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Coronavirus disease 2019: a clinical review

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Abstract. – In December 2019, an outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China, and it subsequently spread in many countries around the world. Many efforts have been applied to control and prevent the spread of COVID-19, and many scientific studies have been conducted in a short period of time. Here we present an overview of the viral structure, pathogenesis, diagnosis, and clinical features of COVID-19 based on the current state of knowledge, and we compare its clinical characteristics with SARS and Middle East Respiratory Syndrome (MERS). Current researches on potentially effective treatment alternatives are discussed. We hope this review can help medical workers and researchers around the world contain the current COVID-19 pandemic.

Key Words:
COVID-19, Pathogenesis, Clinical features, Therapeutics.

Introduction

At the end of 2019, coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused an outbreak in Wuhan, China, and then, spread rapidly around the world by human-to-human transmission. By March 23, 2020, in China, there were 81093 confirmed cases, 72703 cured patients and 3270 deaths. In China so far, the cure rate is 89.65% and mortality rate is 4.0%. Outside China, 210644 cases have been confirmed, accounting for 72.1% of the total number of confirmed cases in the world. SARS-CoV-2 has spread worldwide and so far affected 186 countries. However, the diagnosis is difficult and there are no specific drugs for COVID-19. Therefore, it is important to learn more about the virus in order to develop rapid and accurate diagnostic methods, as well as potentially effective drugs.

SARS-CoV-2 is a single-stranded, positive-sense RNA virus, which belongs to a new evolutionary branch of coronavirus. It belongs to the genus β-coronavirus together with SARS coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV)[1]. SARS-CoV-2 shares 96% genomic sequence identity with bat coronavirus[2], indicating that it may have been initially hosted by bats, similarly to SARS-CoV. However, protein sequence differences between SARS-CoV-2 and SARS-CoV suggest that the former is not a descendant of SARS-CoV[3]. Based on the previous studies of SARS-CoV and MERS-CoV, researchers found that SARS-CoV-2 shares the same receptor as SARS-CoV, angiotensin-converting enzyme 2 (ACE2)[4]. The discovery of the receptor can greatly contribute to learn about the pathogenesis of COVID-19 and guide the development of targeted therapies.

Currently, there are more than 80 ongoing or scheduled clinical trials of COVID-19, but no specific coronavirus treatment or SARS-CoV-2 vaccine of proven efficacy has yet been developed for clinical use. In this review, we summarize data about SARS-CoV-2 structure and about COVID-19 pathogenesis, diagnosis, clinical features and experimental therapeutics. This synthesis may provide guidance for the response to the outbreak around the world.

The Virus

Coronaviruses are single-stranded, positive-sense RNA viruses of the *Coronaviridae* family and *Orthocoronavirinae* subfamily that in-

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fect animals and humans. Coronaviruses are classified into four major genera: alphacoronavirus (α), betacoronavirus (β), gammacoronavirus (γ), and deltacoronavirus (δ)[1]. Currently, seven kinds of human coronaviruses have been identified, including HCoV 229E and HCoV NL63, which belong to the α genus; and HCoV-OC43, HCoVHKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2, which belong to the β genus.

SARS-CoV-2 is an enveloped virus with diameters ranging from 50 to 200 nm, and round or elliptic, often pleomorphic, shape. An electron micrograph of the virus is shown in Figure 1. The single-stranded RNA genome of SARS-CoV-2 contains 29,891 nucleotides. One study found that SARS-CoV-2 has already mutated, and there are two types (L and S). At position 28144 of the viral RNA genome, the L-type contains a T base, while the S-type contains a C base. The S-type is relatively "old", while the L-type carries more mutations[5]. The genome encodes at least 27 proteins, including the following reading frames in sequence: 5'-replicase (orf1/ab)-structural protein [spike (S)-envelope (E)-membrane (M)-nucleocapsid (N)]-3'. The spike protein S is responsible for virus entry into the cell, and comprises subunits S1 and S2[4]. The S1 subunit contains a signal peptide followed by an N-terminal domain (NTD) and a receptor-binding domain (RBD); while the S2 subunit contains a conserved fusion peptide (FP), a heptad repeat (HR) 1 and 2, a transmembrane domain (TM), and a cytoplasmic domain (CP). The S2 subunit of SARS-CoV-2 is highly conserved and shares 99% sequence identity with the S2 subunits of two bat SARS-like coronaviruses (SL-CoV ZXC21 and ZC45) as well as human SARS-CoV[6].

