of adaptive immune system through the antigen-presenting cells (APCs). These cells are able to present the viral antigens by the major histocompatibility complex class II (MHC-II) to be recognized by CD4+ T cells, and then the activated CD4+ T cells prime CD8+ T cells and B cells. In addition, the activated CD4+ T cells secrete cytokines to drive immune cell recruitment. During SARS-CoV-2 infection of the respiratory epithelial cells, viral peptides are presented to CD8+ cytotoxic T cells through MHC-I proteins. As a consequence, CD8+ T cells become activated and start to secrete cytotoxic mediators and pro-inflammatory cytokines to kill virus-infected cells. (Dandekar & Perlman, 2005; de Wilde et al., 2018; Prompetchara et al., 2020). It was shown that COVID-19 patients had hyperactive CD4+ and CD8+ T cells, while there was a marked decrease in the numbers of these cells in severe cases (I. Huang & Pranata, 2020; Z. Xu et al., 2020). Interestingly, recent studied showed that SARS-CoV-2 could infect T lymphocytes, spleen and lymph nodes, which may explain the lymphopenia in severe cases of COVID-19 patients (Y. Chen et al., 2020; X. Wang et al., 2020). With regard to the other arm of adaptive immune system, B cells can be converted into the antibodies secreting cells (plasma B cells) by their activation through the viruses as well as CD4+ T cells. COVID-19 patients showed a rise in both IgG and IgM antibodies levels which target N protein in 10 to 15 days after the onset of symptoms (To et al., 2020; Zhao et al., 2020).

Regrettably, these immune responses are usually associated with immunopathogenesis which results in damage of some normal host tissues and multiple organ failure due to the release of huge quantities of pro-inflammatory cytokines in the context of uncontrolled systemic inflammatory responses (Channappanavar & Perlman, 2017). This phenomenon is called cytokine storm which plays a key role in the

progression of SARS patients to ARDS (Baas, Taubenberger, Chong, Chui, & Katze, 2006; Binnie, Tsang, & dos Santos, 2014; Kong, Chui, Lim, & Salto-Tellez, 2009). Similar to patients with SARS, COVID-19 patients are characterized with lung injury and ARDS which are believed to be the leading cause of death (Huang et al., 2020; D. Wang et al., 2020; Z. Xu et al., 2020). It is expected that the cytokine storm plays a major role in the deterioration of COVID-19 for ARDS, where patients in severe stage had an increase in plasma concentration of some pro-inflammatory cytokines such as IL-1, IL-2, IL-4, IL-6, IL-7, IL-10, IL-12, IL-13, IL-17, granulocyte colony-stimulating factor (GCSF), macrophage colony-stimulating factor (MCSF), monocyte chemoattractant protein 1 (MCP-1, CCL2), macrophage inflammatory protein 1-alpha (MIP-1 α , CCL3), interferon gamma-induced protein 10 (IP-10, CXCL10), hepatocyte growth factor (HGF), IFN- γ and TNF- α (Cheng Chen, Zhang, Ju, & He, 2020; Huang et al., 2020; F. Zhou et al., 2020).

CLINICAL MANIFESTATIONS OF COVID-19

There are variations in the clinical symptoms of COVID-19 in patients starting to appear during the incubation period of the virus which is related to the patient's age and status of his/her immune system. The estimated incubation period of SARS-CoV-2 is about 5 days within the range of 2-14 days (Lauer et al., 2020; Linton et al., 2020). Commonly, most of patients have fever, fatigue, dry cough, dyspnea, myalgia diarrhea and vomiting; however, many confirmed cases are asymptomatic (N. Chen et al., 2020; Guan et al., 2020; Huang et al., 2020; D. Wang et al., 2020). In severe cases that are mainly in older patients and those suffering from chronic diseases (cardiovascular diseases, diabetes mellitus, chronic obstructive pulmonary disease, and asthma), organ dysfunction can occur such as lung injury, ARDS, acute cardiac injury, and/or acute kidney injury (N. Chen et al., 2020; Guan et al., 2020; Huang et al., 2020; D. Wang et al., 2020). In addition, several reports have referred to development of thromboembolic complications mainly pulmonary embolism among hospitalized COVID-19 patients due to the hypercoagulation status in those patients (Cui, Chen, Li, Liu, & Wang, 2020; Klok et al., 2020; Poissy et al., 2020).

