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A REVIEW ON COVID-19 PANDEMIC

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ABSTRACT

The pandemic of coronavirus disease 2019(COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents an unprecedented challenge to identify effective drugs for prevention and treatment.According to WHO(World Health Organization),viral diseases continue to emerge and represent a serious issue to public health.This new virus is very contagious and has quickly spread globally.Intially the new virus was called 2019-nCoV.Subsequently, the task of experts of the International Committee on Taxononmy of Viruses termed it the SARS-CoV 2 as it is very similar to the one that caused the SARS outbreak(SARS-CoVs).The CoVs have become the major pathogens of emerging respiratory outbreaks.The content of this review is mainly about the etiology, epideimology, clinical symptoms, pathogenesis, transmission, diagnosis and treatement of COVID-19.

KEYWORDS: COVID 19,SARS-CoV-2, WHO, SARS-CoVs.

INTRODUCTION

An ongoing outbreak of pneumonia associated with a novel coronavirus, severe acute respiratory syndrome (SARS) coronavirus, was reported in Wuhan, China, in December 2019[1–3]In the following weeks, infections spread across China and other countries around the world.[4–6] The Chinese public health, clinical, and scientific communities took action to allow for timely recognition of the new virus and shared the viral gene sequence to the world.[2,7] On January 30, 2020, the World Health Organization (WHO) declared the outbreak a Public Health Emergency of International Concern.[8] On February 12, 2020, the WHO named the disease caused by the novel coronavirus "coronavirus disease 2019" (COVID-19)[9] A group of international experts, with a range of specializations, have worked with Chinese counterparts to try to contain the outbreak.[10] At present, a real-time reverse-transcription polymerase chain reaction (RT-PCR) assay for COVID-19 has been developed and used in clinics. Although RT-PCR remains the reference standard for making a definitive diagnosis of COVID-19 infection.[11] the high false-negative rate.[12] and the unavailability of the RT-PCR assay in the early stage of the outbreak restricted prompt diagnosis of infected patients.

Etiology

In a preliminary report, complete viral genome analysis revealed that the virus shared 88% sequence identity to two bat-derived SARS-like coronaviruses, but more distant from SARS coronavirus.[13] Hence, the virus was temporarily called 2019 novel coronavirus (2019 nCoV). Coronavirus is an enveloped andsingle-stranded ribonucleic acid named for its solar corona-like appearance due to 9–12-nm-long surface spikes.[14] There are four major structural proteins encoded by the coronaviral genome on the envelope,one of which is the spike protein (S) that binds to angiotensin- converting enzyme 2 receptor and mediates subsequent fusion between the envelope and host cell membranes to aid viral entry into the host cell.[15,16] On February 11, 2020, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses finally designated it as SARS coronavirus 2 based on phylogeny, taxonomy, and established practice.[17] Shortly thereafter, the WHO named the disease caused by this coronavirus COVID-19[9] On the basis of current data, it seems that SARS coronavirus 2 might be initially hosted by bats and might have been transmitted to humans by means of pangolin[18] or other wild animals.[13,19] sold at the Wuhan Market but subsequently spread by means of human to-human transmission.

Epidemiology

In December 2019, the earliest symptoms of patients confirmed to have COVID-19 appeared.[20] At first, the morbidity remained low. However, it reached a tipping point in the middle of January 2020. During the second half of that month, there was a remarkable increase in the number of infected patients in affected cities outside Wuhan because of the population movement before the lunar Chinese New Year.[21] Followed by an exponential growth until January 23, 2020, the outbreak spread to the other countries, attracting extensive attention around the world. Evidence of clusters of infected family members and medical workers confirmed the presence of human-to-human transmission.[12] by droplets, contact, and fomite.[23,24] Thus far, there is no definite evidence of intrauterine transmission[22] Current estimates are that COVID-19 has a median incubation period of 3 days (range, 0–24 days), with potential transmission from asymptomatic individuals.[25,26] At the end of January 2020, the WHO confirmed that there were more than 10000 cases of COVID-19 across China.[27] On February 13, 2020, 13 332 new clinically diagnosed cases were first reported from Hubei. Official reports included clinically diagnosed cases and laboratory-confirmed cases because chest CT findings were recommended as the major evidence for clinically confirmed cases in the Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial version 5) by the National Health and Health Commission of China in February 2020.[28] As of February 19, 2020, the total number of confirmed cases rose to 74 280 in China and to 924 in 25 countries outside China; there was a total of 2009 deaths globally [(10)].To control COVID-19, effective prevention and control measurements must include early detection, diagnosis, treatment, and quarantine to block human-to-humantransmission and reduce secondary infections among closecontacts and health care workers.[10]