The proteins encoded by the SARS-CoV-2 genome differ from SARS-CoV at the amino acid level[7]. The most significant variation in the S protein of SARS-CoV-2 is the Flynn protease recognition site (RRAR) at the S1/S2 protease cleavage site, which differs from the single arginine in SARS-CoV[8]. This indicates that SARS-CoV-2 and SARS-CoV may differ in their efficiency of infecting humans. Researchers analyzed the genome of the SARS-CoV-2 to determine its origin and evolutionary history and found 96% genomic sequence identity to the bat coronavirus[3]. SARS-CoV-2 shares 98.7% nucleotide similarity to bat coronavirus strain BtCoV/4991 based on a 370-nt sequence of the RdRp gene (GenBank KP876546) and 87.9% nucleotide similarity to bat coronavirus strains bat-slcovzc45 and bat-sl-covzxc21, indicating that it is less genetically similar to currently known human coronavirus strains, including SARS-CoV (79.7%)[9]. Phylogenetic analysis showed that SARS-CoV-2 belongs to sarbecoviruses of the β genus, and is connected only by a relatively long branch to its closest relatives bat-sl-covzc45 and bat-sl-covzxc21, confirming the genetic differences from

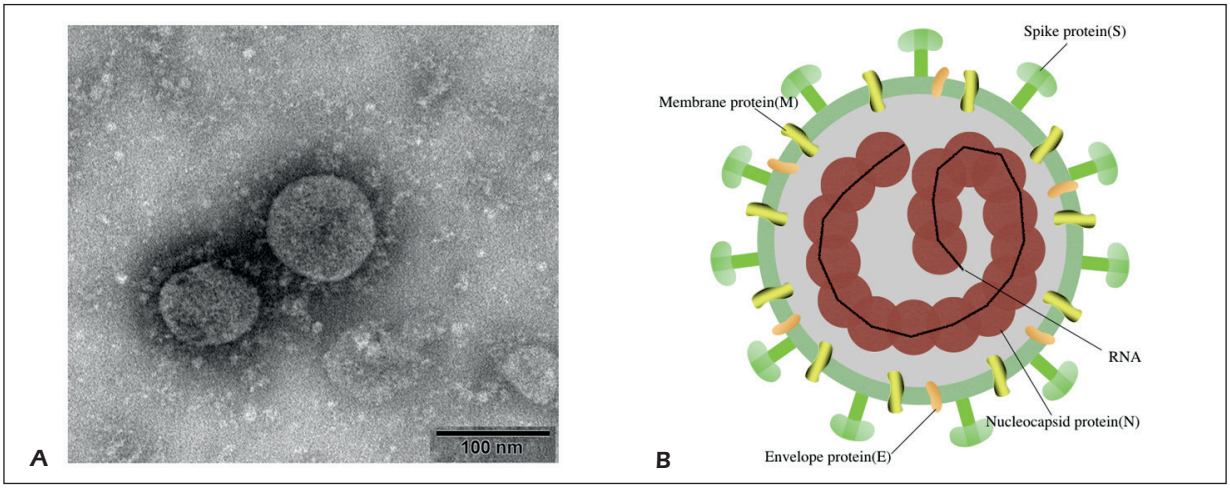

Figure 1. Structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). **A,** Viral particles in ultrathin sections under the electron microscope at 200 kV. Chinese name: 2019-nCoV Wuhan strain 02 (English name: C-F13-nCoV Wuhan strain 02). **B,** SARS-CoV-2 pattern diagram: SARS-CoV-2 includes a single-stranded, positive-sense RNA and four structural proteins: the spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein. Note: the picture in Figure 1A was obtained from the National Pathogen Microbial Resource Bank at the China Center for Disease Control and Prevention (NPRC: 2020.00002).