TREATMENT STRATEGIES OF COVID-19

To date, no effective treatment or vaccine has been clinically proved to treat COVID-19; however, many drugs have been used as a supportive therapy such as antiviral agents, antibiotics, corticosteroids and immunotherapy (N. Chen et al., 2020; Guan et al., 2020; Huang et al., 2020; D. Wang et al., 2020). Oxygen therapy and mechanical ventilation are re-

quired in severe cases (N. Chen et al., 2020; Guan et al., 2020; Huang et al., 2020; D. Wang et al., 2020). Optimistically, many drugs have been tested against SARS-CoV-2 and showed promising results. In the meanwhile, more clinical trials are required to confirm their safety and effectiveness in the treatment of COVID-19.

Antiviral drugs

Several antiviral agents have been proposed and used alone or in combination with other drugs to decrease the replication of SARS-CoV-2. Herein, we will refer to some antiviral drugs that have shown promising results and are being assessed through clinical trials. Multiple small trials have been launched to find an effective treatment for Covid-19, while the WHO and partners have announced the launch of the largest international clinical trial on 18 March, 2020 which was called Solidarity Trial (WHO, 2020, March 18). Solidarity Trial aims to evaluate and compare the effectiveness and safety of the following drugs or drug combination against SARS-CoV2: remdesivir, hydroxychloroquine, ritonavir/lopinavir and interferon beta 1a through several countries. As of July 1, 2020, more than 5500 patients from 39 countries are participating in Solidarity study.

Remdesivir

Remdesivir (GS-5734) is a prodrug metabolized to its active form, adenosine triphosphate analog which has a broad-spectrum antiviral activity (Agostini et al., 2018; T. Warren et al., 2015; T. K. Warren et al., 2016). Its active form hinders viral RNA synthesis by inhibiting viral RNA-dependent RNA polymerase and evading viral exoribonuclease (Agostini et al., 2018; T. Warren et al., 2015; T. K. Warren et al., 2016). Remdesivir was initially developed to treat Ebola virus disease, thereafter some studies have proved its antiviral activity against coronaviruses (Agostini et al., 2018; Sheahan et al., 2017). Since the outbreak of COVID-19, remdesivir is being evaluated as a potential drug against SARS-CoV-2. In January 2020, the first confirmed case of SARS-CoV-2 in the USA was admitted to the hospital and was treated with remdesivir on the 7th day of hospitalization due to the development of severe pneumonia (Holshue et al., 2020). Noteworthy, the clinical state of the patient improved one day after treatment where the supplemental oxygen was withdrawn and the viral load decreased. The Chinese scientists have also reported the efficiency of remdesivir against SARS-CoV-2 in vitro, where its EC₉₀ was 1.76 μ M (M. Wang et al., 2020). A preliminary report described the clinical outcomes of small cohort of patients hospitalized for severe COVID-19 in different countries: 22 from the United States, 21 from Europe, 9 from

Japan and 1 from Canada, who received remdesivir from 25 January, 2020 through 7 March, 2020 (Grein et al., 2020). The report showed an improvement in the clinical condition of 36 patients (68%), and 7 patients (13%) died during the follow-up period after receiving the first dose of remdesivir. However, remdesivir adverse effects such as diarrhea, hypotension, increased hepatic enzymes and renal impairment were reported in 32 patients (60%). On 29 April 2020, the preliminary findings of the first randomized, controlled clinical trial conducted by the National Institute of Allergy and Infectious Diseases in the United States to evaluate the safety and efficacy of remdesivir in hospitalized patients with COVID-19 were available. Preliminary results showed a better recovery time and lower mortality rate in patients treated with remdesivir (median time of recovery was 11 days, mortality rate was 8%) than patients who received placebo (median time of recovery was 15 days, mortality rate was 11.6%) (Beigel et al., 2020). It is surprising that on the same date, 29 April 2020, a randomized, controlled, double blind clinical trial carried out in China for the same purpose displayed different results from the American study, where the Chinese study showed that there was no significant difference in recovery time and mortality rate among COVID-19 patients who used remdesivir and those receiving placebo (Yeming Wang et al., 2020). Further, they found that the adverse effects of remdesivir were reported in 66% remdesivir recipients. Now, other randomized, controlled clinical trials are ongoing to establish the efficacy and safety of remdesivir for treatment of COVID-19 (i.e. NCT04292730, NCT04292899, NCT04302766, NCT04252664, NCT04323761, NCT04365725, NCT04330690).

