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A COMPREHENSIVE REVIEW ON COVID-19 AND ITS PREVENTION AND POSSIBLE TREATMENTS

Pharmacology

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ABSTRACT

Coronavirus disease (COVID-19) is caused by SARS-COV2 and is the causative agent of a potentially lethal disease which is of great concern for global public health. It is proposed that this is possibly the zoonotic origin of COVID-19 based on the large number of infected people who were exposed to the wet animal market in Wuhan City, China. Transmission of COVID-19 infection from one person to another resulted in the isolation of patients who were subsequently given a variety of treatments. To monitor the current outbreak, robust steps have been placed in place to reduce the transmission of COVID-19 from person to person. Special attention and efforts should be given to preventing or reducing transmission in vulnerable populations, including infants, health care providers and the elderly. In this review we highlight the origin, transmission and possible treatments of this heinous infection which has become a global threat.

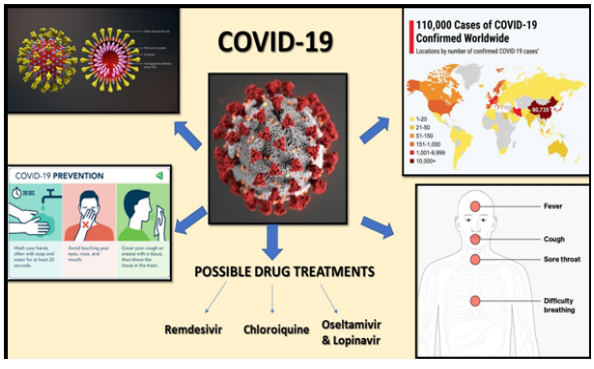
KEYWORDS

COVD-19; SARS-CoV-2; Chloroquine; Anti-malarial

INTRODUCTION:

A novel coronavirus disease (COVID-19), caused by SARS-CoV-2 infection, has spread across 31 provinces across China and more than 40 countries around the world. The transition from initial symptoms to acute respiratory distress syndrome (ARDS) is most likely due to uncontrolled release of cytokines1. There is a growing need to find medications that are safe and appropriate for care. The inhibitory effect of chloroquine (CQ) is positive. Clinical use of CQ can, however, cause severe side effects. We suggest that hydroxychloroquine (HCQ), which has a highly similar antiviral effect to CQ, may serve as a better therapeutic approach.

An outbreak of an unknown illness, caused pneumonia, occurred in Wuhan, Hubei Province, China in late December 2019. The epidemic has spread considerably to infect 3,81,521 people with 16553 deaths around the world in 201 countries by March 24, 20202. The causative virus was initially referred to as the serious acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the resulting infectious disease was referred to by the World Health Organization as Coronavirus Virus 2019 (COVID-19). [Fig1]



Coronaviruses are a highly diverse group of enveloped, positive-sense, single-stranded RNA viruses. They cause many diseases of varying severity in humans and animals affecting respiratory, enteric, hepatic, and neurological systems. Infections with human coronavirus (CoV) have historically caused a small percentage of annual respiratory infections. HCoV-OC43, HCoV-229E, HCoV-NL63 and HCoV-HKU1 are found to cause moderate respiratory illness[3]. Two novel coronaviruses, severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV), have arisen over the past two decades, causing significant human diseases.

Origin Of Pathogen

SARS-CoV-2 is a novel member of coronaviruses, a wide community of extremely complex, enveloped, positive-sense, single-stranded RNA viruses[4]. Recent work has confirmed that SARS-CoV-2 possibly originated in bats, based on its genetic sequence close to that of other coronaviruses. The SARS-CoV-2 intermediate animal host between a possible pool of bat and humans is still unknown[5]. Although this novel coronavirus has genetic characteristics that are consistent with the coronavirus family, it also has distinct gene sequences that vary substantially from previously sequenced coronaviruses[6].

The protein spike (S) in the envelope is important for coronavirus. The S protein mediates receptor binding and membrane fusion, and is critical to determining host tropism and capacity for transmission. The S protein is generally divided functionally into the S1 domain, which is responsible for receptor binding, and the S2 domain which is responsible for cell membrane fusion. Analysis of the structure suggested the receptor-binding domain was composed of a core and an external subdomain. The enzyme-converting angiotensin II (ACE2) was known as SARS-CoV cell receptor. SARS-CoV-2 similarly uses ACE2 as an input receptor in the ACE2-expressing cells, suggesting that SARS-CoV-2 may share the same life cycle with SARS-CoV.

Biophysical and structural research showed that the SARS-CoV-2 protein binds ACE2 with around 10-to 20-fold higher affinity than the SARS-CoV protein.

The high affinity of S protein to human ACE2 can facilitate SARS-CoV-2 spread among human populations7. While, SARS-CoV-2 does not use other receptors of the coronavirus to enter cells, such as aminopeptidase N and dipeptidyl peptidase 4 (DPP4).

Molecular Characterization:

Within just a month of the incident case identification, several Chinese scientists isolated the virus, sequenced its full-length genome and identified its unique morphology. On 12 January 2020, the initial sequence of genomes was shared with the WHO. Several research teams have identified and characterized the viral genome separately, and the sequences have been made publicly accessible on the Global Initiative for Sharing All Influenza Data [GISAID] website[8] (https:/www.gisaid.org).