SARS-CoV[10]. In conclusion, SARS-CoV-2 is not a descendant of SARS-CoV, but an independently evolved branch of coronavirus. The branch may have been initially hosted by bats and transmitted to humans *via* pangolins as intermediate hosts[11].

Pathogenesis

SARS-CoV-2 uses highly glycosylated homotrimeric S proteins to enter host cells. The S1 subunit of the S protein binds to the host cell receptor, which causes its shedding and the transition of the S2 subunit to a highly stable post-fusion conformation[12]. To access the host cell receptor, the RBD in the S1 subunit undergoes a hinge-like movement, very similar to that of SARS-CoV and MERS-CoV. However, the RBD structure in SARS-CoV-2 is closer to the central part of the trimer. One of the three RBDs in the S protein protrudes upwards, allowing the S protein to adopt a structure that can easily bind to the host receptor[8].

SARS-CoV-2 uses the SARS-coronavirus receptor ACE2 and the cellular transmembrane protease serine 2 (TMPRSS2) for entry into target cells[4]. Cryo-electron microscopy showed ACE2 to exist as a dimer, to be able to adopt "open" or "closed" conformations[13]. Sequence analysis showed that the overall sequence similarity between SARS-CoV-2 spikes and SARS-CoV spikes (isolated from humans, civet cats or bats) was about 76-78% for the entire protein and 73-76% for RBD, which provides a structural basis for the ability of SARS-CoV-2 and SARS-CoV to use the same receptor[14].

Virus infectivity is studied using HeLa cells expressing, or not expressing, ACE2 protein from humans, Chinese horseshoe bat, civet, pig, or mouse. SARS-CoV-2 was able to use all but mouse ACE2 as an entry receptor in the ACE2-expressing cells, while it was unable to enter cells without ACE2, suggesting that ACE2 is the receptor for SARS-CoV-2 entry into cells[2]. Kinetic measurements indicated that the affinity of SARS-CoV-2 for ACE2 is much higher than in the case of SARS-CoV, which may be the main reason for the strong infectivity of SARS-CoV-2[8]. SARS-CoV-2 does not use other coronavirus receptors, such as aminopeptidase N or dipeptidyl peptidase 4[2].

TMPRSS2 is expressed in target cells of SARS-CoV in the lung and has been shown to promote virus entry in studies involving a TMPRSS2-positive cell line[15]. Inhibition of TMRPSS2 expression in target cells reduces the efficiency of SARS-CoV-2 entry into target cells, suggesting that SARS-CoV-2-S may use TMPRSS2 for initiation[4].

ACE2 shows relatively high expression in alveolar type 2 cells, thus allowing the virus to enter cells and multiply in large numbers through the mechanism mentioned above. The virus may downregulate ACE2 and activate the renin-angiotensin system (RAS) system, thereby increasing vascular permeability and altering alveolar epithelial cells, leading to lung injury[16]. ACE2 is an ACE homologue that regulates the homeostasis of angiotensin. ACE converts inactive angiotensin I (Ang I) to active angiotensin II (Ang II), while ACE2 converts Ang I to angiotensin 1-9 and Ang II to angiotensin 1-7. The rise in Ang II level activates the RAS system, primarily through the type 1 receptor for angiotensin II (AT1R) (Figure 2).

Some diseases, such as hypertension, diabetes mellitus, and cardiovascular and cerebrovascular diseases, more common in the elderly, can lead to decreased glomerular arterial pressure, hypotension, and hyponatremia, leading to an increase in renin secretion. This, in turn, increases ACE2 secretion through positive feedback regulation. Individuals with these diseases are expected to be more susceptible to severe COVID-19 due to the upregulation of ACE2 expression, consistent with the fact that most COVID-19-associated mortality involves elderly patients with more comorbidities[17]. ACE2 expression is also higher in smoker lung tissue samples, so smokers may be more susceptible to COVID-19[18].