Lopinavir/Ritonavir

Lopinavir/Ritonavir is a co-formulation of lopinavir and ritonavir in a ratio 4:1, which is used to treat HIV infection due to their viral protease inhibitor. Ritonavir is a strong cytochrome P450-3A4 (CYP3A4) inhibitor which is mainly used in combination with other protease inhibitors as lopinavir to decrease their metabolism and boost their plasma concentrations (Zeldin & Petruschke, 2004). Promising results appeared in Korea when the clinical condition of the first confirmed case of COVID-19 improved after the treatment with lopinavir 400mg/ritonavir 100mg once daily (Kim et al., 2020). Interestingly, another report from Korea about using lopinavir 200mg/50mg ritonavir twice daily for treatment of COVID-19 pneumonia showed a decrease in the viral load of SARS-CoV-2 from the next day of lopinavir/ritonavir administration (Lim et al., 2020). On the other side, a randomized, controlled, open-label trial (ChiC-

TR2000029308) was performed in China to assess the effectiveness of lopinavir/ritonavir against SARS-CoV-2 (Cao et al., 2020). The Chinese study involved 199 COVID-19 patients divided randomly into two groups: lopinavir/ritonavir (400 mg/100 mg, twice a day, n=99) group and standard-care group (n=100). No difference was shown in the clinical improvement time, viral load and mortality rate in both groups. Another an open-label control Chinese study carried out to compare between the efficacy of lopinavir/ritonavir and favipiravir in treatment of COVID-19 (ChiCTR2000029600) (Cai et al., 2020). This study reported that lopinavir/ritonavir therapy had less effect on viral clearance time and improvement of chest imaging abnormalities compared with favipiravir. In the United States, the Infectious Diseases Society of America (IDSA) recommended the use of lopinavir/ritonavir therapy for COVID-19 patients in the context of clinical trials only.

On June 29, 2020, hopes of the medical staff and patients participating in a major study called Recovery Trial (NCT04381936) funded by the U.K. government to investigate the benefit of potential drugs including lopinavir/ritonavir in treatment of hospitalized COVID-19 patients were scattered when lopinavir/ritonavir treatment arm was closed due to the unfavorable results. The preliminary results showed that there is no beneficial effect of lopinavir-ritonavir on patients hospitalized with COVID-19, where the mortality rate among lopinavir/ritonavir treated patients was 22.1% compared to 21.3% of patients received usual care alone (Recovery Trial, 2020, June 29). By the same token, the International Steering Committee of the Solidarity Trial established by WHO recommended on 4 July 2020 to discontinue the lopinavir/ritonavir treatment arm for COVID-19 because of the interim trial results indicating that no valuable effect was associated with using lopinavir/ritonavir to treat hospitalized COVID-19 patients when compared to standard of care (WHO, 2020, July 04).

Nevertheless, numerous randomized, controlled clinical trials are still running to estimate the efficacy and safety of lopinavir/ritonavir in treatment of COVID-19 (i.e. ChiCTR2000029741, ChiCTR2000029867, ChiCTR2000029539, ChiCTR2000029541, ChiCTR2000029468, NCT04321174, NCT04307693, NCT04255017, NCT04330690).

