

An Overview of COVID-19: Focus on Pharmacological Aspect

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ABSTRACT

Coronavirus disease 2019 (COVID-19) which has been declared as Public Health Emergency of International Concern by the World Health Organization (WHO) is one of the major disasters in the 21st century. Initially, COVID-19 is called as 2019 novel coronavirus by the Chinese researchers, and later, the disease was named as COVID-19 and the virus as SARS-CoV-2 by the International Committee on Taxonomy of Viruses. It is a single-stranded RNA virus that mainly enters the human cells by angiotensin-converting enzyme 2 (ACE2) receptors like SARS-CoV. The important mode of transmission is through droplets and close contact with the infected people. As soon as the virus enters the human cells, it causes symptoms like cough, fever, headache, and fatigue after an incubation period of 5.2 days. There is no approved treatment or vaccine for this disease so far but many drugs have been tried from the experience obtained while treating SARS-CoV and MERS-CoV. In this article, we discussed the pathogenesis, transmission, clinical features, challenges for control, diagnosis, and treatment advancements to overcome COVID-19.

Keywords: Coronavirus, COVID-19, SARS-CoV-2.

SBV Journal of Basic, Clinical and Applied Health Science (2020): 10.5005/jp-journals-10082-02241

INTRODUCTION

The highly pathogenic coronavirus belongs to the family of Coronaviridae and subfamily Orthocoronavirinae. There are different types of coronaviruses such as α , β , γ , and δ coronaviruses.¹ Corona represents crown-like spikes which are present on the outer surface of the virus.² It is a single-stranded RNA virus sized ranging from 80 to 120 nm in diameter.³ The RNA genome of CoV is one among the largest of all the RNA viruses.⁴ Initially, this virus affects only birds and mammals but it was proved now that it can affect humans as well.⁵ Human CoVs have seven strains such as 229E, NL63, OC43, HKU 1, Middle East respiratory syndrome (MERS)-CoV, severe acute respiratory syndrome (SARS)-CoV, and recently 2019 novel coronavirus found initially in China.⁶ Among these, three are proved to be highly pathogenic: SARS-CoV, MERS-CoV, and 2019 novel coronavirus.⁷ The transmission of MERS-CoV is through camel⁸ while SARS-CoV is unknown but bats are hypothesized.⁹ The SARS and MERS including COVID-19 belong to β -coronavirus family.¹⁰ It was shown that the genomic structure of COVID-19 was similar to β -coronavirus family like that of SARS and MERS.¹¹ More than 82% COVID-19 is similar to SARS-CoV.¹² The novel virus was named as Wuhan coronavirus or 2019 novel coronavirus by the Chinese researchers. The name for the virus as SARS-CoV-2 and for the disease as COVID-19 was given by the International Committee on Taxonomy of viruses.¹³ Later, WHO also declared the official name as coronavirus disease (COVID-19)¹⁴ but the current name for the virus is SARS-CoV-2¹⁵ and also WHO declared COVID-19 as a Public Health Emergency of International Concern.¹⁶ The structural proteins of coronavirus are spike protein, membrane protein, envelope protein, and the nucleocapsid protein. β -Coronavirus family also have hemagglutinin esterase glycoprotein.^{17,18} This COVID-19 pandemic which is spreading worldwide has no registered treatment or vaccine.¹⁹

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How to cite this article: Saravanabavan N, Kumarappan M, Salwe KJ, Datchanamurthy B, Pandian J, Shanmuganathan P, *et al.* An Overview of COVID-19: Focus on Pharmacological Aspect. *J Basic Clin Appl Health Sci* 2020;3(2):75-79.