Zhou et al. demonstrated that COVID-19 shared sequence identity with SARS-CoV at 79.5 per cent. It was then isolated from a critically ill patient's bronchoalveolar lavage fluid, and from similarly contaminated patients, sera found to neutralize it. COVID-19 has also been reported to use the same cell entry receptor, angiotensin converting enzyme 2 as SARS-CoV, which is highly expressed in epithelial airway cells[9].

Even COVID-19 was described and characterized by Zhu et al. They documented virus isolation and provided the initial summary of its basic cytopathic and morphological effects. COVID-19 appears to be the seventh member of the coronavirus family which infects humans[10].

Notably, unlike SARS-CoV or MERS-CoV, COVID-19 has evolved more readily in primary human airway epithelial cells than normal tissue-culture cells, indicating the potential for increased infectivity[11]. Homology analysis showed that at main residues benchmarked with SARS-CoV, COVID-19 had several combinations of amino acids. Whether these improvements contribute to the facilitation of infection

with viruses is not clear.

The knowledge created by this research enables the medical and scientific community to better understand COVID-19 transmission, improve rapid diagnostic testing and efficient epidemiological control, and promote progress[12].

Symptoms

The signs of COVID-19 infection occur after some 5.2 days of incubation. The time from the onset of COVID-19 symptoms to death ranged from 6 to 41 days, with a 14-day median. This time depends on the patient's age and immune system status. For patients >70-year-old it was shorter compared to those under 70. Fever, cough, and fatigue are the most common symptoms at the onset of COVID-19 disease, although other signs include sputum development, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia[13-15].

However, there were pathological symptoms such as RNAaemia, acute respiratory distress syndrome, acute heart injury, and the occurrence of grand-glass opacity that resulted in death. In certain cases, several peripheral ground-glass opacities have been identified in both lungs subpleural areas, which are likely to cause both systemic and localized immune response, leading to increased inflammation. Regrettably, treatment with interferon inhalation in some cases had little therapeutic benefit, and only tended to exacerbate the condition by advancing pulmonary opacity. It is important to remember that the symptoms between COVID-19 and earlier betacoronavirus such as fever, dry cough, dyspnea and bilateral ground-glass opacity on chest CT scans are identica.

Nonetheless, COVID-19 displayed several unusual clinical characteristics that involve targeting the lower airway as evident from symptoms of the upper respiratory tract such as rhinorrhoea, sneezing and sore throat. Furthermore, some of the cases display an infiltrate in the upper lobe of the lung that is correlated with rising dyspnea with hypoxemia based on findings from chest radiographs upon admission. Importantly, although COVID-19 patients reported gastrointestinal symptoms such as diarrhoea, a low percentage of patients with MERS-CoV or SARS-CoV encountered severe GI distress. Therefore, checking faecal and urine samples is necessary in order to eliminate a possible alternative route of transmission, specifically through health care staff, patients etc. Therefore, development of methods for identifying the different modes of transmission such as feacal and urine samples is urgently needed to establish strategies for inhibiting and/or reducing transmission and developing therapeutics to manage the disease.

Pathogenesis

Patients diagnosed with COVID-19 displayed higher numbers of leukocytes, irregular breathing findings and elevated rates of pro-inflammatory cytokines in plasma. One of the COVID-19 case reports revealed a patient with a cough, harsh respiration sounds in both lungs and a body temperature in 39.0 ° C at 5 days of fever. The sputum of the patient showed positive results of the polymerase chain reaction in real-time which confirmed the infection with COVID-19.

Laboratory tests showed 2.91 x 10^{9} cells / L of leucopenia with leukocyte counts, 70.0 percent of which were neutrophils. In addition, a blood C-reactive protein value of 16.16 mg / L was reported that is above the normal range (0–10 mg / L). There was also a high degree of erythrocyte sedimentation and a D-dimer. The major pathogenesis of COVID-19 infection as a virus targeting respiratory system was extreme pneumonia, RNAaemia, together with the occurrence of ground-glass opacities, and acute heart injury.

In patients with COVID-19 infection with IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNÿ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA, substantially elevated blood levels of cytokines and chemokines were reported. Many of the serious cases admitted to the intensive care unit displayed elevated levels of pro-inflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, which are reasoned to encourage severity of the disease[16-18].

Transmission

It is proposed that this is the possible zoonotic origin of COVID-19, based on the large number of infected people who were exposed to the wet animal market in Wuhan City where live animals are regularly sold.

COVID-19 genomic sequence analysis showed 88 percent identification with two bat-derived extreme coronavirus-like acute respiratory syndrome (SARS), suggesting that bats are the most likely link between COVID-19 and humans. Several studies have indicated that transmission from person to person is a likely route for COVID-19 infection to spread. This is reinforced by cases that occurred within families and amongst people who did not attend Wuhan's wet animal market. Transmission from person to person occurs mainly through direct contact, or by droplets released from an infected person through coughing or sneezing[19-20].