SARS-CoV-2 enters alveolar cells and rapidly multiplies, causing a rapid and massive production of a variety of cytokines, including interferons (IFNs), interleukin (ILs), chemokines, colony-stimulating factors (CSFs), and tumor necrosis factors (TNFs), in body fluids. These cytokines in turn continuously activate immune cells and accumulate at sites of inflammation. This immune process is called a cytokine storm[17,19]. As a result, congestion, edema, fever, and lung tissue injury occur, potentially giving rise to acute respiratory distress syndrome (ARDS) and lung function failure. Moreover, excessive activation of T cells, manifested by an increase in T helper 17 (Th17) and cytotoxic $CD8^+$ T cells, may cause hypoimmunity in some patients[20].

ACE2 is expressed not only in the respiratory organs, but also in the small intestine, duodenum, kidney, and testis. The entry of the virus in target cells may result in intestinal dysfunction, renal insufficiency, reduced fertility, and other

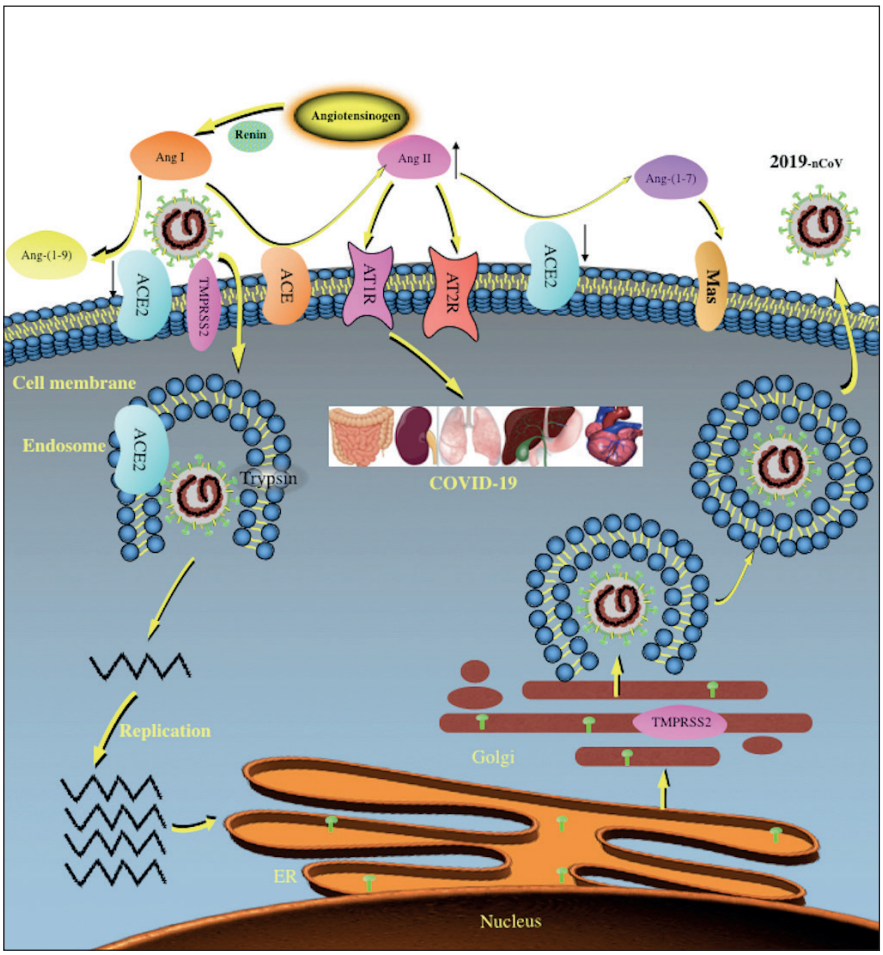

Figure 2. Pathogenesis of coronavirus disease (COVID-19) caused by SARS-CoV-2. The virus uses the SARS-coronavirus receptor angiotensin-converting enzyme 2 (ACE2) and the cellular transmembrane protease serine 2 (TMPRSS2) to enter host cells. Then the virus proliferates substantially within the host cell and reduces ACE2 expression, which in turn causes an increase in angiotensin II (Ang II). Increased Ang II activates the renin-angiotensin system (RAS), leading to coronavirus disease (COVID-19). *Abbreviations:* AT2R: the type 1 receptor for angiotensin II; ER: Endoplasmic Reticulum.

damage[21]. Single-cell RNA sequencing showed that bile duct cells express the SARS-CoV-2 receptor ACE2, and the virus may bind directly to ACE2-positive bile duct cells[22]. This may result in bile duct dysfunction, damaging liver function.