Clinical Symptom Spectrum

Understanding the clinical symptoms of COVID-19 is important,although the clinical symptoms are indicated nonspecific.Common symptoms include fever, cough, myalgia, and fatigue. Patients may initially present with diarrhea and nausea a few days before developing a fever, which suggests that fever is dominant but not the premier symptom of infection. A small number of patients can have headache orhemoptysis.[22,28] and be relatively asymptomatic.[12] Affected older men with comorbidities are more likely to have respiratory failure due to severe alveolar damage.[29] Disease onset may show rapid progression to organ dysfunctio(eg,shock, acute respiratory distress syndrome, acute cardiac injury, and acute kidney injury) and even death in severe cases [(1,28)]. Meanwhile, patients might have normal or lower white blood cell counts, lymphopenia, or thrombocytopenia, with extended activated thromboplastin time and increased C-reactive protein level.[1,22,28,29] In short, COVID-19 should be suspected in a patient with fever and upper respiratory tract symptoms with lymphopenia or leukopenia, especially in those with Wuhan exposure or a history of close contact with people from Wuhan or patients confirmed to have COVID-19.

Pathogenesis

Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection.[30] The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed.[30] The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury.[31] Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity.[31]

Transmission

Based on the large number of infected people that were exposed to the wet animal market in Wuhan City where live animals are routinely sold, it is suggested that this is the likely zoonotic origin of the COVID-19. Efforts have been made to search for a reservoir host or intermediate carriers from which the infection may have spread to humans. Initial reports identified two species of snakes that could be a possible reservoir of the COVID-19. However, to date, there has been no consistent evidence of coronavirus reservoirs other than mammals and birds.[32,33] Genomic sequence analysis of COVID-19 showed 88% identity with two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses(34,35), indicating that mammals are the most likely link between COVID-19 and humans. Several reports have suggested that person-to-person transmission is a likely route for spreading COVID-19 infection. This is supported by cases that occurred within families and among people who did not visit the wet animal market in Wuhan.[36,37] Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual. In a small study conducted on women in their third trimester who were confirmed to be infected with the coronavirus, there was no evidence that there is transmission from mother to child. However, all pregnant mothers underwent

cesarean sections, so it remains unclear whether transmission can occur during vaginal birth. This is important because pregnant mothers are relatively more susceptible to infection by respiratory pathogens and severe pneumonia The binding of a receptor expressed by host cells is the first step of viral infection followed by fusion with the cell membrane. It is reasoned that the lung epithelial cells are the primary target of the virus. Thus, it has been reported that human-to-human transmissions of SARS-CoV occurs by the binding between the receptor-binding domain of virus spikes and the cellular receptor which has been identified as angiotensin- converting enzyme 2 (ACE2) receptor.[35,38] Importantly, the sequence of the receptor-binding domain of COVID-19 spikes is similar to that of SARS-CoV. This data strongly suggests that entry into the host cells is most likely via the ACE2 receptor.[38]

DIAGNOSIS

The first task for the clinical diagnostic workflow is to confirm a history of Wuhan exposure or close contact with people from Wuhan or patients confirmed to have COVID-19 during the past 2 weeks. However, the number of patients with unknown exposure history is increasing due to the rapid and extensive spread of the disease. The National Health Commission of China.[39,40] formulated the Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial version 6)based on WHO recommendations for SARS and Middle East respiratory syndrome.[41–43] Based on trial version 5.[27] chest CT findings of viral pneumonia are regarded as evidence of clinical diagnosis of COVID-19 infection. However, the WHO did not accept CT findings without RT-PCR confirmation until February 17, 2020 (43), and the most recently published Diagnosis and Treatment Program of 2019 New Coronavirus Pneumonia (trial version 6) has deleted the term clinical diagnosis.[40] The final etiologic diagnosis of COVID-19 is necessary and can be further confirmed with a positive real-time RT-PCR assay for COVID-19 using respiratory or blood samples or by means of viral gene sequencing of respiratory or blood samples that are highly homologous with COVID-19. Patients confirmed to have COVID-19 are classified as having mild, moderate, severe, or critical disease according to clinical manifestations.[27,40,45]

Treatment

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also have immunomodulatory effects through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells.[46,47] Chloroquine inhibits SARS-CoV-2 in vitro with a half-maximal effective concentration (EC50) in the low micromolar range. Hydroxychloroquine has in vitro activity with a lower EC50 for SARS-CoV-2 compared with chloroquine after 24 hours of growth. Reports from China shows that chloroquine was successfully used to treat a series of more than 100 COVID-19 cases resulting in improved radiologic findings, enhanced viral clearance, and reduced disease progression.39 However, the clinical trial design and outcomes data have not yet been presented or published for peer review, preventing validation of these claims. A recent open-label nonrandomized French study of 36 patients (20 in the hydroxychloroquine group and 16 in the control group) reported improved virologic clearance with hydroxychloroquine, 200 mg, by mouth every 8 hours compared with control patients receiving standard supportive care. Dosing of chloroquine to treat COVID-19 has consisted of 500 mg orally once or twice daily.[48,49]

