Review Article

Review on Therapeutic Trials for Coronavirus Disease-19

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Abstract

Our world was gripped by the coronavirus disease-19 (COVID-19) pandemic during the first months of the year 2020. It has been characterized as a new coronavirus (i.e., severe acute respiratory syndrome-CoV-2, which is an acute severe respiratory syndrome coronavirus, and later, it has been referred to as the coronavirus disease-19 or COVID-19. Whereas this disease has been originated in Wuhan city in the Chinese province of Hubei, it was capable of rapidly spreading all over the world, which has resulted in a human disaster as well as massive economic damages. By the middle of June 2020, there were more than 8 million COVID-19 cases all over the world, with more than 436,000 death cases. The aim of this review study was to investigate the most effective therapeutic trials for COVID-19.

Keywords: Control, coronavirus disease-19, diagnosis, prevention, treatments

Introduction

A very recent outbreak of a more severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV-2) which one causes COVID-19 disease, a most concerned factor, now-a-days, to human health. Not only the health but it caused a disaster in human social, economic, and many other aspects of life, being the disease is highly infectious and fatal too. It has been characterized as a new coronavirus (i.e., SARS-CoV-2, which is an acute severe respiratory syndrome coronavirus, and later, it has been referred to as the coronavirus disease-19 (COVID-19).[1] Whereas this disease has been originated in Wuhan city in the Chinese province of Hubei, it was capable of rapidly spreading all over the world, which has resulted in a human disaster as well as massive economic damages. By the middle of June, there were more than 8 million COVID-19 cases all over the world, with more than 436,000 death cases.

Considering the speed of COVID-19 spread, the governments worldwide took numerous public health measures that have been aimed at the prevention of its spreading, those measures included social distancing,[2] part of which the schools, businesses, nongovernmental organization, and community centers were forced to shut down, any mass gathering was forbidden, and measures of lockdown were adopted in several of the countries, which has allowed the travels for the vital needs only. The aim of the social distancing is for the countries to be capable of "flattening the curve, reducing the numbers of the new COVID-19 cases from a day to the other for the purpose of halting the exponential growth, thereby, reducing the pressure on the medical service facilities John Hopkins Univ.

COVID-19 spread is projected to be resulting in a dramatic slowdown of the economic events. Based on an early projection of the International Monetary Fund, the global economy would be contracting by approximately 3% in 2020. Such contraction would be expected to have a considerably higher magnitude compared to the magnitude of the Global Financial Crisis of 2008–2009. None-the-less, in the latest updates,[3] the International Monetary Fund has revised those projections to 4.90% contraction in 2020. The report has cited the following reasons behind updating the projection: (a) higher determination in the activities of the social distancing; (b) greater uncertainty; (c) lower levels of activities throughout the

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lockdown periods; and d) sharper reduction of the productivity among the companies that were open up for business.[4]

Structure of the Virion and Infection Pathophysiology

SARS-CoV-2 is from the beta coronavirus family, it is a single-stranded, positive-sense, RNA, enveloped virus which has a diameter of 50–200 nm. Genomic RNA is 30Kb, spike glycoprotein (S) is a vital encoded structural protein consisting of 3 S1-S2 heterodimers binding to the receptor of angiotensin-converting enzyme 2 (ACE-2) on type 2 pneumocytes. SARS-CoV-2 entry in type 2 pneumocytes is through the endocytosis and after that will multiply in the cytoplasm.[5] The high stress of the manufacturing of protein which has been induced on type 2 pneumocytes results in the apoptosis. In addition to all that, RNA from SARS-CoV-2 plays the role of PAMP (i.e., pathogen-associated molecular pattern) and will be identified with toll-like or pattern recognition. Receptors, which results in a surge of the chemokine, causing the activation and migration of the neutrophil, and also results in an alveolar-capillary wall destruction. At a level of the microscopic, it results in the loss of interface between intra-alveolar space and surrounding stroma, which is why,the fluids leak through and fill in alveolar sacs.[6]

Transmission Modes

Transmission modes that are traced in imported cases are through the transmission of the droplets, conjunctiva, fecal–oral route, and fomites. In addition to that, the local transmission may be traced back to the bodily fluids of the patient such as the saliva, respiratory droplets, urine, and feces. Four of 18 stabilized at smaller temperature values, in other words, 4°C is of a greater survival rate compared to 22°C. Due to the fact that the virions of COVID-19 are shed over the clinical course, SARS-CoV-2 patients have the ability of spreading the infection before the appearance of any symptoms, throughout the symptomatic course and throughout the period of the clinical recovery. More considerations have to be made in concern to the SARS-CoV-2 virion's residence time on the surfaces.[7]

