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AN OVERVIEW OF PANDEMIC COVID-19 AND ITS INVESTIGATIONAL POTENTIAL TREATMENTS

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ABSTRACT

In the late December 2019, the novel coronavirus disease (COVID-19) emerged in Wuhan, Hubei province city, has spread throughout China resulting in a formidable worldwide outbreak and was recognized as a pandemic by the WHO (World Health Organization). On February 11, 2020, WHO has officially named the disease as Coronavirus Disease – 2019. This contagious disease is also known as 2019-nCoV or SARS-CoV-19 (Severe Acute Respiratory Syndrome) as this virus is known to cause severe pneumonia, a respiratory infection. It has been classified under the zoonotic diseases as some coronaviruses that are found in animals have the potential to infect both animals and humans. Person to person transmission may occur through air droplets expelled when an infected individual coughs or sneezes within a range of about 6 feet (1.8 cm) or also through contact transmission. If proper preventive measures are not followed, then this could be a serious threat for an individual and society. As such no specific treatments has been yet approved for novel coronavirus. Although some available drugs have been promising against the novel coronavirus but still it is under investigation and could be a possible alternative for the treatment of the COVID-19. This review article focuses on novel corona virus (SARS-CoV-2) infection along with its investigational potential treatments.

KEYWORD: Coronavirus, respiratory infection, antivirals, treatment.

INTRODUCTION

In the late December 2019, clusters of patients in Wuhan, China were reported to have atypical pneumonia by local health facilities.[1] In an emergence, a rapid response team was

developed by the Chinese Center for Disease Control and Prevention (China CDC) to investigate the cause for symptoms of atypical pneumonia through an epidemiologic and etiologic investigation. The patients were epidemiologically linked to the wet animal wholesale market and sea food in Wuhan, China. After investigation, it was found that the infectious agent, a coronavirus SARS-CoV-2, responsible for atypical pneumonia (respiratory infection), which caused the first fatality during the January 2020.[2] Several cases were reported during the first 2 to 6 weeks of the outbreak in more than 37 countries including Japan, USA, South Korea and Iran.[3] The contagious infection emerged in Wuhan; Hubei province city of China resulted in a formidable worldwide outbreak as it rapidly spreads over the globe. In order to control the outbreak, several strategies including massive lockdown and suspension of transport to and from Wuhan were implemented to curb the spread of novel coronavirus.[4] The rapid spread of SARS-CoV-2 is believed to be through asymptomatic persons which are potential sources of infection.[5] To overcome this transmission, a complete quarantine for the general public is mandatory.[6]

Clinical manifestations

Symptoms associated with SARS-CoV-2 are same as to that of SARS-CoV, MERS-CoV ranging from mild respiratory illness to severe acute respiratory disease. In later stages, SARS and MERS patients develop respiratory disease and renal failure.[4,7] Symptoms associated with SARS-CoV-2 are fever, cough, shortness of breath and breathing difficulties, dyspnea and bilateral infiltrates on chest imaging.[4] In most severe cases, coronavirus infection can cause atypical pneumonia, severe acute respiratory syndrome, kidney failure and even death of patient.

Virology

Coronaviruses are large, enveloped, positive single stranded RNA genome and a nucleocapsid of helical symmetry.[7] The genome size of coronaviruses ranges from approximately 26 to 32 kilobases, the largest for an RNA virus.[8] The virus classification is given in table no: 1.

Table no 1: Virus Classification.[9]

Realm	Riboviria
Phylum	Incerta sedis
Order	Nidovirales
Family	Coronaviridae
Subfamily	Orthocoronavirinae

They fall into genus "beta-coronavirus" which can be divided into several subgroups.[10] SARS-CoV, bat SARS like CoV and SARS-CoV-19 belong to serbecovirus, while the MERS-CoV to Merbecovirus.[11] Each of the subgroup cause diseases in humans but may have mild to different biologic characteristic and virulence.[12-14]

Structure

The name "Coronavirus" is derived from the Latin word "Corona" meaning "Crown or Halo", which refers to the characteristic appearance of the virus particles as they have crown like spikes or finger-like projections on their surfaces as shown in figure no: 1.[12]

