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LIFE CYCLE OF COVID-19 STAGES AND TREATMENT

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Abstract
The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)bat viruses, therefore bats could be the possible primary reservoir , which emerged in Wuhan, China and spread around the world. The intermediate source of origin and transfer to humans is not known, however, the rapid human to human transfer has been confirmed widely. There is no clinically approved antiviral drug or vaccine available to be used against COVID-19. However, few broad-spectrum antiviral drugs have been evaluated against COVID-19 in clinical trials, resulted in clinical recovery. We also discuss the approaches for therapeutic combinations to cope with this viral outbreak.
Chloroquine has been sporadically used in treating SARS-CoV-2 infection. Hydroxychloroquine shares the same mechanism of action as chloroquine, but its more tolerable safety profile makes it the preferred drug to treat malaria and autoimmune conditions. We propose that the immunomodulatory effect of hydroxychloroquine also may be useful in controlling the cytokine storm that occurs late-phase in critically ill SARS-CoV-2 infected patients.

Introduction

December 2019 the epidemic of a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2 or COVID-2019), was chief reported in Wuhan, China.

Coronaviruses are relate to the Coronaviridae family in the Nidovirales order. It represents crown-like spikes on the outside surface of the virus; thus, it was named as a coronavirus. Coronaviruses are smaller in magnitude (65–125 nm in diameter) and contain of a single-stranded RNA as a nucleic material, range ranging from 26 to 32kbs in length. The subgroups of coronaviruses family are alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus.

The severe acute respiratory syndrome coronavirus (SARS-CoV), H5N1 flu A, H1N1 2009 and middle East respiratory syndrome coronavirus (MERS-CoV) foundation acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary malfunction and product in fatality. These viruses were reflection to infect no more than animals until the earth witnessed a severe acute respiratory syndrome (SARS) eruption caused by SARS-CoV, 2002 in Guangdong, China. Only a decade later, a new pathogenic coronavirus, renowned as median East respiratory syndrome coronavirus (MERS-CoV) caused an prevalent in middle Eastern countries.

Recently at the bring to an end of 2019, Wuhan an emerging commerce focal point of China qualified an eruption of a novel coronavirus that killed additional than eighteen hundred and infected over seventy thousand individuals contained by the firstly fifty living of the epidemic. This virus was reported to be a member of the beta-group come together of coronaviruses.

Entry mechanism of human coronaviruses

Every single one coronaviruses restrain particular genes in ORF1 downstream regions that encode proteins for viral replication, nucleocapsid and spikes formation. The glycoprotein spikes on the superficial surface of coronaviruses are conscientious for the attachment and account of the virus to mass cells. The receptor-binding domain (RBD) is loosely bonded along with virus therefore; the virus may infect compound hosts. Other coronaviruses frequently recognize aminopeptidases or carbohydrates as a secret receptor for doorway to person cells while SARS-CoV and MERS-CoV appreciate exopeptidases. The entry mechanism of a coronavirus depends upon cellular proteases which include, human airway trypsin-like protease (HAT), cathepsins and transmembrane protease serine 2 (TMPRSS2) that

separates the spike protein and creates broaden penetration changes. MERS coronavirus employs dipeptidyl peptidase 4 (DPP4), despite the fact that HCoV-NL63 and SARS-coronavirus require angiotensin-converting enzyme 2 (ACE2) as a basis receptor. SARS-CoV-2 possesses the conventional coronavirus formation with spike protein and moreover articulated other polyproteins, nucleoproteins, and crust proteins, such as gene polymerase, 3- chymotrypsin-like protease, papain-like protease, helicase, glyciprotein, and accessory proteins.(Pyrck K et al.,2007)

Genomic variations in SARS-CoV-2 :

The genome of the SARS-CoV-2 has been reported over 80% different creatures apart from the previous creatures coronavirus (SARS-like bat CoV). The Structural proteins are encoded by the four structural genes, counting spike (S), envelope (E), membrane (M) and nucleocapsid (N) genes. The orf1ab is the largest gene in SARS-CoV-2 which encodes the pp1ab protein and 15 nsps. The orf1a gene encodes for pp1a protein which moreover contains 10 nsps.