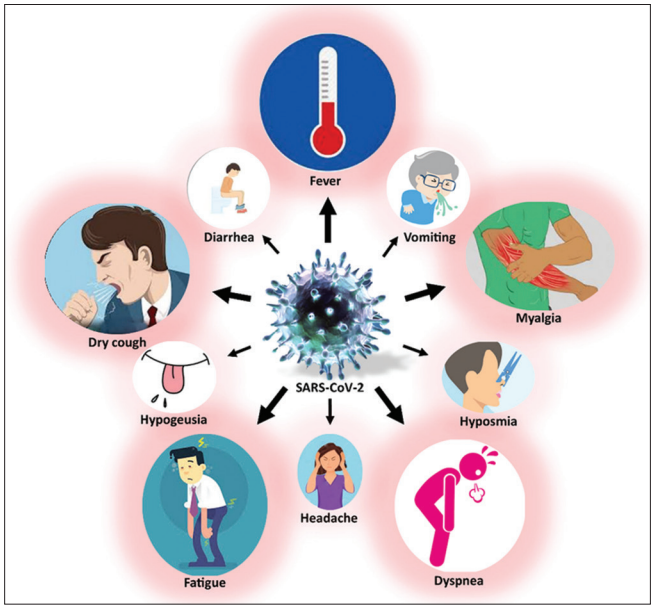

Figure 1: Clinical manifestations of coronavirus disease-19 disease

Severe Acute Respiratory Syndrome-Coronavirus-2 Clinical Presentations

The infection which results from COVID-19 has been termed as COVID-2019, and its symptomatology has been studied thoroughly in a joint report by China and the WHO about the SARS-CoV-2 (n = 55,924). The patients that have this infection present with the pyrexia in 85% of the cases throughout the course of their illness; however, merely of them 45% have been found febrile on the early presentations. In addition to that, the cough has been observed in 67.70% of the infected and sputum has been produced in 33.40% of them. The respiratory signs such as sore throat, dyspnea, and nasal congestion have been found, respectively, in 13.90%, 18.60%, and 4.80% of the patients. The constitutional signs such as the chills, bone or muscle aches, and headaches have been observed, respectively, in 11.40% 14.80%, and 13.60% of patients,[8] The gastrointestinal signs, such as diarrhea and nausea or vomiting were observed, respectively, in 3.70% and 5% of patients. Babaei *et al.* from Shahid Beheshti University of Medical Sciences, Iran, illustrated in their review article the main symptoms and clinical manifestations of COVID- 19 disease.[9]

Those clinical SARS-CoV-2 symptoms have been in consistency with other similar researches on patients with SARS-CoV-2 in China (n = 41, 81, 99, and 138). More serious insults on lung tissues may happen in the ARDS (i.e., the acute respiratory distress syndrome) that has the ability of additionally precipitating the septic shock. Those two problems have been found as the main contributors to the intensive care unit care and mortality from this virus in the patients with smoking history, who were older than 60 years old, and the comorbid medical condition. Patients from the older age and the smoking group have the tendency of having a higher ACE2 receptor density, with variable chronic medical conditions that affect the SARS CoV 2 clinical course [Figure 1]. The general analysis of the present study (n = 1458) has shown that the main comorbid conditions comprise diabetes, cerebrovascular and cardiovascular diseases, and hypertension.[10]

Treatments

Azithromycin

This is a bacteriostatic that belongs to the class of the macrolides, inhibiting the synthesis of the bacterial protein, thereby interfering with the growth of the bacteria. It has been known as well, to be having antiviral impacts, besides its

antibacterial characteristics. It was utilized for the treatment of the respiratory viral infection as a result of the former characteristic. The treatment with the azithromycin combined with the hydroxychloroquine (HCQ) showed important antiviral activity toward COVID-19. The researches on the azithromycin on its own as one of the options for treating SARS-CoV-2 have been quite rare, and it is unclear whether or not the macrolides may be utilized exclusively or have to be combined with the HCQ.[10] In a research by Ohe M *et al*., they have stated that the macrolides on their own, or combined with some other medications, have high efficiency against the COVID 19.[11] There are numerous clinical experimentations that are carried out for checking the HCQ-azithromycin efficacy for treating COVID-19. An interventional clinical experimentation is being conducted for the determination of the HCQ-azithromycin's safety and efficacy.[12]