Favipiravir

Favipiravir (T-705) is a guanine analogue antiviral drug having a broad spectrum activity against all strains of influenza viruses as well as other RNA viruses (Furuta et al., 2005; Shiraki & Daikoku, 2020). It is a prodrug metabolized intracellularly to the ac-

tive favipiravir-RTP which blocks the viral replication by inhibiting RNA dependent RNA polymerase (Furuta et al., 2005). Because SARS-CoV-2 is an RNA virus, it is believed that favipiravir has antiviral activity against it. A recent study tested the efficacy of some approved antiviral drugs against SARS-CoV-2 in vitro, and showed that a high concentration (EC50 = 61.88 µM) of favipiravir was required to reduce SARS-CoV-2 infection (M. Wang et al., 2020). Furthermore, an open-label control study carried out in China to compare between the efficacy of favipiravir and lopinavir/ritonavir in treatment of COVID-19 (ChiCTR2000029600) (Cai et al., 2020). The study revealed that administration of favipiravir was associated with shorter viral clearance time and more improvement in chest imaging abnormalities compared with lopinavir/ritonavir therapy. Another open-labeled, randomized multicenter clinical trial (ChiCTR200030254) was conducted in three hospitals in China from 20 February to 1 March, 2020 to compare between the antiviral activity of favipiravir and arbidol among patients with COVID-19 (Chang Chen et al., 2020). The results displayed that using favipiravir was not associated with improvement of clinical recovery rate compared to arbidol; however, post-hoc analysis showed that favipiravir treatment ameliorated the clinical recovery rate within 71.43% of moderate COVID-19 patients compared to arbidol (55.86%) and decreased the need to support oxygen therapy. Currently, several randomized, controlled clinical trials are in progress to evaluate the efficacy and safety of favipiravir in the treatment of COVID-19 (i.e. ChiCTR2000029544, ChiCTR2000029548, ChiCTR2000030113, ChiCTR2000029996, ChiCTR2000030894, ChiCTR2000030254, ChiCTR2000030987, NCT04319900, EUCTR2020-001435-27-FR, NCT04303299, NCT04310228, NCT04333589, NCT04336904, NCT04346628, NCT04359615, NCT04349241, NCT04358549).

Chloroquine and Hydroxychloroquine

Chloroquine and its analogue hydroxychloroquine are originally used as prophylaxis and treatment of malaria (Plantone & Koudriavtseva, 2018). Both drugs are effectively used to treat neurosarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome and other immunological diseases (Plantone & Koudriavtseva, 2018). Moreover, hydroxychloroquine has efficient functional activity to kill intracellular pathogens as *Coxiella burnetii* and *Tropheryma whipplei* (Fenollar, Puéchal, & Raoult, 2007; Raoult et al., 1999). Interestingly, several studies have demonstrated that both drugs have antiviral activity against various viruses such as HIV type 1, hepatitis B virus and SARS-CoV

through different mechanisms. Herein, we will mention the potential mechanisms which may be involved in the infection of SARS-CoV-2 (Rolain, Colson, & Raoult, 2007; Vincent et al., 2005). First, when these drugs enter into the cells, they are protonated and trapped inside the endosomes and lysosomes (acidic organelles) leading to increasing the pH level. This is critical for viruses depending on a low pH for entry into their host cell and those depend on the endosomal pathway for their replication cycle, because the increased pH will prevent their infection (Rolain et al., 2007). Second, chloroquine and hydroxychloroquine may inhibit the entry of SARS-CoV-2 into the target cell by suppressing the terminal glycosylation of ACE-2 receptor which may reduce the binding efficiency between the viral S protein and ACE-2 receptor (Rolain et al., 2007; Vincent et al., 2005). Since the prevalence of SARS-CoV-2, vast data have been published about the safety and efficiency of chloroquine and hydroxychloroquine in COVID-19 patients. Firstly, M. Wang et al. (2020) from China demonstrated that chloroquine could act effectively against SARS-CoV-2 in vitro before and after its entry to the target cell, and its EC₅₀ and EC₉₀ values were 1.13 μ M and 6.90 μ M, respectively. Another study found that hydroxychloroquine was more effective against SARS-CoV-2 in vitro compared with chloroquine (EC₅₀=0.72 μ M and 5.47 μ M, respectively) (Yao et al., 2020). Based on these results, several clinical trials were oriented in China to assess the safety and efficacy of chloroquine and hydroxychloroquine in treatment of patient with COVID-19 (Gao, Tian, & Yang, 2020). The results were optimistic due to the effective antiviral activity of chloroquine against SARS-CoV-2 without significant side effects. Accordingly, the National Health Commission of the People's Republic of China recommended to include chloroquine in the guidelines for the prevention, diagnosis, and treatment of COVID-19. In March 2020, the first open label, non-randomized clinical trial was conducted in Marseille-France to assess the effectiveness of hydroxychloroquine against SARS-CoV-2 (Gautret et al., 2020). The French study included 20 patients with COVID-19 treated with hydroxychloroquine, whereas azithromycin was added in certain cases. The findings pointed to a significant decrease in the viral load in patients receiving hydroxychloroquine compared to the control group and the reduction was more pronounced when co-administered with azithromycin. Following this study, the same team performed an uncontrolled non-comparative observational study including 80 patients with COVID-19 treated with hydroxychloroquine in combination with azithromycin for three days (Gautret et al., 2020). Again, they found a significant reduction in

