The possible therapeutic options against COVID-19

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Abstract

Aim: COVID-19 which is caused by SARS-CoV-2 is among the severe respiratory disease to be witnessed to date. SARS-Cov-2 brought about therapeutic difficulties all over the globe. The aim of this review is to evaluate the best possible therapeutic options to tackle the Novel Coronavirus related disease.

Method: Relevant published studies with keywords such as COVID-19 therapy, Sars-Cov-2 treatment and Novel Coronavirus antiviral therapy were extracted from different scientific journals and studied carefully.

Results: Some antiviral drugs, traditional Chinese medicine, immunomodulator drugs and quinoline have shown therapeutic abilities against Sars-Cov-2. However, tocilizumab and remdesivir have shown superiority over other groups of drugs.

Conclusion: Tocilizumab, an immunomodulator drug and viral protease inhibitor remdesivir have shown high efficacy against new coronavirus which raise the necessity for more research about these drugs.

Keywords: COVID-19, SARS-Cov-2, Tocilizumab, Remdesivir, Quinoline, Cytokines.

Introduction

Over decades, the world has witnessed the outbreak of Coronaviruses diseases such as Severe Acute Respiratory Syndrome (SARS) with the first case witnessed in Guangdong Province, Southern China in 2002 and identified as SARS-CoV in 2003. Middle East Respiratory Syndrome (MERS) with the first case witnessed in Saudi Arabia in April 2002.and Severe Acute Respiratory Syndrome Coronavirus-2(Sars-CoV-2) which causes Coronavirus Disease-2019 (COVID-19) with the first case witnessed in Wuhan, China in December 2019. Coronaviruses are enveloped non-segmented positive-sense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals. Since the outbreak of first case of COVID-19 in December 2019 the scientists all over the world have been busy in conducting research for possible treatment and vaccine. To date there is neither treatment nor vaccine against coronavirus. The novel coronavirus outbreak in December 2019 caused mass panic all over the world since this new strain of coronavirus is by comparison very deadly than the former strains. Clinically, COVID-19 patients manifest with high grade fever, anorexia, shortness of breath, dry cough and fatigue. Laboratory investigation reveals increased levels of neutrophil, aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and C-reactive protein and decreased level of albumin and platelets. Image studies reveals massive pleural effusion, ground-grass opacities (GGO) and ground-glass opacity with consolidation.

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This new strain is widely distributed all over the world regardless of the climate, geographical location or gender but according to the data, COVID-19 affects more elder than children. This has raised the alarm for urgency in finding the possible therapy as soon as possible. The WHO have proposed social distancing, frequent hand washing, use of sanitizers and use of masks as possible preventive measures which if followed properly may lower the rate of transmission from person to another because the virus spread by cross contamination and aerosols. But these measures are aimed at prevention only. It became necessary to find the proper cure of this disease as soon as practicable in order to save lives. So many scientists are working day and night to find the permanent solution to this deadly disease. This review summarizes the therapeutic possibilities of ongoing drugs trials.