According to the evolutionary tree, SARS-CoV-2 deception particular to the convene of

SARS coronaviruses. Recent studies grasp indicated notable variations in SARS-CoV and

SARS-CoV-2 such as the absence of 8a protein and fluctuation of amino acids in 8b and 3c protein in SARS-CoV-2. (Keyaerts E et al., 2004)

STAGES

●Stage I

Stage 1 is what time belongings are imported from exaggerated countries without any native derivation and who declare travelled abroad investigation encouraging for the respiratory illness. The disease does not spread locally at this stage.

●Stage II

This is the stage when local transmission happens and its spokesperson is proven and be capable of be located. At this stage, people enclose approach in communication with a long-suffering who has travelled outside the country. They are mostly make contact with the long-suffering such as family members or others who state been in affect with the infected. Fewer people are exaggerated at stage 2 and it is easier to carry out phone tracing and limit the put out by way of self-quarantining. India is at present in step 2.

●Stage III

This is the stage of district transmission and takes home once the foundation of an individual's infection can't be traced and isolated. During this stage, individuals who allow not been exposed to an infected personality or a person who has a history to affected countries will put to the test sure for the coronavirus. The epidemic will spread fast in clusters once the public transmission starts.

●Stage IV

It is the nearly all dreaded stage during which nearby are more than a few clusters of the infection and it takes the start of an epidemic. Larger number is infected community, it will difficult to control the spread of disease.

METHOD

Viral gene Extraction and RT-PCR

Viral gene was extracted from 100 µL of supernatant of infected cells via the automated nucleic acid extraction system (TIANLONG, China) and the manufacturer's instructions. Detection of the SARS-CoV-2 virus was performed by the one stride get ready speech RT-PCR equipment (TaKaRa, Japan) on the illumination Cycler 480 Real-Time PCR system (Roche, Rotkreuz, Switzerland) with primers.

PBPK exemplar Development, validation and Simulation

The PBPK models for chloroquine and hydroxychloroquine were urban via Simcyp simulator. The chloroquine compound file was provided by Simcyp limited (a Certara company, Blades activity Centre, Sheffield, UK) and the hydroxychloroquine compound file was self-built. Physical and chemical parameters were obtained from the literature. Pharmacokinetic parameters, such as liver intrinsic clearance, fa and ka, were strong-minded from clinical records. The lung to blood concentration ratio for chloroquine and hydroxychloroquine (obtained from animal studies) were used to predict the drug concentration in the lungs.(Vincent MJ et al.,2005)

Validation method

Concentration-time profiles were simulated under different available clinical experiment protocols by means of the industrial PBPK models for hydroxychloroquine and chloroquine. The Simcyp "Healthy volunteer", "Chinese healthy volunteer" and "Pediatric" virtual populations were used in the simulations as the clinical trials were conducted in Caucasian, Chinese and family populations, respectively.

Simulated exposure numbers was compared to experiential data. The criterion to establish mode correctness was based on whether the practical

information knock down in the 90% confidence space of the predicted values.

Validation result

Intravenous numbers was used to be familiar with the distribution and elimination phase of the two drugs, and, oral was use to understand the intracorporal concentration process. On the whole of the practical numbers knock out contained by the 90% prediction interval. The ratio of predicted to experimental PK parameters (Cmax and AUC) were contained by the sort of 0.5 to 2.0, indicating that the prediction truth of the industrial PBPK models was customary and may be used to simulate the discrete dosing scenarios.

Simulation method

The exposure of chloroquine and hydroxychloroquine in the lungs, plasma and blood were simulated under assorted dosing regimens by the validated PBPK models. A amendment cause for chloroquine corrupt and hydroxychloroquine root was input into the example simulations. Chloroquine phosphate 500 mg is corresponding to 300 mg of chloroquine build and 200 mg of hydroxychloroquine sulfate is counterpart to 155 mg of hydroxychloroquine base.