the nasopharyngeal viral load, where the viral load was not detected in 93% of patients at day 8 after treatment. In parallel, the results of a Chinese study was issued which were compatible with the French results (Z. Chen et al., 2020). Nevertheless, some studies indicated that the use of hydroxychloroquine alone or in combination with azithromycin was associated with severe QT prolongation and arrhythmias (Chen, Wang, & Lin, 2006; Chorin et al., 2020; Morgan, Patel, & Dvorkina, 2013). In the United State, the IDSA recommended the use of chloroquine and hydroxychloroquine alone or in combination with azithromycin for treatment of COVID-19 patients in the context of clinical trials only. Although the US Food and Drug Administration (FDA) authorized the use of hydroxychloroquine and chloroquine under an Emergency Use Authorization for treatment of COVID-19, it revoked its emergency authorization for them due to the serious cardiac adverse effects associated with using the drugs in COVID-19 (FDA, 2020, June 15).

On June 17, 2020, it was a new blow to hopes that hydroxychloroquine could be effective in the treatment of COVID-19 when the WHO announced the dropping of hydroxychloroquine arm within the Solidarity trial. The decision was based on the preliminary findings of Recovery Trial (NCT04381936) conducted to test the benefit of potential drugs including hydroxychloroquine in treatment of hospitalized COVID-19 patients, and the recently published results of the clinical trial (NCT04308668) conducted in the United States and Canada to assess the efficacy of hydroxychloroquine as a prophylactic treatment postexposure to confirmed COVID-19 cases. Both studies have found that hydroxychloroquine had no benefit for hospitalized patients with COVID-19 as well as did not prevent the incidence of new cases of COVID-19 among people who had been exposed to SARS-CoV-2 (Boulware et al., 2020; Recovery Trial, 2020, June 05). In the same context, the WHO accepted the recommendations from the International Steering Committee of the Solidarity Trial on 4 July 2020 to discontinue the hydroxychloroquine treatment arm for COVID-19 due to the interim trial results showing that hydroxychloroquine did not significantly reduce the death of hospitalized COVID-19 patients when compared to standard of care (WHO, 2020, July 04).

However, several studies are ongoing to answer the mystery of the benefits versus harms caused by using these drugs for treatment of COVID-19 (i.e. ChiCTR2000029741, ChiCTR2000029992, ChiCTR2000029803, ChiCTR2000030054, ChiCTR2000029898, NCT04328493, NCT04362332, NCT04344951, NCT04333732, NCT04331470,

NCT04351724, NCT04322396, NCT04324463,
NCT04341727, NCT04325893, NCT04328285,
NCT04329832).

Umifenovir

Umifenovir (Arbidol) is a broad-spectrum antiviral drug approved in Russia and China for prophylaxis and treatment of influenza A and B viruses as well as other enveloped and non-enveloped RNA or DNA viruses such as Zika virus, Lassa virus, Ebola virus, SARS-CoV, hepatitis B and C viruses (Blaising, Polyak, & Pécheur, 2014; Boriskin, Leneva, Pécheur, & Polyak, 2008). Unlike other antiviral drugs, the broad-spectrum antiviral activity of umifenovir is related to its direct virucidal effect and its effect on different stages of the viral life cycle as cell entry replication and budding (Blaising et al., 2014; Boriskin et al., 2008). Based on previous clinical data from SARS, the National Health Commission of China announced in February 2020 to test umifenovir as a possible treatment for COVID-19.

