Disease and Diagnosis

Dis Diagn. 2022; 11(3):122-127

doi 10.34172/ddj.2022.23

Review Article

COVID-19 Treatments Based on Pathogenicity

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Abstract
The new coronavirus was first identified in China in December 2019 and then, it created a widespread pandemic around the world. There is currently no definitive cure for it and it will not be possible to make a vaccine soon. Pathogenic mechanism of the virus includes virus entry, binding to angiotensin-converting enzyme 2 (ACE2) receptors on the surface of host cells, proliferation, membrane fusion, assembly, subsequent infection, cytokine secretion, and the host immune response to the virus. By identifying at what stage the patient is, possible effective drugs can be used to control each stage. Therefore, identifying the mechanism of action of the virus in different stages of the disease makes it possible to use the appropriate drug for each stage of the disease and control the disease.
Keywords: Coronavirus, COVID-19, Pandemic

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Received: September 4, 2020, Accepted: September 21, 2020, ePublished: July 23, 2022

Introduction

COVID-19 is the name of a disease that has recently spread around the world and has infected many people. The virus was first detected in China and spread around the world. As of July 26, 2020, 15 783 641 cases have been confirmed and 640 016 deaths have been reported, according to the World Health Organization (WHO). Currently, there is no specific treatment for this disease. It is important to know the mechanism by which the virus enters the host cell and consequently causes infection in the host. The virus is mainly transmitted through respiratory droplets, contact, and possibly fecal-oral route. The virus first binds to its primary receptor at the surface of the host cell, angiotensin-converting enzyme 2 (ACE2), through its surface proteins, especially the receptor-binding domain (RBD) of the spike 1 protein. ACE2 is widely expressed in the mucous membranes of the nose, bronchi, lungs, heart, esophagus, kidneys, stomach, bladder, and ileum, which are all vulnerable to SARS-CoV-2. Additionally, the presence of transmembrane protease serine 2 (TMPRSS2) in the host cell facilitates this binding and eventually the virus enters the host cell (1,2). Upon entering the host cell, the virus begins to replicate the genome, fuses its membrane with the host membrane, and assembles it. These steps are performed by RNA dependent enzymes, RNA polymerase, and viral proteases. As the virus multiplies in the host body, the host activates its immune systems for self-defense, and it is in this state that the symptoms of the disease appear (3). Understanding the pathogenesis of the virus, as well as identifying the drugs that prevent the virus from spreading in each of these stages makes it possible to control the disease, accelerate the recovery of patients, and reduce the mortality rate. In this review article, we tried to take a step towards choosing the right drug for patients with covid-19 by fully examining the stages of virus replication and pathogenicity in the host, as well as drugs that inhibit each stage of the virus pathogenesis. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is usually transferred through the respiratory tract, droplets, physical contact, and oral-faecal route. First, the proliferation of the virus happens in the epithelial cells of the mucus of the upper respiratory system which includes the nasal cavity and pharynx. Following that, more proliferation happens in the lower respiratory system and the mucus of the digestive tract (1).

Pathogenesis of COVID-19

Stage 1: Asymptomatic State (Initial 1–2 Days of Infection)

The inhaled SARS-CoV-2 virus is likely to attach to epithelial cells in the nasal cavity and begin to multiply. Laboratory data on SARS-CoV show that ciliated cells

are the main infected cells in the airways. At this stage, although the viral load may be low, the patients are infectious. The reverse transcription polymerase chain reaction (RT-PCR) value for viral RNA may be useful for predicting viral load, subsequent infection, and clinical course (4).

Stage 2: Upper Airway and Conducting Airway Response (Next Few Days)

The virus travels in the respiratory tract along the airways, triggering a strong innate immune response. At this time, COVID-19 disease becomes clinically apparent. Levels of CXCL10 or some other innate response cytokine may be predictive of the next clinical course (4).