Source of support: Nil

Conflict of interest: None

PATHOGENESIS

The ACE2 controls human-to-human as well as cross-species transmission; hence, it is called as cell receptor for SARS-CoV.^{20,21} The ACE2 is seen in the lower respiratory tract of humans.²² Zhou et al. have proved that SARS-CoV-2 also uses ACE2 like SARS-CoV²³ for an entry into the human cell. On the surface of coronavirus, there is a presence of the virion called as S-glycoprotein which attaches to the ACE2 receptor which is present in the human cell.²⁴ Once the membrane has been fused, the viral RNA enters the cytoplasm, translates two polyproteins, pp1a and pp1ab,²⁵ and forms replication transcription complex in double-membrane vesicle.²⁶ This replication transcription complex replicates continuously and synthesizes subgenomic RNA. Finally, the virion containing vesicles fuses with the plasma membrane and releases the virus.^{22,27}

TRANSMISSION

The camels, dogs, cats, bats serve as hosts for coronavirus.²⁸ The coronavirus does not spread from animals to humans, but there is

an exception like SARS and MERS that mainly spread through the infected people by respiratory droplets like cough and sneezing or close contact with the infected people.²⁹ But initially COVID-19 was thought that it was from animal-to-human transmission because in earlier few cases had some contact with Huanan Seafood Market in Wuhan, China but later cases confirmed that they had no contact with the seafood market which proved as an indication for human-to-human transmission.^{30,31} On January 2020, the first case was reported in the USA via human-to-human transmission.³² Old reports mentioned two species of snakes may be the possible reservoir for the COVID-19. In a small study which was conducted during the third trimester of pregnant females who were infected with the coronavirus showed no transmission occurred from mother to child but all pregnant mothers underwent cesarean section.³³ Recently, it was said that the coronavirus also transmitted through eyes and the patients experience redness of eyes within 3 hours of the viral infection.

CLINICAL FEATURES

The symptoms occur after an incubation period of 5.2 days.³⁴ The period ranging from symptoms onset to death is 6–41 days but this may vary according to the immune response of the patient as well as the age of the patient.³⁵ If the patient is more than 70 years, this period may be shorter when compared to the patients who are less than 70 years of age. COVID-19 is contagious during the latency period.³⁶ Most common symptoms are cough, fever, fatigue, headache, hemoptysis, diarrhea, dysentery, and lymphopenia.^{37–39} Chest CT shows pneumonia. The ground-glass opacities were also noted in the subpleural regions of both the lungs. When treated with interferons, inhalation progresses the disease by increasing the opacities.⁴⁰ These symptoms are almost similar to the previous β -coronavirus but the unique feature about COVID-19 is it mainly targets the lower airways and also GI symptoms are more with COVID-19 when compared to SARS and MERS. Thus, fecal and urine sample testing plays a vital role in excluding alternate transmission routes.⁴¹ Increased proinflammatory cytokines, leukocytes number, high ferritin level, high erythrocyte sedimentation rate, and D-dimer are also observed.⁴⁰ The conditions that increase the susceptibility to COVID are hypertension, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease. The complications like septic shock, respiratory distress syndrome, coagulation dysfunction, metabolic acidosis, and multiple organ failure may occur.³⁸

CHALLENGES FOR CONTROL

Implementing control measures like social isolation, environmental disinfection, quarantine or distancing, follow-up of contacts, and the use of personal protective equipment will be helpful.⁴² The infection control measures can reduce the frequency of the occurrence of infection. Though there is no antiviral agent or vaccine if all infection control measures are properly undertaken, we can reduce the number of cases and also the impact on global health is also minimized.⁴³

DIAGNOSIS

For diagnosing the COVID-19, the following procedure should be done with the patients who are suspected to have the infection:

Real-time PCR, to identify SARS-CoV-positive nucleic acid in throat swab, sputum and secretions of lower respirator in throat

swab, sputum and samples from the secretions of lower respiratory tract.⁴⁴

TREATMENT

No approved vaccine or antiviral drugs are available for the treatment of coronavirus.⁴⁵ But many agents are being tried in the treatment of coronavirus or COVID-19 from the experience gained while treating SARS-CoV and MERS-CoV.⁴⁶