In April 2020, Z. Zhu et al. (2020) published the results of their study which was conducted in China to evaluate the safety and efficiency of lopinavir/ritonavir and arbidol in patients with COVID-19. Their results revealed that arbidol was better than lopinavir/ritonavir in treating COVID-19, where patients in the arbidol group had no detection of viral load compared to those in the lopinavir/ritonavir group (viral load was detected in 44.1% of patients) at day 14 of admission. At the same time, the findings of an exploratory, randomized, open-labelled, controlled study (NCT04252885) carried out to assess the safety and antiviral effects of arbidol and lopinavir/ritonavir as treatment for COVID-19 were available and showed a little improvement in the clinical outcome of patients hospitalized with mild/moderate COVID-19 and treated with arbidol or lopinavir/ritonavir monotherapy over supportive care (Y. Li et al., 2020). With the continues spread of SARS-CoV-2, many randomized, controlled clinical trials are ongoing to determine the efficacy and safety of umifenovir as a possible treatment of COVID-19 in comparison with other drugs (i.e. NCT04260594, NCT04350684, ChiCTR2000029621, ChiCTR2000029592, IRCT20180725040596N2).

Anti-inflammatory and immunomodulatory drugs

In general, anti-inflammatory and immunomodulatory drugs are included in regimen of COVID-19 treatment as adjunctive therapies to minimize the progression of COVID-19 pneumonia to ARDS. In China, the origin of SARS-CoV-2, corticosteroids were used to reduce the uncontrolled host immune responses that could then diminish the role of cytokine storm in development of ARDS in patients with

COVID-19 pneumonia. For example, a retrospective cohort study of 201 patients with COVID-19 pneumonia was performed in Wuhan, China to describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia (Wu et al., 2020). The findings showed that COVID-19 pneumonia developed to ARDS in 84 patients, and administration of methylprednisolone for those patients was associated with a decreased risk of death (23/50, 46% with methylprednisolone compared to 21/34, 62% without methylprednisolone). Another study from Wuhan, China found that patients receiving a low-dose and a short-term methylprednisolone revealed a better improvement of clinical symptoms (Yin Wang et al., 2020). However, several adverse effects of corticosteroids including hyperglycemia, delayed viral clearance and increased risk of secondary infection were associated with SARS and MERS patients receiving corticosteroids (Russell, Millar, & Baillie, 2020). Due to the limited evidences about the benefit of corticosteroids in COVID-19 patients and their potential adverse effects, the WHO recommended that corticosteroids should not be regularly used for the treatment of COVID-19 patients with pneumonia or ARDS except if corticosteroids were used for other conditions. On 16 June, 2020, the WHO welcomed the initial results of the Recovery Trial (NCT04381936) about the benefit of dexamethasone treatment for patients hospitalized with COVID-19. Dexamethasone reduced the death among patients with severe respiratory complications of COVID-19, but not among patients with mild to moderate cases (Horby et al., 2020).

Regarding the immunomodulating agents, the efficacy of some monoclonal antibodies in treatment of COVID-19 patients was tested and are being in clinical trials such as tocilizumab, sarilumab, bevacizumab and eculizumab. Tocilizumab, IL-6 receptor antagonist, is thought to be effective against SARS-Cov-2 due to the potential role of IL-6 in the development of ARDS and organ failure, where severe cases of COVID-19 patients are characterized by elevation of IL-6 and other cytokines (Cheng Chen et al., 2020; Huang et al., 2020; F. Zhou et al., 2020). Tocilizumab is also used to treat cytokine storm resulting from chimeric antigen receptor T-cell therapy (Riegler, Jones, & Lee, 2019). In April 2020, promising preliminary findings of a Chinese study were published and indicated that 91% of COVID-19 patients receiving tocilizumab showed an improved clinical outcome within 5 days after treatment without serious adverse effects (Xiaoling Xu et al., 2020). In June 2020, the results of two retrospective cohort studies conducted to assess the benefit of tocilizumab in patients with severe COVID-19 were published (Guaraldi et al., 2020; Kewan et al., 2020). The results showed that tocilizumab