Stage 3: Hypoxia, Ground Glass Infiltrates, and Progression to ARDS

Unfortunately, about 20% of infected patients progress to stage 3 of the disease and develop a lung infection. At this stage, the virus reaches the gas exchange units of the lung and infects the alveolar epithelial type II cells. In the elderly, especially due to a decreased immune response and reduced ability to repair damaged epithelium, as well as reduced mucociliary clearance, the virus may spread to the gas exchange units of the lung easily (4).

Virus Entry and Spread

Coronavirus has a number of proteins including spike protein, Nucleocapsid protein, envelope protein, and membrane protein. The S protein is a glycoprotein composed of two subunits of S1 and S2. S1 contains a component called RBD, which is the basic Ag for binding to ACE2, and it is mainly found in the epithelial cells of the lung alveoli in the lower respiratory tract. S2 protein also contains essential elements for the fusion of viral membranes with host cells (5). ACE2, which is the main receptor for both SARS-COV2 and SARS-COV, is widely expressed in the nasal mucosa, bronchi, lungs, heart, esophagus, kidneys, stomach, bladder, and ileum, which are all vulnerable to SARS-CoV-2 (1). Overexpression of ACE2 may facilitate virus replication in lung tissue and promote pulmonary vascular permeability, which is one of the causes of severe COVID-19 (6).

Treatment Candidates for COVID-19

There are various drugs for the treatment of this disease that have a positive effect on the treatment process in various ways, some of which are used specifically in diseases other than coronary heart disease, such as Ebola, malaria, and so on. However, they have also been shown to be effective in treating coronary arteries and facilitating treatment with indirect methods. The mechanisms of these drugs are different from each other, which include inhibition of some cellular receptors, prevention of virus entry, inhibition of some intracellular proteases, and so on. These drugs are divided into separate categories as follows: inhibitors of SARS-CoV-2 entry into the cell and inhibitors of proliferation, membrane fusion, and assembly of SARS-CoV-2, each of which will be explained below in detail (7).

Inhibitors of SARS-CoV-2 Entry Into the Cell

The primary strategy involved is to prevent the binding of the SARS-CoV2 virus to the angiotensin-converting enzyme. Angiotensin-converting enzyme 2 receptor is an exopeptidase expressed on respiratory epithelial cells and may be a drug target to limit the entry of SARS-CoV-2 cells. The binding of SARS-CoV-2 S protein to the angiotensin-converting enzyme is 10 to 20 times higher than that of SARS-CoV S protein. The process of binding of S protein to the angiotensin-converting enzyme 2 receptor is facilitated by host cell-derived transmembrane protease serine (TMPRSS2). Factors that inhibit TMPRSS2 may be useful in blocking the entry of the virus into the host cell (7).

TMPRSS2 Inhibitors

The results of previous studies show that a variety of viruses (including Ebola, SARS, MERS, and influenza viruses) use host cell serine proteases to activate their glycoprotein coatings. Activation of the SARS-CoV S protein, which is required for membrane attachment and entry into host cells, is mediated by the TMPRSS2. Recently, SARS-CoV-2 has also been shown to use TMPRSS2 to synthesize the SARS-CoV-2 S protein and the entry of S protein into the cell. Camostat mesylate is a clinically proven and commercialized serine protease inhibitor that partially prevents infection with SARS-CoV and HCoV-NL63 in HeLa cells by expressing the angiotensin-converting enzyme 2 and TMPRSS2, and it has been shown that inhibition of TMPRSS2 in human lung Calu-3 cells by camostat mesylate significantly reduces SARS-CoV-2 infection (7).

Camostat Mesilate

It is a serine protease inhibitor that was used decades ago to treat oral epithelial cell carcinoma, dystrophic epidermolysis bullosa, exocrine pancreatic enzyme inhibition, and chronic pancreatitis. In a clinical trial using camostat mesilate against dyspepsia associated with mild non-alcoholic pancreatic disease, 95 patients received camostat mesilate (200 mg) three times daily for 2 weeks and showed only mild side effects, indicating that camostat mesylate is a good drug (7).