However, both agents can cause rare and serious adverseeffects (<10%),includingQTc prolongation, hypoglycemia, neuropsychiatriceffects, andretinopathy. Baselineelectrocardiograpby toevaluate for prolonged QTc isadvisable prior to and following initiation of these medications because of the potential for arrhythmias, especially in critically ill patients and those taking concomitant QT-interval prolonging medications such as azithromycin and fluoroquinolones.[50] No significant adverse effects have been reported for chloroquine at the doses and durations proposed for COVID-19. Use of chloroquine and hydroxychloroquine in pregnancy is generally considered safe.[50,51]

Lopinavir/Ritonavir and Other Antiretrovirals

US Food and Drug Administration (FDA) approved oral combination agent for treating HIV, demonstrated invitro activity against other novel coronavirusesvia inhibition of 3-chymotrypsin-like protease[52,53] No published SARS-CoV-2 in vitro data exist for lopinavir/ritonavir. Clinical studies in SARS were associated with reduced mortality and intubation rates, although conclusions could not be made. The timing of administration during the early peak viral replication phase (initial 7-10 days) appears to be important because delayed therapy initiation with lopinavir/ritonavir had no effect on clinical outcomes. Although additional clinical trials of lopinavir/ritonavir are ongoing, the current data suggest a limited role for lopinavir/ritonavir in COVID-19 treatment. The most commonly used and studied lopinavir/ritonavir dosing regimen for COVID-19 treatment is 400 mg/100 mg twice daily for up to 14 days[46,54] Given the significant drug-drug interactions and potential adverse drug reactions, careful review of concomitant medications and monitoring are required if this drug is used. Adverse effects of lopinavir/ritonavir include gastrointestinal distress such as nausea and diarrhea (up to 28%) and hepatotoxicity (2%-10%)[56] In patients with COVID-19, these adverse effects may be exacerbated by combination therapy or viral infection because approximately 20% to 30% of patients have elevated transaminases at presentation with COVID-19. A recent trial showed approximately 50% of lopinavir/ritonavir patients experienced an adverse effect

and 14% of patients discontinued therapy due to gastrointestinal adverse effects.

Ribavirin

Ribavirin, a guanine analogue, inhibits viral RNA-dependent RNA polymerase. Its activity against other nCoVsmakes it a candidate for COVID-19 treatment. No evidence exists for inhaled ribavirin for nCoV treatment, and data with respiratory syncytial virus suggest inhaled administration offers no benefit over enteral or intravenous administration.48 Ribavirin causes severe dose-dependent hematologic toxicity. The high doses used in the SARS trials resulted in hemolytic anemia in more than 60% of patients.[56]

Remdesivir

Remdesivir is a monophosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside triphosphate analogue. The agent was discovered during the screening process for antimicrobials having activity against RNA viruses, such as Coronaviridae and Flaviviridae. Currently, remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent invitro activity against several nCoVs, including SARS-CoV-2 with EC50 and EC90 values of 0.77 μM and 1.76 μM, respectively.

Intravenous infusions between 3 mg and 225 mg were well-tolerated without anyevidence of liver orkidney toxicity. Remdesivir demonstrated linear pharmacokinetics within this dose range and an intracellular half-life of greater than 35 hours. Following multiple-dose administrations, reversible aspartate aminotransferase and alanine transaminase elevations occurred.dose under investigation is a single 200-mg loading dose, followed by 100-mg daily infusion. No hepatic or kidney adjustments are recommended at this time, but initiation is not recommended in patients with an estimated glomerular filtration rate less than 30 mL/min.

The first clinical use of remdesivir was for the treatment of Ebola64; however, successful case reports describing the use of remdesivir for COVID-19 have been reported.[57,58]

Favipiravir

Favipiravir a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. The activeagent inhibits the RNA polymerase, halting viral replication. Most of favipiravir's preclinical data are derived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses.In vitro, the EC50 of favipiravir against SARSCoV-2 was 61.88 μM/L in Vero E6 cells.A loading dose is recommended (2400 mg to 3000 mg every 12 hours × 2 doses) followed by a maintenance dose (1200 mg to 1800 mg every 12 hours).The agent has a mild adverse effect profile and is overall well-tolerated, although the adverse event profile for higher-dose regimens is limited.[59,60]

Corticosteroids

The role of corticosteroids is to decrease the host inflammatory responses in the lungs, which may lead to acute lung injury and acute respiratory distress syndrome (ARDS).However, this benefit may be outweighed by adverse effects, including delayed viral clearance and increased risk of secondary infection. Although direct evidence for corticosteroids in COVID-19 is limited, reviews of outcomes in other viral pneumonias are instructive.[61]

CONCLUSION

The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high quality evidence even in the middle of a pandemic. No therapies have been shown effective to date.

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