Clinical Features

At the beginning of the outbreak, most of the patients with COVID-19 had a history of direct or indirect contact with the Wuhan epidemic area. However, local transmission is currently occurring in many countries. All ages are susceptible to infection, and the median age of COVID-19 patients is 48.4 years. Moreover, around 59.1% of COVID-19 patients are men in China[23]. The main clinical symptoms are fever, dry cough, fatigue, expectoration, and dyspnea. Some patients also develop symptoms, such as myalgia, pharyngodynia, headache, nausea, upper respiratory tract congestion, and diarrhea. Some patients are asymptomatic carriers[24]. About 27.7% of COVID-19 patients have preexisting systemic morbidity, mainly hypertension, diabetes, and cardiovascular and cerebrovascular diseases. Most patients show a mild presentation of the disease and have good prognosis, while about 17.8% of patients require intensive care. Patients over 50 years of age with a neutrophil/lymphocyte ratio (NLR) $\geq$ 3.13 are at high risk of severe COVID-19[25]. Compared with non-cancer patients, cancer patients are at higher risk of developing severe COVID-19[26]. The more frequent serious complications are ARDS and shock, with a higher incidence of complications among elderly patients with comorbidities. 63% of COVID-19 patients have renal diseases, such as proteinuria[21], and nearly 50% of patients have abnormal liver function[22].

Laboratory tests indicate decreased absolute lymphocyte counts in most patients, suggesting that SARS-CoV-2 may act on lymphocytes in a similar way as SARS. Patients frequently present lymphopenia (70.3%), prolonged coagula-

tion (58%), and increased lactate dehydrogenase levels (39.9%)[27]. White blood cells, hemoglobin, and platelets are lower than the normal range in some patients[17], while C-reactive protein and erythrocyte sedimentation rate are elevated[17,23].

Computed tomography (CT) shows shadows or frosted glass opacity in the lung in most COVID-19 patients[27]. Clinically relevant indicators of the disease that significantly deviate from normal values (including oxygen saturation, respiratory rate, white blood cell/lymphocyte count, and chest X-ray/CT findings) predict poor clinical outcomes[28].

Young patients may mount strong immune responses, and some of them are prone to suffer cytokine storms, worsening their prognosis[29,30]. Compared with the adverse pregnancy outcomes caused by SARS-CoV infection, pregnant COVID-19 patients show milder symptoms and better prognosis[31]. So far, pediatric clinical manifestations are not typical, and relatively milder, compared with that of adult patients[32]. Most deaths caused by SARS-CoV-2 are due to multiple organ dysfunction syndrome, rather than respiratory failure[26]. Compared with SARS and MERS, the clinical symptoms of COVID-19 are more similar to SARS, and the overall clinical symptoms are lighter than SARS. The incidence of severe cases of COVID-19 and SARS is significantly lower than that of MERS[35] (**Supplementary Table I**[25-28,32-34,36-49]).

Diagnosis

The diagnosis of COVID-19 mainly relies on genetic tests, such as Real Time-PCR (RT-PCR) and gene sequencing[50]. Respiratory tract specimens (including nasopharyngeal swabs, bronchoalveolar lavage fluid, sputum or bronchial inhalation fluid) or blood specimens of patients are used for RT-PCR detection[51], which commonly amplifies open reading frames 1a or 1b and the nucleocapsid protein[52]. Gene sequencing can reveal whether genes in the specimen are highly homologous to SARS-CoV-2[10]. A positive RT-PCR result indicates that the patient may have SARS-CoV-2 infection, but a negative result cannot exclude SARS-CoV-2 infection. The RT-PCR positive rate of patients is about 38%[53]. Negative results may be attributed to degradation of RNA or to inadequate methods of material collection, cryopreservation, or quality control of detection reagents. Probable cases must be evaluated through clinical observations, patient history, and epidemiological information again.