Nafamostat Mesilate

Serine protease inhibitor has been approved in Japan for the treatment of chronic pancreatitis, diffuse intravascular coagulation, and anticoagulant in the external circulatory system. In an FDA-approved screening of approximately 1,100 drugs, nafamostat mesylate was detected to inhibit protein-mediated MERS-CoV virus membrane fusion

by inhibiting serine protease activity of TMPRSS2 in Calu-3 lung cells. Because S proteins of MERS-CoV and SARS-CoV-2 share considerable amino acid sequence homology, nafamostat mesilate may also inhibit cell entry of SARS-CoV-2. In a multistage randomized trial, nafamostat mesylate was administered intravenously to 19 patients with severe acute pancreatitis at a daily dose of 240 mg for 5 days without severe side effects (7).

Angiotensin-Converting Enzyme 2 Inhibitors and Antimalarial/Parasiticide Drugs

Beta-coronaviruses bind directly to the host cell angiotensin-converting enzyme 2 through their S proteins. It has also recently been shown that SARS-CoV-2 also uses the angiotensin-converting enzyme 2 as a receptor for S protein-driven host cell entry. Therefore, the angiotensin-converting enzyme 2 forms a molecular target to prevent SARS-CoV-2 from entering host cells. Unfortunately, a number of drugs and compounds have been shown to inhibit the angiotensin-converting enzyme (7).

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine as well as their derivatives have been used for decades in the prevention and treatment of malaria and the treatment of chronic fever and various autoimmune diseases, which have recently been introduced as broad-spectrum antiviral drugs. Chloroquine has shown to inhibit the terminal phosphorylation of ACE2 and raise the pH in the endosomes involved in virus entry into the cell. Additionally, it increases antigen processing, inhibits TLR7 and TLR9 (Toll-like receptor), and enhances the activity of regulatory T cells. In the body, hydroxychloroquine is metabolized to chloroquine (7). Recently, due to cardiac complications, these drugs were removed from the COVID-19 treatment program (8).

Cepharanthine, Selamectin and Mefloquine Hydrochloride

It has recently been shown that the triple combination of cepharanthine, Selamectin, and mefloquine hydrochloride inhibits infection of Vero E6 cells with pangolin coronavirus GX_P2V/2017/Guangxi (GX_P2V), whose S protein shares 92.2% amino acid identity with that of SARS-CoV-2. In addition, it has been shown that GX_P2V also uses the angiotensin-converting enzyme 2 as a receptor for viral cell entry (7).

Inhibitors of Proliferation, Membrane Fusion, and Assembly of SARS-CoV-2

Upon entering the host cell, viral single-stranded positive RNA is released to replicate the virus RNA and translate the virus polyproteins, which are eventually converted to effective proteins by virus proteases. RdRP is an RNA-dependent RNA polymerase required for replication of the viral genome in the host cell. The two viral proteases, 3Clpro and Plpro, break down viral polyproteins into functional units in host cells. Lopinavir and ritonavir are candidates for SARS-CoV-2 treatment in humans. Finally, some phytochemicals and natural products with antiviral activity can be considered for the treatment of SARS-COV-2 infection (7).

Remdesivir

Remdesivir is a new small-molecule adenine nucleotide analog antiviral drug that has been shown to be effective against the Ebola virus in monkeys. Remdesivir exhibits antiviral activity against other single-stranded RNA viruses, including filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses MERS-CoV and SARS-CoV. Remdesivir is a prodrug that is actively metabolized by GS-441524, interferes with viral RNA polymerase activity, and evades proofreading by viral exoribonuclease, leading to the inhibition of viral RNA synthesis. Remdesivir acts early in infection and reduces viral RNA levels in a dose-dependent manner (7). In a new clinical trial with remdesivir, 53 COVID-19 patients received oxygen or mechanical ventilation due to an oxygen saturation of 94% or less. It was revealed that intravenous injection of 200 mg at the first day, followed by 100 mg daily for 9 days, resulted in clinical improvement in 36 of 53 patients (68%). However, the mortality rate among patients receiving invasive mechanical ventilation was 18% and among patients who did not receive it was 5%, indicating that remdesivir is a treatment option for patients with COVID-19 who do not receive invasive treatment (9).