Ribavirin

Ribavirin which is the broad spectrum antiviral agent and a nucleoside analog is used in the treatment of hepatitis C. When given in combination with steroids became the standard regimen in treating SARS-CoV. But, however, *in vitro* testing lacks to prove the efficacy of ribavirin against SARS-CoV.¹⁹ Another disadvantage is it causes serious adverse effects like hemolytic anemia, hypomagnesemia, and hypocalcemia.⁴⁷ It was reported that when interferon- β (INF- β) is given in combination with ribavirin, they act synergistically to inhibit the SARS viral replication.⁴⁸ The viral load also has been increased in the patients who are treated with the combination of corticosteroid and ribavirin. Because of these drawbacks, the use of ribavirin has been declined or used in combination with other antiviral agents. Galidesivir and favipiravir are other nucleoside analogs that are not investigated in treating coronavirus.⁴⁵

Oseltamivir

Antiviral agent, oseltamivir, neuraminidase inhibitors proved to be effective in the treatment of influenza virus⁴⁹ and MERS-CoV.⁵⁰ It is also used in the treatment of COVID-19 but lack of efficacy is the main drawback.

Lopinavir/Ritonavir

Lopinavir and ritonavir are the protease inhibitors. The most important inhibitor of coronavirus protease is lopinavir while the least powerful is saquinavir.⁵¹ Lopinavir is given in combination with ritonavir mainly to enhance the half-life of lopinavir. Thus, these boosted protease inhibitors are widely used in the HIV management.⁵² The triple-therapy lopinavir/ritonavir/ribavirin and interferon- $\alpha 2a$ in South Korea were effective in the management of MERS-CoV.⁵³ This combination is considered in the treatment of the early stage of COVID-19.

Remdesivir

A nucleoside analog, remdesivir, is effective in SARS-CoV. Remdesivir decreases the virus load in the lungs and enhances the lung function that was not possible by lopinavir/ritonavir and INF- β .⁵⁴ Remdesivir worsens the clinical conditions of the first coronavirus-affected patient in the USA.³² Thus, the combination of remdesivir with INF- β is effective in the management of COVID-19. Hence, the combination of remdesivir with INF- β is superior to the triple combination of lopinavir/ritonavir and INF- β . Further trials are required to assess the efficacy and safety of remdesivir.⁵⁵

Nelfinavir

A protease inhibitor, nelfinavir, inhibits the SARS-CoV replication, and hence, it can also be a part of the treatment of COVID-19.⁵⁶

Arbidol

Arbidol which is an indole derivative approved for the treatment of viral respiratory infections and also for influenza in China and Russia in the cell culture, was proved that it has antiviral activity for SARS.

The arbidol mesylate, the derivative of arbidol, is five times more effective in minimizing the SARS virus reproduction.⁵⁷

Nitric Oxide

The inhalation of nitric oxide can also be one of the options for the management of COVID-19. The nitric oxide forms peroxy-nitrite because of its interaction with superoxide which is responsible for cytotoxic reactions.⁵⁸ It also has a vital role in the management of inflammatory airway disease. Beneficial effects of using nitric oxide have also been proved in the management of SARS-CoV.^{59,60}

Corticosteroids

In the management of both SARS-CoV and MERS-CoV, steroids play an important role by delayed clearance of viral RNA. They are also used in the treatment of COVID-19 either alone or in combination with the other drugs. But the use of steroids in the routine treatment has been prohibited by WHO unless indicated for other clinical needs.⁶¹

Interferons

The broad-spectrum antiviral interferons are used in the treatment of hepatitis B infection. Interferon- α inhibits the human and animal coronaviral replication while INF- β inhibits the SARS-CoV replication.^{62,63} The transcription of INF is arrested in the tissue cells that are affected with SARS-CoV, and thus after priming with less amount of INFs, the cells can be able to partially restore innate immune response.⁶⁴ Thus, the combination of INF- α with high-dose steroid was effective in the treatment of SARS-CoV.⁶⁵ The INF- α is given along with lopinavir/ritonavir combination for the management of COVID-19.³⁶