High-resolution CT (HRCT) is another important method for patient assessment. Chest CT of early-stage COVID-19 patients shows multiple small patchy shadows and interstitial changes, which are evident in the lung periphery. Further development of multiple ground-glass shadows and diffuse shadows in the lungs may lead to consolidation of the lung[54], while pleural effusion or lymphadenopathy are rare. Hematology tests are not specific, but the absolute lymphocyte count is decreased in most patients, which can be used for early diagnosis of non-febrile patients at their first visit[23].

Treatment

There is currently no specific treatment for COVID-19. In clinical practice, the treatment of COVID-19 in China mainly includes oxygen therapy, antiviral therapy, and traditional Chinese medicine treatment. For patients with severe disease, invasive oxygen therapy and circulatory support are needed, but the results are not satisfactory.

Studies[55,56] have shown that the key drug-binding sites in the corresponding enzymes of SARS-CoV-2, SAR-CoV and MERS-CoV may be the same. Therefore, at the emergency stage, drugs used against SARS and MERS may guide the quick discovery of specific drugs to treat COVID-19. As of March 23, 2020, we have compiled information on approximately 81 kinds of promising therapeutic drugs for COVID-19 from ClinicalTrials.gov of the US National Institutes of Health, the Chinese Clinical Trial Registry, and other clinical and scientific research centers around the world. We present promising treatments that may be effective for COVID-19 patients divided into three categories: antiviral therapy (**Supplementary Table II**[57-63]), immune therapy (**Supplementary Table III**[17,64]), and traditional Chinese medicine treatment (**Supplementary Table IV**). Among them, antiviral drugs are divided into those with virus-based or host-based effects, while immune therapies are divided into immunosuppressive or immunoenhancing.

Antiviral Therapy

Virus-Based Treatment Strategies

Nucleoside analogs

Nucleoside analogs exert antiviral effects by blocking RNA synthesis by the RNA-dependent RNA polymerase. Representative drugs include

favipiravir, ribavirin, and remdesivir. Favipiravir and ribavirin are RNA polymerase inhibitors with broad-spectrum antiviral effect *in vitro*. Favipiravir is completed in clinical studies and shows good curative effects. It is recommended that favipiravir can be included in the treatment programs as soon as possible[65]. According to *in vitro* activity tests, favipiravir can effectively inhibit the replication of SARS-CoV-2 without toxic effects on cells. For treating SARS, patients treated with the combination lopinavir/ritonavir (Kaletra®, Abbvie, North Chicago, IL, USA) and ribavirin were found to be at lower risk of ARDS or death than patients treated with ribavirin alone[66].

Remdesivir is widely used in the treatment of Ebola virus infection, and relatively complete data are available on its human pharmacokinetics and safety[57]. Not only can remdesivir inhibit nucleoside RNA-dependent RNA polymerase, but its triphosphate form can compete with ATP binding to the polymerase, interfering with viral RNA synthesis. Remdesivir was highly effective at treating a patient with severe SARS-CoV-2 infection[67].

Protease inhibitors

Kaletra (lopinavir and ritonavir) inhibits the 3C-like protease. Kaletra is mainly used to treat human immunodeficiency virus-1 (HIV-1) infection in adults and children older than two years, and it can be combined with other antiretroviral drugs. Kaletra may have therapeutic effects in SARS and MERS by reducing the ability of the replicated virus to infect cells. The therapeutic effect of Kaletra on COVID-19 may be mainly due to the inhibitory effect of ritonavir on coronavirus endopeptidase C30[66,68].

Nafamostat is a broad-spectrum serine protease inhibitor that targets S protein-mediated membrane fusion to block the virus from entering the cell[69]. It has been proposed as a potential candidate for the treatment of COVID-19[58].

Virus-cell fusion inhibitors

Arbidol® (umifenovir; Pharmstandard, Dolgoprudny, Russia) is an antiviral drug used in Russia and China for influenza infection. Arbidol blocks the replication of the virus by inhibiting the fusion of influenza virus lipid membranes with host cells and inducing an immune response. Arbidol hydrochloride can be used to treat SARS[70], and it can significantly inhibit replication of SARS-CoV-2 *in vitro*[71].