Ribavirin

Ribavirin, as an analog of guanine, inhibits RNA-dependent RNA polymerase. However, in laboratory conditions, its activity against SARS-CoV was limited and high concentrations were required to inhibit virus replication and combination therapy. A review of the clinical experience with ribavirin for the treatment of SARS-CoV showed inconclusive results due to the adverse effects including hemolytic anemia, bleeding, and liver toxicity. Similarly, in the treatment of MERS-CoV, ribavirin, generally in combination with interferons, did not work and patients developed anemia, as well as teratogenic complications, which is contraindicated during pregnancy. Due to the above-mentioned reasons, it is unlikely to be used against the new coronavirus, but in the form of combination therapy, it can be effective in reducing complications (10).

Lopinavir and Ritonavir

Lopinavir is a highly potent inhibitor of the human immunodeficiency virus protease used for intracellular HIV assembly that was developed in 1998 to circumvent HIV resistance to the protease inhibitor ritonavir, which

was induced by a valine mutation at position 82 (Val 82) in the active site of HIV protease. Because the metabolism of lopinavir is severely inhibited by ritonavir, a combination of lopinavir and ritonavir has been identified as an oral drug for the treatment of HIV in combination with other antiretroviral agents. It has also been used to treat SARS-CoV2, according to a study on the efficacy of lopinavir/ritonavir in SARS-CoV and MERS-CoV (7). In a new study, researchers concluded that drug metabolism enzymes are inhibited by systemic inflammation and therefore reduce the effectiveness of drugs. In addition, a study on the accumulation of these drugs in the lungs of patients with COVID-19 found that they did not accumulate in the lungs to fight the coronavirus. The WHO agreed to discontinue prescribing ritonavir and lopinavir for patients with COVID-19 (11).

Umifenovir (Arbidol)

It is a derivative of indole molecule made by JSC Pharmstandard, Russia. By inhibiting clathrin-mediated endocytosis, umifenovir prevents the fusion of viral membranes and cytoplasmic membranes of host cells, thereby preventing the virus from entering the host cell and causing infection. Umifenovir was licensed in Russia and China for the oral prevention and treatment of infections with influenza A and B and other respiratory viruses. It has been introduced worldwide to control pathogenic viruses, including hepatitis C and B viruses, Ebola virus, Lassa virus, human herpesvirus 8, poliovirus, and vesicular stomatitis virus. Finally, umifenovir is known as a broad-spectrum antiviral drug (7).

Favipiravir (Avigan)

Favipiravir is an oral pyrazinecarboxamide derivate and guanine analog developed by Toyama Chemical, Japan, which selectively and potently inhibits RNA-dependent RNA polymerase, causing lethal RNA mutations, thus creating unusable phenotypes. Favipiravir inhibits the replication of a large number of RNA-carrying viruses, including influenza A virus, flavi-, alpha-, filo-, bunya-, arena-, and noroviruses, as well as West Nile virus, yellow fever virus, foot-and-mouth disease virus, Ebola virus, and Lassa virus (7).

In one study in China, one group received oral favipiravir and interferon by aerosol inhalation and the control group received lopinavir/ritonavir and interferon by aerosol inhalation. The results showed that the duration of viral clearance was shorter in patients treated with favipiravir and chest tomography scan showed a higher improvement rate in the favipiravir group (91.43%) compared to the control group (62.22%). Additionally, fewer adverse events were observed in the favipiravir group than in the control group (12).

Corticosteroids for the Treatment of COVID-19

Due to anti-inflammatory activity, corticosteroids (CS) are administered as an adjunct therapy for acute respiratory distress syndrome and cytokine storm. However, widespread CS-mediated suppression of the immune system increases the likelihood that the appropriate immune response to the virus will be disrupted. A meta-analysis of 5,270 patients with MERS-CoV, SARS-CoV or SARS-CoV-2 showed that CS treatment was associated with higher mortality. The new meta-analysis evaluated 2636 patients with only SARS-CoV-2 infection and found that there was no difference in mortality rate associated with CS treatment (13). Recently, preliminary results of clinical trials with dexamethasone (6 mg, once daily for 10 days) have shown a reduction in mortality in patients receiving respiratory support. Dexamethasone reduced mortality by one-third in patients receiving invasive mechanical ventilation and by one-fifth in patients receiving oxygen support without invasive mechanical ventilation. However, no effect of the drug was seen in patients with mild conditions who did not require supportive oxygen therapy. The WHO has also authorized the use of dexamethasone only in critical situations (14).