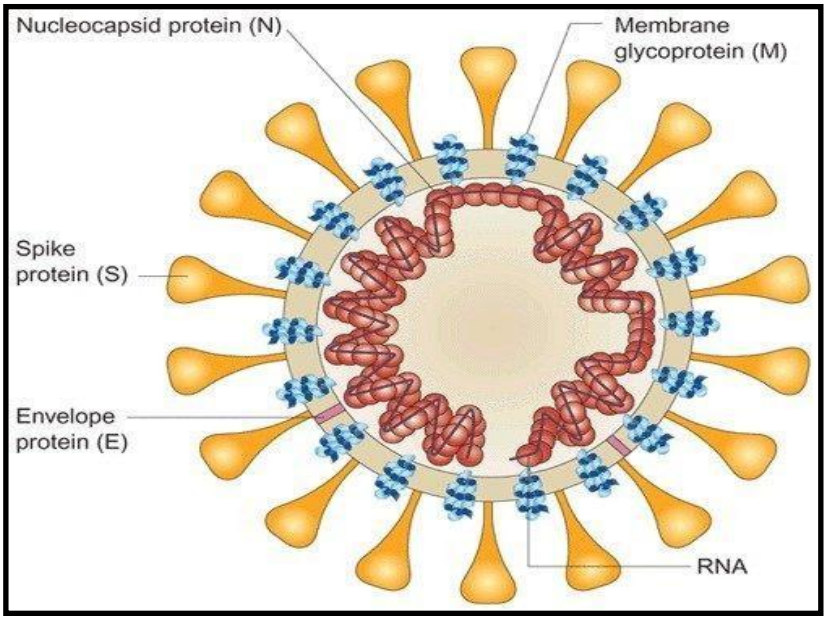

Figure no 1: Structure of Coronavirus.[15]

Helical capsid formed by the nucleocapsid protein (N) encapsulates the genetic material RNA of coronavirus and further coated by an envelope. Envelop of virus is associated with at least three structural proteins:

a) The membrane protein
b) The envelope protein
c) The spike protein

Among the mentioned proteins, the membrane and envelop proteins are involved in virus assembly whereas the spike protein is responsible for mediating the virus entry into host cells. Some of the coronaviruses also encode an additional envelope-associated hemagglutinin-esterase protein (HE). Apart from mediating virus entry into host cells, the

spike protein becomes a critical determinant of viral host range and tissue tropism and a major inducer of host immune responses. The spike protein most likely attach to Angiotensin converting enzyme 2 (ACE 2) receptors on the cell membrane allowing the virus entry. The coronavirus spike protein consists of three segments: a large ectodomain, a single-pass transmembrane anchor, and a short intracellular tail. During virus entry, receptor subunit S1 of spike protein binds to a receptor on the host cell surface for viral attachment, and the membrane-fusion subunit S2 of spike protein fuses the host and viral membranes, allowing the entry of viral genomes into host cells. Receptor binding through S1 subunit whereas membrane- fusion through S2 subunit of spike protein becomes the most initial and critical steps in the coronavirus infection cycle.[16]

Mechanism[17]

Stage 1: Cell invasion and viral replication in the upper respiratory tract Stage 2: Replication in the lung and immune system altered.

Stage 3: Pneumonia.

Stage 4: Acute respiratory distress syndrome, the cytokine storm, and multiple organ failure.

ACE2 receptors predominantly found in ciliated epithelial cells in the upper and lower airway and in type Ⅱ pneumocytes in the alveoli in the lower airway. Type Ⅱ pneumocytes present in the alveoli produces lung- lubricating proteins important for lung function.

Stage 1: Cell invasion and viral replication in the upper respiratory tract

SARS-CoV enters the host cell via a receptor called ACE2 (Angiotensin converting enzyme 2). These receptors are involved in controlling blood pressure and electrolytes.

Stage 2: Replication in the lung and immune system altered

Once inside the host cell, it releases the viral genetic material and signals the cell to produce millions of new copies of itself using host genetic machinery. It has been reported that SARS-CoV-2 can bind 10 times more tightly to insert its genetic material RNA into the host cell. As soon as the body identifies the foreign material, it activates the lymphocytes to produce the first defense IgM-type antibodies and then the longer-term specific neutralizing antibodies, IgG against the foreign invaded material.

Stage 3: Pneumonia

ACE2 receptors present on the lung cells called type Ⅱ pneumocytes. These cells play an important role in producing surfactant which is responsible for lubricating alveoli sacs by

forming a coat around it, thus helps in maintaining enough surface tension which allows the air sacs to be open for the exchange of oxygen and carbon dioxide gases.

Due to pneumocytes destruction in the lungs, there is reduced surfactant level in the alveoli resulting in the lesser lubrication of the alveoli and thereby disrupts the opening of air sacs, responsible for gases exchange and develops difficulty in breathing. This condition is referred to as pneumonia as breathing becomes difficult due to reduced surface area in the lung where oxygen transfer takes place.