Simulation result

The simulated lung, blood and plasma concentration time profiles for chloroquine and hydroxychloroquine under different dosing regimens. It know how to be seen that the lung, blood and plasma concentrations of chloroquine augmented gradually after the primarily dose was known and was so far to arrive at steady express on day 10. The simulated chloroquine concentration in lung tissue was to a great extent elevated than in plasma, where the lung to plasma ratio greater than before with time and reached a ratio of approximately 400. The projected lung, blood and plasma concentrations of hydroxychloroquine rapidly increase and reached steady state next the early loading dose and ensuing maintenance doses.

Treatment

Contemporary therapies

Certain lack of antiviral therapy against COVID-19, current treatments primarily focussing carefully on symptomatic and respiratory according to the Diagnosis and management of Pneumonia Caused by COVID-19 (updated to version6) issued by National HealthCommission of the People's nation of China. Near every patients accepted oxygen therapy, and WHO recommended extra corporeal membrane oxygenation (ECMO) to patients with refractory hypoxemia. Rescue treatement with recovery plasma and immunoglobulin G are delivered to certain critical cases according to their conditions.

Antiviral treatment

Based on the know-how of fighting the rise in SARS-CoV and MERS-CoV previously, we may gain knowledge of more or less instruction for a number of medicine strategies against coronavirus. Antiviral drugs and systemic corticosteroid medicine normally use in clinical training previously, together with neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc), ganciclovir, acyclovir, and ribavirin, as fortunate as methylprednisolone, for cold virus, are void for COVID-19 and not recommended.

Treatment option under study

•Based on indication from laboratory, subconscious and clinical studies, the next medication options were selected: Remdesivir; Lopinavir/Ritonavir; Lopinavir/Ritonavir with Interferon beta-1a; and Chloroquine or Hydroxychloroquine.

•Remdesivir was before hardened as an Ebola treatment. It has generated shows potential domino effect in instinctive studies for Middle East Respiratory Syndrome (MERS-CoV) and Severe acute respiratory syndrome (SARS), which are caused by coronaviruses, symptomatic of it may grasp selected impression in patients with COVID-19.

•Lopinavir/Ritonavir is a certified healing for HIV. Confirmation for COVID-19, MERS and SARS is nevertheless to agricultural show it container convalesce clinical outcomes or avoid infection. This probationary aims to ascertain and corroborate any gain for COVID-19 patients. While in attendance are indications from laboratory experiments that this number sequence may be operative against COVID-19, studies ready consequently long ways in COVID-19 patients obtain been inconclusive.

•Interferon beta-1a is used to act toward numerous sclerosis.

•Chloroquine and hydroxychloroquine are especially compactly allied and use to talk about malaria and rheumatology situation respectively.

Discussion and conclusion

The origination of novel coronavirus was from Wuhan, China. Analysis suggested bats as the key reservoir. Recombination of DNA was found to be involved at spike be the reason for rapid infections and cross-species transmission much closer to SARS-like bat CoV. But still now, no preventive strategies have been developed for human coronavirus. However, the researchers are working to exploit resourceful curative

strategies to manage with the novel coronaviruses. A variety of broad-spectrum antivirals formerly used against influenza, SARS COVID-19 patients and mice models, and clinical isolates knowingly blocked the COVID-19 infection in infected patients. Now it is to be concluded that the virus takes time for the evaluation to produce back the effects in a nation from infected region by a variety infected people in others countries. There are numerous companies operational for the incident of effective SARS-CoV-2 vaccines, CureVac, and Codagenix. But nearby there is need of rapid human being and animal-based trails as these. Vaccines still require 3–10 months for commercialization. There have to be ban on utilizing wild animals and birds as a resource of food. Beside the development of helpful drug, a strategy to fast identify SARS-CoV-2 in suspected individuals is also required. The sign and symptoms of SARS-CoV-2 induced COVID-19 are a spot comparable to infection and continuing allergies (pollen allergies).

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