Recombinant Interferon as an Antiviral Therapy

One of the first-line defense mechanisms of the human body against RNA viruses such as SARS-CoV-2 is the release of type I and III IFNs. It is important to note that type I IFN (IFNα/β) receptors are widely expressed, so IFNα/β signaling can not only have antiviral effects but also activate immune cells that potentially exacerbates pathogenesis. In contrast, the third type of IFN (also called IFNλ) is found mainly in epithelial cells, as well as in a reservoir surrounded by immune cells. Because IFNs have the function of regulating the immune system, subsequent signaling can produce a strong antiviral effect without increasing pathogenic inflammation. Recently, there has been great interest in the therapeutic effect of modulating the IFN response to inactivate the pathogenesis of COVID-19. Prior to the current epidemic, some research groups have studied the role of IFNs in other beta-coronavirus infections (13).

Blocking Cytokines

Strong and severe inflammatory response is one of the pathogenetic mechanisms of COVID-19 which consists of complicated interleukin groups such as IL-6 and IL-10 (15). The cause of this cytokine storm is not yet known; however, it may initially be caused by a combination of viral pathogen associated molecular patterns(PAMP) and host danger signals. In the case of generalized lymphopenia, one group reported that certain subsets of CD4 T cells expressing GM-CSF and IL-6 were more common in severe COVID-19 patients than in COVID-19 patients who did not require intensive care. Other important inflammatory cytokines (TNF-α, IFN-ɣ, and IL-2) and chemokines (CCL2, CCL3, and CCL4) were increased by TH1/2 in COVID-19. Histological and unicellular analysis

identified monocytes and macrophages as other powerful sources of inflammatory cytokines in the COVID19 cytokine storm. Following initial reports of IL-6 as an important cytokine in COVID-19 associated cytokine secretion syndrome (CRS), monoclonal antibodies that target the IL-6 signaling pathway have been suggested as treatment candidates. The anti-IL-6R antibodies tocilizumab and sarilumab and the anti-IL-6 antibody siltuximab are being tested for efficacy in managing COVID-19 CRS and pneumonia in 13 ongoing clinical trials. In addition to the IL-6 signaling pathway, other cytokine/chemokine-related elements, including IL-1R, GM-CSF, and the chemokine receptor CCR5, have been suggested as potential block targets for the management of COVID-19 CRS (13).

Neutralizing Antibodies and Plasma Therapy for COVID 19

While vaccines are developed to train the immune system to generate nAbs against SARS-CoV-2, there is interest in using selective transfer of nAb as a treatment. This strategy has already been proven to be effective against SARS-CoV-1 and MERS-CoV. In the case of SARS-CoV-2, these efforts are made primarily to identify nAb produced during natural infections or to produce nAb through animal vaccination methods (13).

Antibodies Derived from COVID-19 Patients

Patients recovering from SARS-CoV-2 infection are a potential source of nAbs. In an effort to obtain these nAbs, the scientists sorted RBD-specific memory B cells and cloned their heavy and light variable regions to express the recombinant forms of the corresponding antibodies. The four antibodies produced in these studies (31B5, 32D4, P2C-2F6, and P2C-1F11) showed high neutralizing activities in vitro and all inhibited ACE2/RBD binding. However, it showed that almost all the antibodies obtained from the serum of 26 recovered patients were limited to S1 and RBD, with only 3 actually inhibiting ACE2/RBD binding. Note that a SARS-CoV-derived neutralizing antibody (47D11) and a chain antibody against SARS-CoV2 (n3130) have also been shown to neutralize SARS-CoV2 without inhibiting ACE2/RBD binding. Therefore, blocking this interaction may not be a prerequisite for an effective SARA-CoV-2 nAb. The generation of a hybridoma producing a monoclonal antibody against SARS-CoV-2 provides the potential for antibody therapy that can be directly administered to patients to inhibit infection (13).