Drugs investigated for treatment of COVID-19 in clinical trials/ in vivo studies

Pathological studies done on people suffered from COVID-19 showed bilateral diffuse alveolar injury with cytomyxoid fibroma exudate. Another study also showed evident desquamation of pneumocytes, hyaline membrane formation and pulmonary edema. This signifies that the patients had cytokine storm secondary to Cytokine Releasing Syndrome (SRS). This happens when Innate and adaptive immune systems are activated after the SARS-Cov-2 bind to the alveolar epithelial cells in the lungs, resulting in the release of large number of cytokines such as IL-6. This causes increased vascular permeability which in turn result in the infiltration of fluids in the alveolar spaces. Without intervention, this may result in acute respiratory failure and ultimately death. Hence, the immunosuppressive medication which is actually the IL-6 antagonist such as Tocilizumab may be of greater importance in the interference of inflammatory response which reverse the vascular permeability and easing the breathing problems. Another study shows that, in the patients with COVID-19, there is large number of T cells and monoclonal macrophages, that means SARS-Cov-2 activates the inflammatory response. This in turn activates the cytokines such as IL-6 which binds to the IL-6 receptors in the target cells. The result is Cytokines storm and severe inflammatory response in lungs and other tissues. Because Tocilizumab is recombinant humanized anti-human IL-6 monoclonal antibody, it can prevent the binding process of IL-6 to its receptors and ultimately prevent the immune damage to the target cells hence alleviate the inflammatory response. Another evidence is the case of 60years old Wuhan resident who was under treatment of Multiple Myeloma (MM) for more than two years. He experienced respiratory problems and on admission, was diagnosed with COVID-19. His CT Scan revealed bilateral multiple ground-glass opacities and pneumatocele. His laboratory studies revealed increased serum IL-6. The patient was given intravenous Tocilizumab 8mg/kg once a day and the symptoms disappeared and the laboratory studies also showed the decreased level of IL-6 within 10 days. In the study done by Capra, R and collogues, tocilizumab showed great efficacy against Coronavirus after 33 patients with confirmed to be affected by COVID-19 treated by a single dose of 400mg intravenously and other 27 were given 324mg tocilizumab subcutaneous once. Mihai and colleagues reported a 57 years old WHO Grade I obese female diagnosed with systemic sclerosis interstitial lung disease (SSc-ILD) and type 2 diabetic was treated with tocilizumab for the SSc-ILD. She was diagnosed with mild COVID-19 and discharged home with symptomatic treatment only and was declared COVID-19 free 10 days later In a study reported from Barcelona, 58 Covid-19 patients were given tocilizumab and other received tocilizumab in combination with corticosteroids. 8 patients (13.8%) died. In this report, Campins L. et al advised that the timing on when to initiate the immunomodulators to the Covid-19 patients is vital.

Tocilizumab, apart from being effective in fighting the cytokine storms with good efficacy, it also has superiority status in safety too.

Chloroquine/Hydroxychloroquine

Known for many years for its role as treatment and prophylaxis against malaria, the 9-aminoquinoline known as chloroquine has shown great efficacy in curing viral infections by inhibiting the viral replication processes. This is done by altering the required PH Level inside the target cells. Viruses such as coronaviruses, flaviviruses and retroviruses need certain levels of PH in some steps of their replication. By altering the PH within the target cells, Chloroquine and Hydroxychloroquine has shown good ability to inhibit the viral replication and hence lower the viral load in the affected patient. The chloroquine and its hydroxy-analogue, hydroxychloroquine are basically weak bases. This property affects the acidic vesicles leading to dysfunction of some enzymes. Since they are positively charged, chloroquine and hydroxychloroquine cannot cross the plasma membrane but only its non-protonated portion can enter the intracellular compartment. According to the Henderson-Hesselbach law, non-protonated molecules can become protonated once enters the intracellular membrane since it is inversely proportional to the PH. When enters intracellular compartment, it ultimately lowers the PH of the cells and hence inhibit the viral replication. In a study conducted in China, chloroquine had demonstrated great efficacy in treating pneumonia caused by SARS-CoV-2. Studies revealed that the chloroquine has broad-spectrum antiviral activities since it can increase endosomal pH required for the virus to bind to the cells and also can interfere the glycosylation of cellular receptors of SARS-CoV. This ability of chloroquine and hydroxychloroquine can warrant their use against SARS-CoV-2 associated pneumonia. However, it is highly recommended that, when

taken concomitantly with azithromycin and oseltamivir, the high dosage of CQ should be avoided when treating critically ill COVID-19 patients due to its potential safety hazard. Hydroxychloroquine should not be used as postexposure prophylaxis against Covid-19 since has shown no efficacy against the individual with high-risk or moderate-risk exposure to Covid-19.