Immunoglobulins

For enhancing immunomodulation, intravenous gammaglobulin (IVIg) can be used when the response to initial empirical treatment was poor. Though it is safe for long-term use,⁶⁶ it causes venous and pulmonary embolism despite using LMW heparin when it has been used in SARS outbreak. Intravenous gamma globulin may enhance the viscosity in SARS patient and worsens the hypercoagulable states leading to adverse effects.⁶⁷

Chloroquine

An antimalarial drug, chloroquine, also has antiviral activity against SARS-CoV by increasing the endosomal pH. The chloroquine makes the environmental conditions unsuitable for cell/viral fusion. It also affects the ACE2 glycosylation process. ACE2 is the important cell surface receptor in the host which is essential for binding S-protein of SARS-CoV. Thus, chloroquine prevents the spread of infection and proves to be an effective drug candidate.⁶⁸ It is also easily available and nonexpensive.⁴⁵

Baricitinib

ACE2 is the important receptor through which the SARS and 2019 novel coronavirus enter the host. Downstream signaling events of ACE2 receptor mediate endocytosis and AAK1 (AP2-associated protein kinase). Hence, AAK1 is one of the most vital targets. Baricitinib is a Janus kinase inhibitor which binds to AAK1 and also has the ability to bind to cyclin G-associated kinase which is also an endocytosis regulator protein. Hence, it is important to assess the baricitinib for its effectiveness in the coronavirus management.⁶⁹

Other Compounds

α -Lipoic Acid

The α -lipoic acid, an antioxidant because of its free radical scavenging effect, is used in many diseases mainly in the management of polyneuropathy and hepatic diseases.⁷⁰ α -Lipoic acid also inhibits the HIV-1 replication. Oxidative stress and G6PD deficiency are two important factors that enhance human coronavirus infection.⁷¹ Thus, α -lipoic acid being an antioxidant can be evaluated for its effectiveness as an add-on therapy in the management of COVID-19.

Mucroporin-M1

It is a peptide with broad-spectrum virucidal action against many viruses like H5N1, measles, influenza, and SARS-CoV. Hence, this may be one of the potential agents to target coronavirus infection.⁷²

Zinc

Zinc inhibits coronavirus RNA polymerase and affects its replication. Hence, zinc has antiviral property also.⁷³ As cytokines have a vital role in the pathogenesis of coronavirus, a drug which inhibits the proinflammatory cytokines like tocilizumab (which inhibits IL-6) can also be evaluated for its effectiveness in the management of COVID-19.⁷⁴

REPURPOSING OF DRUGS IN COVID-19

When the drugs have been repurposed for different clinical conditions than for which it has been approved, it is known as drug repurposing or reprofiling. Apart from the drugs discussed above like hydroxychloroquine which was approved for its antimalarial property, lopinavir and ritonavir which were approved for their antiviral property, remdesivir which was approved for the management of Ebola virus can be used in the management of COVID-19, there are some other agents which are under trials for coronavirus infection but which has been approved for other conditions. Some of them are azithromycin (an antibiotic) and colchicine which was approved for gout treatment currently under study for its role in decreasing the lung complications. Anticoagulants like enoxaparin are also under study in Italy. Dipyridamole (vasodilator) is also suggested as a management of COVID-19 and fibrates like fenofibrate and bezafibrates are also used to treat COVID-19 symptoms. Cimetidine has also been proposed as a management of COVID-19.⁷⁵ Phase 3 clinical trial is also going on for sildenafil in the management of COVID-19.⁷⁶ In Korea, niclosamide, nanofenretinide, and ciclesonide were found in an *in vitro* drug screening assay as candidate antivirals.⁷⁷

CONCLUSION

COVID-19 originated from Wuhan, China, spreads widely to many countries all over the world. Initially, the source was thought to be zoonotic but later human-to-human transmission had also been confirmed. Though there is no antiviral agent or vaccine has been approved for this dreadful epidemic, implementing control measures like social isolation, environmental disinfection, quarantine or distancing, follow-up of contacts, and the use of personal protective equipment will be helpful in minimizing the impact on global health.

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