The SARS-CoV Antibody Neutralizing SARS-CoV-2

The SARS-CoV and SARS-CoV-2 sequences share about 80% identity. Therefore, a wide range of SARS-CoV nAbs have been tested for cross-reactivity with SARS-CoV-2 because they can help accelerate the development of potential COVID-19 therapies (13). In a new study, in order to target SARS-CoV-2, assistance was taken from a person who had been infected with the SARS in 2003. An antibody named s309 with the potential of neutralizing SARS-CoV-2 was detected in his body (16). The combination of s309 with a weak neutralizing antibody that could bind another RBD epitope resulted in an increased neutralizing activity. In addition, CR3022 was found to bind SARS-CoV-2 RBD, but this antibody did not neutralize SARS-CoV-2. Computational simulations identified 3 amino acids that can be modified in CR3022 to enhance its binding affinity to SARS-CoV-2 RBD, potentially increasing its neutralization potential (13).

Antibodies from Animals

Animal models are another tool for producing nAbs against SARS-CoV-2. In one study, scientists developed a protocol for synthesizing human nanobodies, smaller antibodies that contain only a variable heavy chain as first discovered in camelids. Other antibodies isolated from camelids immunized with SARS-CoV and MERS-CoV S proteins were then ligated into a human Fc fragment and demonstrated neutralization potential against SARS-CoV-2 (13). Another research conducted on llamas which were immunized by the injection of the MERS-CoV and SARS-CoV spikes demonstrated that there are single-domain antibodies with neutralizing ability (17). Genetically modified mice with human antibody genes can also be used to produce therapeutic monoclonal antibodies, as successfully tested against the Ebola virus. Similar studies are now being carried out on the use of SARS-CoV-2 or derivatives to produce highly effective nAb in animal models, which can be directly given to infected patients. Finally, another approach to nAb development is to combine ACE2 and RBD with the Fc part of antibodies because ACE2-Fc and RBD-Fc have been shown to neutralize both SARS-CoV and SARS-CoV-2 in vitro (13).

Plasma Therapy

Although recombinant nAbs can provide an effective treatment, a significant investment is required to develop, test, and produce on an initial scale before it is widely available to patients. A faster strategy involves transferring plasma (CP) from people previously infected with SARS-CoV-2 who have high nAbs titers. Despite the lack of appropriate controlled trials, CP therapy has already been used in infectious diseases such as influenza 1918, H1N1 flu, and SARS-CoV. Some studies on plasma therapy and case reports on COVID-19 have evaluated the safety and potential efficacy of plasma therapy in patients with severe disease. These studies were neither controlled nor random, but they showed that plasma therapy is safe and can have a beneficial effect on the clinical course of the disease. Plasma therapy has also been suggested for prophylactic use in high-risk individuals, such as people with special health conditions or health care workers

exposed to patients with COVID-19. The FDA has approved the use of this method to treat selected patients. Determining the timing of its implementation is also important as a study in SARS-CoV patients showed that it is very effective when given to patients before day 14 of the disease. In general, plasma therapy appears to be associated with improved outcomes and appears to be safe; however, randomized clinical trials are needed to confirm this (13). The FDA has approved using the plasma of the people who have survived COVID-19 infection in order to treat infected people (18).

Conclusion

In this study, the mechanism of virus pathogenesis and effective drugs in blocking each stage of virus spread were investigated. Choosing the right medicine for people with COVID-19 is especially important. Therefore, it is important to know the pathogenesis of the virus and its inhibitory drugs. However, choosing the right drug to treat this disease still requires more extensive research.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

Acknowledgment

The authors would like to appreciate the Research Committee of Hormozgan University of Medical Sciences for collaboration.

Ethical Statement

This article does not contain any studies involving human participants performed by any of the authors.

Authors' Contributions

All authors contributed to the study design, data collection, writing, and preparation of this study.

Funding/Support

No funding was received for this study.

Informed Consent

Not required.

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