Traditional Chinese Herbal Medicine (CHM)

According to study by Yu and collogues, Traditional Chinese Herbal Medicine have unique role in treating viral infections including COVID-19. The study showed that a non-cytotoxic concentration of astragalus polysaccharide can inhibit the expression of two early viral proteins, Zta and Rta in the Epstein-Burr Virus lytic cycle to exert an antiviral effect. Other study revealed that two Chinese drugs, Forsythiae Fructus and Lonicerae Japonicae Flos have an ability to combine with 3CLpro and ACE2 to work against COVID-19. CHM can alleviate or prevent the respiratory infections by inhibiting respiratory pathogens. In combination with western medicine, CHM can be used effectively in treating COVID-19 patients.

Yang and his colleagues studied in vivo use of Lianhua Qingwen capsules against influenza B virus (IBV) in Mice in combination with oseltamivir. Their study revealed that, the combination of 200mg/kg/day of Lianhua qingwen capsules with 2mg/kg/day of oseltamivir reduce the infection of lungs by IBV. In China, after the outbreak of Sars-Cov-2, some hospitals tried to use 6g Lianhua qingwen granules three times a day in combination with western medicine to treat covid-19 and yielded a good results.

Lopinavir/Ritonavir

Ritonavir and Lopinavir are under the class of protease inhibitor antiviral drugs. They work by inhibiting the synthesis of protein needed by the viral replication in the host cells. They do so by blocking the actions of protease enzyme and results in the formation of defective viruses which are unable to infect the body cells. So, by using these drugs in the earlier stage of the viral disease, we expect to block the viral replication and ultimately lower the viral load. But Cao and colleagues concluded that, Ritonavir-lopinavir combination has no benefits beyond standard care in treating COVID-19 adult patients.

Remdesivir

Remdesivir, a 1'-cyano-substituted adenosine nucleotide inhibitor that has broad-spectrum antiviral activity against RNA Viruses. In a study done by Mulangu and colleagues demonstrated good tolerance and positive effect of Remdesivir in the lowering the viral load as well as mortality rate on the patients affected by 2018 Ebola virus in the Democratic republic of Congo. In vitro study including primary human epithelial cells culture, Remdesivir, a nucleotide prodrug, GS-5734 showed that it can inhibit the replication of SARS-Cov and MERS-Cov.

Since it is nucleoside analogue prodrug, Remdesivir can inhibit the viral RNA polymerases hence it can block the activity of SARS-CoV-2. In patients hospitalized for severe COVID-19, Remdesivir was given and yield a good result after 36 out of 53 (68%) patients had shown good clinical improvement.

Another case of 35-years old man who was diagnosed with COVID-19 on January 2020 in United States. The compassionate administration of Intravenous Remdesivir was done on hospitalization day 7 and yielded good result with no any adverse effect recorded..

Another evident study conducted in Italy on March, 2020 where the compassionate administration of 200mg loading dose of Remdesivir followed by 100mg maintenance dose to the COVID-19 severely ill patients showed a good result. But few patients had multiple organ failure, cardiac problem such as torsade de pointes and QT Prolongation due to arrythmia and some had altered biochemical readings such as increased ALT and AST. Remdesivir which showed strong antiviral activity against MERS-CoV compared to Ropinavir/Litonavir can be used against Sars-CoV-2 as well since these viruses have the same origin and bear same characteristics.

Conclusion

Since Tocilizumab and Remdesivir have shown superiority against COVID-19 over other drugs discussed in this review, it is highly recommended that these two classes of drugs should be given priority on doing more research about them. Tocilizumab can block the inflammatory response induced by SARS-CoV-2 infection and hence prevent the vascular permeability which in turn prevents the pulmonary edema and Disseminated Intravascular Coagulation (DIC). Remsevidir in other hand can be used to block the viral replication. By so doing it will lower the viral load and make it easier for the natural immunity to fight the low dose of viruses. It is recommended that these drugs have to be used simultaneously in order to get the full benefits of them.

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Conflicts of interest

The authors declare no conflicts of interest.

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