Neuraminidase inhibitors

Oseltamivir is a broad-spectrum anti-influenza drug functioning as a neuraminidase inhibitor to block the release of the virus from host cells. It can effectively treat MERS-CoV infection[72]. Oseltamivir is used against COVID-19 only when flu is present[61], because evidence of its efficacy against SARS-CoV-2 is lacking.

Host-Based Treatment Strategies

Interferons

IFN-α, a type I IFN that activates the IFN-α/β receptor complex, activates the intracellular Jak/Stat signaling pathway and regulates the transcription of multiple target genes, the so-called IFN-stimulated genes. Modulation of IFN-stimulated genes causes an antiviral response in target cells that limits the replication and transmission of virus. Based on its extensive antiviral effects, IFN-α is one of the clinical candidates for COVID-19 treatment.

Polyinosinic-polycytidylic acid injection, a broad-spectrum antiviral drug, produces antiviral effects by inducing IFN and stimulating phagocytosis of macrophages. It is currently in clinical trials to treat COVID-19.

Nitazoxanide is a broad-spectrum antiviral and antiparasitic drug used to treat the flu. Nitazoxanide promotes the production of type I IFNs (α and β) by host fibroblasts and blocks viral maturation. In cell culture studies, nitazoxanide showed promise for the treatment of viral respiratory infections, and it may be effective for the treatment of COVID-19[58].

Antimalarial agents

Chloroquine is a widely used drug against malaria and some autoimmune diseases. Chloroquine prevents SARS-CoV from invading cells by changing the glycosylation of the virus receptor ACE2 *in vitro*[73]. A time-of-addition assay demonstrated that chloroquine functioned at both entry and post-entry stages of SARS-CoV-2 infection in Vero E6 cells[58]. Chloroquine also has an immune-modulating activity, which may synergistically enhance its antiviral effect *in vivo*. Chloroquine phosphate is therefore an antiviral drug option which was clinically tested against COVID-19.

Janus kinase inhibitors

Baricitinib is a Janus kinase inhibitor that not only interrupts virus entry, but also disrupts the

assembly of virus particles in cells. Bioinformatic analysis has proposed baricitinib as a potential drug that may inhibit SARS-CoV-2[74].

Immune Therapy

Immunosuppressive Therapies

Glucocorticoid therapies

Glucocorticoids have powerful anti-inflammatory and immunosuppressive effects; methylprednisolone is the main hormone in clinical use. This hormone may have a good effect on the cytokine storm produced by patients with severe COVID-19[17]. While glucocorticoids can reduce mortality among patients with severe pneumonia, they can have serious adverse effects on patients with mild pneumonia[75]. The World Health Organization recommends glucocorticoids for treating patients with severe, but not mild, COVID-19. A prospective clinical trial evaluating the efficacy and safety of methylprednisolone in the treatment of patients with severe COVID-19 is ongoing (the Chinese Clinical Trial Registry, ChiCTR2000029386).

Host-directed therapies

Based on experience with SARS and MERS, a range of host-directed therapies, such as metformin, glitazones, fibrates, sartans, and atorvastin have demonstrated an acceptable safety profile[76,77]. These drugs can also be combined with antiviral drugs to enhance antiviral efficacy. Host-directed therapies may be effective against SARS-CoV-2 infection in patients with severe COVID-19 and frequent cytokine storms[17].

Cell therapies

Cell therapy is the engineering of bone marrow mesenchymal stem cells (BMSCs) to release therapeutic factors. Such substances can reduce the inflammatory response and pulmonary edema in ARDS[78]. Therefore, they may be useful for treating ARDS in patients with severe COVID-19.

Immuno-enhancing Therapies

Antioxidant treatment

Vitamin C prevents oxidative damage and improves immunity. Studies have shown that significant doses of vitamin C not only increase antiviral ability, but more importantly prevent and treat acute lung injury and acute respiratory distress caused by other respiratory viruses[64]. A team from Wuhan University is conducting a clinical trial of vitamin C for COVID-19 (ClinicalTrials.gov of the US National Institutes of Health, NCT04264533).