Possible Treatment And Therapy

The transmission of COVID-19 infection from person to person has contributed to the isolation of patients despite a range of treatments. There are currently no effective antiviral medications or vaccines against infection with COVID-19 for future human therapy. The only alternative available is to use wide-spectrum antiviral drugs such as nucleoside analogs, as well as HIV-protease inhibitors that can attenuate viral infection before the actual antiviral is available. The therapy so far tried has shown that proven antiviral medications have been given to 75 patients. Treatment course included oral administration of 75 mg oseltamivir twice a day, 500 mg lopinavir and 500 mg riton[21-22].

The study showed that wide-spectrum antiviral remdesivir and chloroquine are highly effective in managing in vitro infection of 2019-nCoV. Such antiviral compounds have been used with safety track record in human patients. Therefore, treating COVID-19 infection may be considered as such therapeutic agents. Additionally, a variety of other compounds are under development[23-25].

Which include the clinical candidate compound EIDD-2801 which has demonstrated seasonal and pandemic influenza virus infections with high therapeutic potential aganist and this represents another potential drug to be considered for the treatment of COVID-19 infection[26-27].

Before more precise therapies are available, more broad-spectrum antivirals that include drug treatment options for COVID-19 infection should be considered, including Lopinavir / Ritonavir, Neuraminidase inhibitors, peptide (Ek1), RNA synthesis inhibitors. Nonetheless, it is clear that further work is required urgently to identify novel chemotherapeutic drugs for the treatment of COVID-19 infections[28]. There is an immediate need for an animal model to reproduce the serious disease currently found in humans and improve pre-and post-exposure prophylaxis against COVID-19.

Several groups of scientists are currently working hard to build a non-human primate model for studying COVID-19 infection in order to create fast track novel therapies and to evaluate new vaccines in addition to having a deeper understanding of virus-host interactions. The fifth edition of the Guidelines recommends antivirals for the diagnosis of COVID-19 including IFN-α, lopinavir / ritonavir and ribavirin. The sixth edition of the Recommendations contains chloroquine phosphate and arbidol, based on the provisional findings of clinical trials. For adults, the main procedure for administering IFN-α is vapor inhalation at a dosage of 5 million U (and 2 mL of sterile water for injection), 2 times a day. The lopinavir / ritonavir dosage for adults is 400 mg/100 mg, 2 times / day. Ribavirin should be administered in conjunction with IFN-α or lopinavir / ritonavir by intravenous infusion at a dosage of 500 mg for adults 2 to 3 times / day. For adults, chloroquine phosphate is administered orally at a dosage of 500 mg (300 mg chloroquine), 2 times a day. Arbidol is given orally to adults at a dosage of 200 mg, 3 times a day. Treatment period is no greater than 10 days.

IFN-α is a broad-spectrum antiviral widely used to treat hepatitis although it is stated to inhibit in vitro reproduction of SARS-CoV. Lopinavir / ritonavir is a human immunodeficiency virus (HIV) drug used in combination with other drugs for the treatment of HIV-1 infected adults and children over 14 days of age. Chu et al. found that in vitro and in clinical trials, lopinavir/ ritonavir has anti-SARS-CoV activity. Ribavirin is an equivalent nucleoside with a wide spectrum of antiviral activity.

A research compared 111 patients with severe acute respiratory syndrome (SARS) treated with ribavirin monotherapy, and 41 patients with SARS treated with lopinavir / ritonavir and ribavirin; patients treated with combination therapy had a lower risk of acute respiratory distress syndrome (ARDS) and death. Chloroquine is a commonly

used antimalarial which was reported in 2006 as a possible broad-spectrum antiviral. Chloroquine was found to prevent infection with low micromolar concentrations of SARS-CoV-2, with a half-maximum effective concentration (EC50) of 1.13 μM and a half-cytotoxic concentration (CC50) greater than 100 μM.

Control And Preventive Measures

Controlling the current outbreak requires rigorous steps to reduce the transmission of COVID-19 from person to person. Specific attention and efforts should be given to preventing or reducing transmission in vulnerable populations, including infants, health care providers and the elderly. For medical professionals, health care practitioners, and public health individuals and researchers involved in the 2019-nCoV, a guideline has been written. The early death cases of COVID-19 outbreak occurred mainly in the elderly, likely due to a poor immune system that allows for faster viral infection progression. The public utilities and facilities will regularly include decontaminating hand washing reagents. When dealing with the virus, direct contact with wet and infected materials should be considered, when particular agents such as faecal and urine samples which may potentially serve as an alternate transmission path. China and other nations, including the US, have adopted significant prevention and control initiatives to monitor further spread of the virus, including travel screenings[29].

Epidemiological changes in the COVID-19 infection should be monitored taking into account potential transmission routes and subclinical infections, as well as the adaptation, evolution and dissemination of viruses among humans and possible intermediate animals and reservoirs. A large number of issues still remain to be answered. They provide information about how and how many were screened, what proportion of these turned positive and whether this rate remains constant or variable, but are not restricted to that.

There is an alarming need to work on these studies discussed above inorder to bring an effective solution to stop the spread of this dangerous threat to the world.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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