Remdesivir

The remdesivir is a very promising drug that, Remdesivir (GS5734) has been presented by Gilead Science Inc. in 2017 to be used against the re-emerging of the Ebola virus. Automatically, it plays the role of an analog of the adenosine and results in the premature termination of the replication of the virus. It is incorporated to the newly formed chains of the viral RNA and inhibits the RdRp16 considering its wide range of the antiviral activities, it has been tested against other virus types, which include the Middle East respiratory coronavirus (MERS-CoV) as well as SARS-CoV-1 (i.e., SARS coronavirus of 2003–2004). Recently, de Wit et al., have shown promising therapeutic and prophylactic results in a model of the live rhesus macaque against the MERS CoV-1.[13] In the case of the initiation of the remdesivir 24 h before the inoculation, the replication of the virus in the tissues of the lungs has been inhibited and as a result, the histologic lung lesions and clinical disease have been prohibited. In the case of being given 12 h following the inoculation of the MERS-CoV, the remdesivir has resulted in the decreased clinical disease severity, reduced replication of the virus in the tissues of the lung, and less severe and fewer lesions of the lungs. In a different research that has examined the human epithelial cells of the airways, it has been discovered to be inhibiting the SARS-CoV-1 and MERS-CoV viral replications.[14]

Before the pandemic of COVID-19, remdesivir has a well-known broad-spectrum activity against wide range of virus families, including Ebola virus disease, SARS-CoV and MERS-CoV (Middle East respiratory syndrome coronavirus), and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses.[13] Remdesivir reduced the severity of disease, virus replication, and damage to the lungs when administered either before or after animals were infected with MERS-CoV, showing that remdesivir is a promising antiviral treatment against MERS that could be considered for implementation in clinical trials.[20] even though the direct causes were hart to prove, there have been considerable decreases in the viral loads of COVID-19 by the oropharyngeal and nasopharyngeal swabs after the administrations. The dosing regimen that has been used has been a 200 mg loading dose of the intravenous infusions, succeeded by 100 mg intravenous infusion per day for a 10-day total duration of the treatment. Considering robust responses to the remdesivir in the other diseases of coronavirus, there have been ongoing experimentations that looked at its efficiency in the treatment of SARS-CoV-2. At present, there is a multicenter, randomized, adaptive, double-blinded trial that enrolls the patients in South Korea, U. S., and Singapore, and two trials ongoing in China.[15]

Chloroquine and hydroxychloroquine

Throughout the struggle against the pandemics public health emergencies, the main drugs can be re-purposed. Stated by the WHO as one of the "essential medicines," the chloroquine was utilized as antimalarial since it has been created by Bayer in Germany, in the 1930s. The HCQ is part of the same molecular family and it is different from the chloroquine only with a group of the hydroxyl. Those medications showed massive treatment potentials toward the viral infection types. The antiviral activities of the chloroquine are considered to be working through the alkalization of a phagolysosome of the virus, increasing the value of the lysosomal pH. Numerous viruses need a rather acidic environment for promoting the fusion of the host cell. Which is why, the alkalization of pH is impeding the uncoating and fusion, and as a result, the replication of the virus. *In vitro* researches showed that the chloroquine is active against the COVID-19.[16]

In vivo, it was demonstrated to be commonly distributing over the body and penetrating the tissues of the lungs well.[16] With a low cost and side effect profiles, the chloroquine has been one of the obvious choices for the trials throughout the first few months of the outbreak of COVID-19. Gao *et al*. have stated in February 2020 that China already carried out a minimum of 15 clinical experimentations, which were used to evaluate chloroquine and/or HCQ's efficacy and safety in COVID-19 pneumonia treatments. More than 100 infected individuals have participated at ten of the participating clinical sites.[17] Results have declared that the chloroquine is "better than the control treatment for the inhibition of the pneumonia exacerbation, which resulted in the enhancement of the results of the lung imaging, promotion of virus-negative conversions, and shortening of the course of this disease." Results from one hydroxychloroquine versus placebo trial have been released to the med-Rxiv, which is an online server for the scientific researches.[18] Authors have reached the conclusion that the group of the hydroxychloroquine had speedier enhancement in fever and cough, and greater enhancement rates in the pneumonia on the imaging. Unluckily, this research, as well as researches that have been stated by Gao *et al*., was not published nor peer-reviewed, and any results have to be cautiously viewed.[19]