Antibody therapies

Antibody therapies include plasma and monoclonal antibody therapies. Plasma therapy is a kind of passive immunotherapy, in which multivalent specific antibodies are extracted from the plasma of cured individuals to make convalescent blood products (CBP), which are then injected into sick patients. The use of antiviral antibodies from recovered patients was evaluated during the SARS outbreak[79]. This approach has also been tested on a large scale against Ebola virus, without particular evident effects. This technique requires further development in order to achieve greater results in the battle against viruses. Monoclonal antibody therapy refers to the extraction of memory B cells from patients in the recovery stage, which then produce specific antibodies for antiviral therapy given to patients not recovered. Monoclonal antibodies can be obtained by cloning antibody genes from a small number of memory B cells that have neutralizing and specific effects. Studies have shown that monoclonal antibody treatment can significantly reduce the mortality of patients infected with Ebola virus[80]. Monoclonal antibody therapy has become a focus of research for COVID-19 treatment.

Traditional Chinese Medicine Therapy

Traditional Chinese medicine has gained widespread attention in the clinic and plays an important role in the current coronavirus epidemic in China. As of March 23, 2020, we retrieved approximately 28 Chinese medicines and their extracts from clinical trials registered in the Chinese Clinical Trial Registry, such as glycyrrhizin, and *shuanghuanglian* oral solution. Traditional Chinese medicine has the advantages of bypassing drug resistance and targeting multiple processes to treat viral infections[81]. The combination of traditional Chinese medicine and Western medicine has played an important role in the treatment of SARS[81]. The following Chinese medicines may be useful for the treatment of SARS-CoV-2.

Glycyrrhizin

Five traditional Chinese medicines (glycyrrhizin, baicalin, scutellarin, hesperetin, and nicotia-

namine) can bind ACE2 on cells[82], and thereby prevent SARS-CoV-2 from entering cells. For example, glycyrrhizic can inhibit the replication and adsorption of SARS-CoV[83]. Glycyrrhizic can also inhibit the production of inflammatory factors and block inflammatory responses. Therefore, glycyrrhizic may be useful for treating patients with COVID-19. One study at Wuhan University found that diammonium glycyrrhizinate combined with vitamin C treatment showed good efficacy in patients with COVID-19. The treatment scheme of diammonium glycyrrhizinate combined with vitamin C has been tested in clinical trials in Wuhan (the Chinese Clinical Trial, ChiCTR2000029768).

Shuanghuanglian

Shuanghuanglian injection has also attracted wide attention as an extensive antiviral Chinese medicine preparation. It may relieve the symptoms of cough and fever in acute upper respiratory tract infections[84]. On January 31, 2019, a Chinese study announced preliminary findings showing that *shuanghuanglian* oral solution exerts anti-viral against SARS-CoV-2. A clinical trial for COVID-19 is underway to verify its efficacy (the Chinese Clinical Trial, ChiCTR2000029605).

Overview

SARS-CoV-2 is rapidly transmitted from human to human and is spreading globally, posing a current threat to public health. Given such a serious outbreak, timely prevention and control measures were taken in China: the movement of people was restricted to control the spread across regions, and all large gatherings were canceled. The importance of wearing masks and washing hands frequently was emphasized. Within one month of the outbreak, rapid progress was made in etiology identification, diagnostic reagent development, virus characterization analysis, and clinical treatment strategies. However, no specific treatment for COVID-19 is yet available, and therefore it is necessary to conduct further studies on the pathogenesis of SARS-CoV-2 infection to identify appropriate therapeutic targets. Currently, a number of potential drugs and therapies are under development. The greatest challenge will be deciding how to select and evaluate different approaches to develop effective treatments of COVID-19. In this process, effective communication and cooperation among institutional partners are required. Given current research, it seems likely that one or more potential therapeutic agents currently in later stages of development will prove effective against COVID-19.

Conclusions

Strict and timely epidemiological measures are essential to prevent the rapid spread of the virus and gain time to develop vaccines and drugs. Under a situation where SARS-CoV-2 is rapidly spreading around the world, the lessons and experience acquired in China should be given adequate attention in many other countries, and the same or similar approaches infection containment should be adopted as soon as necessary.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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