Stage 4: Acute respiratory distress syndrome, the cytokine storm, and multiple organ failure

White blood cells, such as neutrophils and macrophages, known to be a part of immune response rush into the alveoli. White blood cells release inflammatory chemicals and these chemicals are responsible for leaky vasculature around the alveoli resulting in building up fluid in air sacs thereby creating pressure on the alveoli from outside and, in combination with the reduced surfactant level coating around the alveoli, causes them to collapse.

Due to fluid accumulation in alveoli, it prevents enough oxygen from getting to the lungs and into the bloodstream. This deprivation of oxygen results in a life-threatening condition called "Acute respiratory distress syndrome".

It has also been reported that the patients with COVID-19 has high levels of immune proteins called cytokines. Scientists believe that these cytokines are evidence of an immune response called a cytokine storm. Cytokine storm is a condition in which body itself starts to attack its own cells and tissues rather than fighting against the virus.

Diagnosis[18]

The U.S. CDC has set criteria for persons under investigation (PUI). Immediate prevention and infection control measures are to be undertaken, if a person is deemed a PUI. Epidemiological factors are also to be taken into consideration for accessing the requirement of test. These include travel history to an infected area within 14 days of symptom onset or close contact with a laboratory-confirmed patient within 14 days of symptoms.

The WHO recommends samples collecting from both the upper as well as lower respiratory tracts. The sample can be collected through expectorated sputum, bronchoalveolar lavage or endotracheal aspirate. Samples collected are then detected for presence of viral RNA using

Real-Time Polymerase Chain Reaction (RT-PCR). If a test is positive, it is recommended to carry out the test again for re-verification purposes. If a test is negative, then also it is recommended for repeat testing to confirm the presence or absence of viral RNA in collected samples.

Investigational Potential Treatment

As such no treatments for COVID-19 are available. For time being, symptomatic and supportive care such as maintaining proper level of oxygen, blood pressure and treating complications, such as secondary infections or organ failure, keeping vital signs are the main strategies. Many investigational treatments are going on for COVID-19 as the potential mortality is very high for it. Following are the investigational treatments which are mentioned below in the table no: 2

Table no: 2 Investigational Potential Treatments.

Sr.no.	Classification	Drugs
1	Anti-malarial drugs	Chloroquine, Hydroxychloroquine
2	HIV Protease Inhibitor	Lopinavir, Ritonavir
3	Synthetic Serine Protease Inhibitor	Nafamostat
4	Synthetic Guanosine Nucleoside	Ribavirin
5	Nucleotide Analogue Prodrug	Remdesivir
6	Nucleoside analog (Viral RNA polymerase inhibitor)	Favipiravir
7	Anti-protozoal agents	Nitazoxanide
8	Nucleoside analog	Penciclovir, Acyclovir, Ganciclovir
9	Neuraminidase inhibitor	Oseltamivir
10	Macrolide Antibacterial	Azithromycin
11	Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody	Tocilizumab
12	Immunomodulating agents	Alfa-interferon, Sarilumab
13	Other	COVID-19 Convalescent Plasma

1. Antimalarial agents

e.g. Chloroquine, Hydroxychloroquine

Mechanism of action

Possible mechanisms may be inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, inhibition of virus assembly, inhibition of viral protein glycosylation, virus

particle transport and release of viral genetic material into host cells.[19-25]

Through in-vitro study, it has been reported that hydroxychloroquine is more potent against the COVID-19 as compared to chloroquine in terms of efficacy and safety.[26] Some protocols have recommendations for use of hydroxychloroquine for treatment of COVID-19.[27-29]

2. HIV Protease inhibitor

e.g. Lopinavir, Ritonavir

Mechanism of action

This is a drug combination used against HIV viruses which works by inhibiting or blocking viral key proteins called as "Proteases", a key enzyme for replication.

This combination can enhance the natural defenses of the body's cells against SARS-CoV-19.[30-32]

3. Synthetic Serine Protease Inhibitor

e.g. Nafamostat.

Mechanism of action

This drug works by preventing membrane fusion of virus with host cell lowering the release of cathepsin B and it has also been shown to have anticoagulant activities.

This drug has been used for the treatment of influenza, MERS (Middle East Respiratory Syndrome) and Ebola.[33,34]

4. Synthetic Guanosine Nucleoside

e.g. Ribavirin

Mechanism of action

This drug exhibits a broad-activity against several DNA and RNA viruses. This drug works by interfering with the viral mRNA synthesis.