Lopinavir/ritonavir

Lopinavir/ritonavir has recently been approved for once-daily dosing in antiretroviral-naive patients.[26] Ritonavir inhibition is usually combined with the lopinavir for the

purpose of increasing the half-life of its plasma. Combining the lopinavir/ritonavir (LPV/r) has been proposed for resulting in the decrease of the negative results in the 2004 outbreak of SARS. Structures and sequences of the binding site of LPV/r to the SARS-CoV-1 and SARS-CoV-2 protease types have been 96% conserved, and it was initially thought that LPV/r could be an effective treatment for COVID-19 by inhibiting the virus' main protease (Mpro). The case reports documented the utilization of the LPV/r in Korea, whereas a limited amount of the case series have shown mixed results. A research in China observed using the umifenovir in combination with the LPV/r. The umifenovir (referred to as Arbidol as well) can be defined as a "wide-range antiviral" which has been utilized earlier in the treatment of the influenza in China and Russia.[20] The research has discovered faster SARS-CoV-2 clearance by the polymerase chain reaction (PCR) and speedier improvements of chest CT which has only been a small surveying research with a small-sized sample; however, it had assumed that the LPV/r can be having an impact on treating SARS-CoV-2.[21] The latest research, an open-label and randomized trial that compared the LPV/r versus placebo in the patients who have severe case of SARS-CoV-2 did not find any statistical significance of the differences in the time to the clinical improvements or a 28-day mortality.[22]

Laboratory diagnoses

The attempts at controlling SARS-CoV-2 spread, instituting the isolation measures and quarantine, and appropriate clinical management of the patients, all need good tools for diagnostic and screening. Throughout the spread of COVID-19, other infections to the respiratory tract can be more widespread in the local community. The WHO had presented guidelines on the case surveillances of SARS-CoV-2 on January 31, 2020. For individual meeting specific criteria, the WHO recommends initially screening for more common respiratory illness causes, taking under consideration the location and the season. In the case of finding adverse results, the sample has to be sent to the referral laboratory for detection of the COVID-19.[23]

The definitions of the case may differ according to the country and will be evolved throughout the time with the change of epidemiological conditions in a certain place. In China, one of the confirmed cases from January 15 of this year needed an epidemiological link to Wuhan in 2 weeks and clinical characteristics such as pneumonia, fever, and low count of the white blood cells. On January 18, the epidemiological aspect has been expanded for the purpose of including the contact with any person who was in Wuhan in the last couple of weeks. After that, case definitions have eliminated epidemiological links.[24]

The WHO had put the definitions of cases forward. The suspected SARS-CoV-2 cases are individuals (i) who have acute severe infections of the respiratory tract (the cough and fever history, which require the admissions to the hospital) and without other etiology, entirely explaining clinical presentations and a travel history to or living in China throughout 2 weeks before the appearance of the symptoms; or (i) the patient who has any acute respiratory illnesses and a minimum of one of the following throughout 2 weeks before the symptoms appear: contacting with any potential or confirmed cases of the COVID-19 or attended or worked in one of the health-care facilities, in which the patients that have potential or confirmed patients of the COVID-19 acute respiratory disease.[20] The potential cases are the ones for whom the testing for the COVID-19 is inconclusive or the ones testing positive with the use of pan-coronavirus assays and with no laboratory evidence of other respiratory pathogens. The confirmed case is the case that has a laboratory confirmation of being infected with the COVID-19, in spite of the clinical symptoms and signs.[25]

Strategies of Control and Prevention

SARS-CoV-2 is obviously one of the serious diseases of an international level. By some of the estimations, it is of a greater reproductive number compared to the SARS, and a greater number of the people were reported to be infected or die spread of this pandemic. A variety of strategies have to be taken in the healthcare setting and at global as well as local levels.[22]

Unfortunately, the health-care settings may be one of the most significant viral transmission sources. As can be seen in the SARS model, applying the triages, after the accurate measures of the infection control, the isolation of the infected and tracing of the contact are the keys for limiting the additional spread of SARS-CoV-2 in the hospitals and health-care facilities. The suspected individuals presenting at the health-care facilities with the respiratory infection signs (such as fever, cough, and runny nose) have to be wearing face masks for the purpose of containing this virus and strictly adhering the process of the triage. They should not be allowed to be waiting with other patients who seek the medical care at hospitals. They have to be isolated in separate rooms with full ventilation and about 2 m away from other patients who have convenient access to the supplies of the respiratory hygiene.[15]

Conclusion

This review was concluded that a variety of therapeutic trails including novel antivirals, modifiers of the immune response or other intrinsic pathways, as well as combination approaches are needed for improvement the outcomes in those suffering from Covid-19.

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Conflicts of interest

There are no conflicts of interest.

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