reduced the median time to clinical improvement and duration of invasive ventilation. Several randomized, controlled clinical trials are underway to determine the safety and effectiveness of treatment with tocilizumab alone or in combination with other drugs for patients with COVID-19 (i.e. NCT04317092, NCT04331795, NCT04332094, NCT04359667, NCT04320615, NCT04356937, NCT04310228, NCT04333914, NCT04320615, ChiCTR2000029765, ChiCTR2000030894, ChiCTR200002976). Other monoclonal antibodies are being evaluated in clinical trials for treatment of COVID-19 patients such as sarilumab (another IL-6 receptor antagonist; NCT04341870, NCT04315298, NCT04327388, NCT04359901), bevacizumab (anti-vascular endothelial growth factor; NCT04275414, NCT04305106) and eculizumab (antibody inhibiting terminal complement; NCT04346797, NCT04355494).

Convalescent plasma

Convalescent plasma (hyper-immunoglobulins) therapy is using the plasma of recovered patients for treating other patients. To date, no efficient vaccine is available for COVID-19 and its development needs months. So, convalescent plasma could be a suitable alternative therapy because the plasma of recovered patients contains specific antibodies which can boost the immune responses against SARS-CoV-2. Using the convalescent plasma for treating severe cases of COVID-19 patients is justified by its effective results as a rescue therapy for other diseases as SARS, MERS, H1N1 influenza and Ebola (Arabi et al., 2015; Hung et al., 2013; Soo et al., 2004; van Griensven, Edwards, Gallian, & Ebola-Tx Consortium, 2016) and the effectiveness of ribavirin-steroid therapy is unclear. Forty SARS patients with progressive disease after ribavirin treatment and 1.5 g of pulsed methylprednisolone were given either convalescent plasma ($n=19$). The preliminary findings of the first uncontrolled case series study carried out in China to identify the effectiveness of convalescent plasma transfusion in the treatment of severely ill patients with COVID-19 and ARDS (Shen et al., 2020). As a result, all the patients were clinically improved, where the viral load became negative and ARDS resolved in 80% of patients within 12 days after convalescent plasma transfusion. Other promising results appeared in April 2020 when Duan et al. (2020) issued the outcomes of transfusion of convalescent plasma into 10 patients with critical COVID-1. This study showed that convalescent plasma therapy was well-tolerated and associated with improvement of the clinical symptoms within 3 days following transfusion. Based on these preliminary results, numerous randomized, controlled clinical trials are still being performed globally to assess the safety and efficacy of convalescent plasma in the treatment

for patients with COVID-19 (i.e. NCT04345991, NCT04343755, NCT04353206, NCT04372368, NCT04338360, NCT04358211, NCT04345523, NCT04374526, NCT04340050, NCT04359810, NCT04346589, NCT04354766, NCT04345289, NCT04346446, NCT04356482).

CONCLUSION

A novel coronavirus disease 2019 (COVID-19) caused by a new virus identified as SARS-CoV-2 has been appeared in Wuhan, China in December 2019 and then quickly spread worldwide. SARS-CoV-2 is a zoonotic virus related to enveloped RNA β -coronaviruses which is originated in bats and has been transmitted to humans by unidentified intermediate. The virus enters the human host cell by binding to ACE-2 receptors highly expressed on the surface of epithelial cells of the lungs. Although the symptoms of COVID-19 infection are usually mild and self-limited, some patients show severe symptoms due to the development of ARDS and multiple organ damage. Until now, no specific treatment or vaccine has been validated against COVID-19 infection. Several proposed drugs that could have efficacy against SARS-CoV-2 have been evaluated and some of them showed promising results. Now, numerous clinical trials are underway to establish the safety and efficiency of the potential drugs in the treatment of COVID-19 infection.

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