This drug has been approved for the treatment of HCV, SARS and MERS.[35-37]

5. Nucleotide Analogue Prodrug

e.g. Remdesivir

Mechanism of action

It is an intravenous antiviral drug that was developed to block infection with related coronaviruses and even Ebola. This drug works by targeting key viral proteins which are involved in producing multiple copies of virus. This drug is also known to work by interfering with the post-entry of virus.

It has been used in some of the COVID-19 patients in the US and appears to be safe but still it is under investigation.

This drug has been used for the treatment of Ebola, SARS, MERS.[38-40]

6. Nucleoside analog (Viral RNA polymerase inhibitor)

e.g. Favipiravir

Mechanism of action

It is under investigation for the use of it against the SARS-CoV-19. This drug works by acting on viral genetic copying to prevent its reproduction, without altering or affecting host cellular RNA or DNA synthesis.

This drug has been used for the treatment of Ebola, influenza A (H1N1).[41-43]

7. Anti-protozoal agents

e.g. Nitazoxanide

Mechanism of action

This drug has been used against the wide range of viruses including animal or human coronaviruses. It has been approved for the treatment but still it is under investigation. This drug works by modulating the growth, proliferation and survival of a wide range of extracellular and intracellular protozoa, anaerobic, helminths, microaerophilic bacteria and viruses.[44-46]

8. Nucleoside analog

e.g. Penciclovir, Acyclovir, Ganciclovir

Mechanism of action

Penciclovir / Acyclovir, a synthetic acyclic guanine derivative, resulting in chain termination whereas Ganciclovir is a potent inhibitor of herpesvirus family including cytomegalovirus.

Penciclovir/Acyclovir: used in the treatment of HSV, VZV.

Ganciclovir: Used in the treatment of AIDS associated cytomegalovirus infection.[47,48]

9. Neuraminidase inhibitor

e.g. Oseltamivir

Mechanism of action

This approved drug works by inhibiting the activity of the viral neuraminidase enzyme, thereby preventing budding from the host cell, inhibiting the viral replication, and infectivity. This drug has been used in the treatment of influenza viruses A.[49,50]

10. Macrolide Antibacterial

e.g. Azithromycin

Mechanism of action

Macrolides has been used as they have immunomodulating properties and this could be effective in treatment of pulmonary inflammatory disorders. This drug works by down regulating the inflammatory responses and lower the excessive production of cytokine associated with respiratory viral infections. This drug also works by reducing chemotaxis of neutrophils to the lungs by inhibiting cytokines, decreased reactive oxygen species production, inhibition of mucus hypersecretion, inhibiting the activation of nuclear transcription factors and accelerating neutrophils apoptosis.[51-54]

11. Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody

e.g. Tocilizumab

Mechanism of action

Tocilizumab binds competitively to both soluble and membrane-bound IL-6 receptors and thereby inhibits IL- 6 mediated signaling. As IL-6 is a proinflammatory cytokine produced by various cells such as B-cells and T- cells, monocytes, lymphocytes and fibroblasts, it is involved in diverse physiological processes such as activation of T-cell, induction of immunoglobulin secretion, initiation of hepatic acute-phase protein synthesis, stimulation of differentiation and proliferation of hematopoietic precursor cell.[55]

12. Immunomodulating agents

e.g. sarilumab, alfa-interferon

These agents are being evaluated and used as an adjunctive therapy.[56,57]

13. Others

COVID-19 Convalescent Plasma[29]

Mechanism of action

This therapy is known to induce passive immunization against the coronavirus. This therapy aims at using the antibodies from the blood of a recovered COVID-19 patient to treat those who are critically ill. This therapy can be used to passive immunize those frontline workers at a high risk of contracting virus such as health workers, families of patients and other workers who are at high risk. It is a preventive measure and not a treatment against COVID-19.

Vaccine

As such no vaccines for COVID-19 are available for its prevention from infection. The spike protein may serve as a vaccine candidate as it plays an important role in infection, but still it requires further evaluation for its effect on human.[58]

CONCLUSION

This review article focuses on the overview of the current ongoing scenario of COVID-19. This article covers general introduction about coronavirus along with its virology, mechanism of coronavirus on host cells, diagnosis and investigational potential treatments for COVID-19. This study will help to understand the basics of coronavirus, its investigational potential treatments and also gives an idea for the future scope towards the research development.

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