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Review Article

The Possible Therapeutic Options against COVID-19

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Abstract: 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 and preventive 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. We extracted relevant published studies with keywords such as COVID-19 therapies, Sars-Cov-2 treatment and Noval Coronavirus antiviral therapy from Pubmed and carefully studied them. We focused on Tocilizumab, chloroquine and hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir, Traditional Chinese Medicine and Ivermectin. Coronavirus induce Cytokines Releasing Syndrome (CRS) which in turn causes Cytokines Storm. This is the inflammatory response which causes the releasing of large number of IL-6. This causes increased vascular permeability which in turn result in the infiltration of fluids in the alveolar spaces and causes breathing problems. 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) and hence prevent respiratory failure. Remdesivir which is an adenosine nucleotide analogue, has broad-spectrum antiviral activity against RNA Viruses. This means remdesivir can prevent the viral replication and hence lower the viral load and ultimately reduce the duration of illness and hospitalization. Ivermectin which is FDA approved broad spectrum antiparasitic agent, works by preventing the entrance of viral protein in the host cell nucleus. Ivermectin binds to the viral protein transporters Importin (IMP) α and β1. This action prevents the binding of the viral protein to the Importin (IMP) which results in the lower infection rate and decreased viral load. Lower rate of infection and decreased viral load will reduce duration of illness and prevent transmission of SARS-CoV-2. So, the concomitant use of tocilizumab, remdesivir and ivermectin is recommended to all severely-ill COVID-19 patients while remdesivir and ivermectin is recommended for non-severe patients on an outpatient's settings.

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

1. INTRODUCTION

Over decades, the world has been witnessing 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 [1-3], Middle East Respiratory Syndrome (MERS) with the first case witnessed in Saudi Arabia in April 2002 [4, 5] 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 [6-8]. 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 no proper cure for COVID-19 but there are many vaccines under trials against coronavirus [9-13]. 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 and can spread more faster than the former strains [6, 14, 15].

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1.1. Structural features of Sars-Cov-2.

Coronaviruses are enveloped non-segmented positive-sense, single-stranded RNA viruses belonging to the family Coronaviridae and the order Nidovirales and broadly distributed in humans and other mammals [7, 10, 16, 17]. They are classified as alphacoronaviruses and betacoronaviruses which have gene source from bats and are found on bats, civets, humans and some rodents [18].

1.2. Clinical manifestations of COVID-19 affected individual.

Clinically, COVID-19 patients manifest with high grade fever, anorexia, shortness of breath, dry cough and fatigue [19-21]. Some fatal symptoms observed are high venous thromboembolism (VTE) as well as Disseminated Intravascular Coagulation (DIC) [22].

1.3. Laboratory investigation results of COVID-19 affected individuals.

Laboratory investigation reveals increased levels of neutrophil, aspartate aminotransferase (AST), lactate dehydrogenase (LDH) and C-reactive protein and decreased level of albumin and platelets[11, 20, 23]. Another study reveals increased Ferritin level in all severely ill COVID-19 patients and increased D-dimer levels in some patients [22, 24, 25].

1.4. Radiological images

X-ray reveals massive pleural effusion, ground-grass opacities (GGO) and ground-glass opacity with consolidation [21, 26]. One COVID-19 patient in Italy performed Chest CT-Scan on admission which shows Diffuse, bilateral, and symmetric ground-glass and bronchiectasis [26]. In general, the most common initial Chest CT findings are bilateral ground glass opacification and consolidation superimposed on GGO while the less common are bronchiectasis, septal thickening and pleural thickening which are observed in later stages [27-29]. Uncommon but possible signs are pericardial effusion, pleural effusion, pneumothorax and lymphadenopathy [27, 28].

1.5. Contributing factors: Geographical Location, age, gender, weather and climate.

This new strain of coronavirus is widely distributed all over the world regardless of the geographical location but according to the data, COVID-19 affects more elder than children [21]. Another data shows that coronavirus affects more male elders than females, this is because male elders have more hACE2 in their blood circulation than most women [30]. Coronavirus become more prevalence during lower temperature while higher temperature is associated with lower COVID-19 prevalence [31-33]. This means the infective rate becomes more severe during the cold seasons and drop during warm season.

1.6. Comorbidity.

Immune dysfunction patients such as HIV, advanced age and patients with underlining diseases such as cancer, diabetic mellitus (DM) and pulmonary insufficiency have bad prognosis after being affected by COVID-19 [34-36]. Another study reveals that patients with hypertension and cardiovascular problems, when affected by COVID-19 will be at more risk of developing severe symptoms compared to other underlining diseases [37].

1.7. Mode of transmission and preventive measures.

The WHO proposes social distancing, frequent hand washing, use of sanitizers and use of facial 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 [38-42]. But these measures are for prevention only. It is necessary to find the proper cure and possible vaccine for 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 is intended to summarize the therapeutic possibilities of ongoing drugs trials.

2. Druggable targets of Sars-Cov-2

The goal of COVID-19 therapies starts with the efforts to lower the viral load and preventing effects of the immune response. This will be done by inhibiting the viral entry to the host cell nucleus and preventing viral replication within the host cells as well as preventing the immune response.

2.1. Angiotensin Converting Enzyme-2

The entry of the Sars-Cov-2 into host cell is aided by attachment of the viral Spike Protein to the host's angiotensin converting enzyme 2 (ACE-2) receptor [2, 43, 44]. This attachment will cause the fusion of the virus with the cell membrane. This means that ACE-2 is valuable druggable target for the COVID-19 therapy since the inhibition of it will prevent the viral entry to the host's cells and hence suppress viral proliferation[1, 45, 46]. The goal here is to use soluble ACE2 or any other antibody to Spike (S) Protein in order to inhibit the virus-cell interaction.

2.2. Protease enzyme.

The proliferation of Sars-Cov-2 requires a special enzyme called protease which is synthesized within the human host cells [47]. If the viral genome is successfully injected into the host cell is then translated and processed to virus-derived structural proteins, including nucleocapsid (N) protein, Spike (S) protein, membranous (M) as well as envelope (E). The reaction process is done using Chymotrypsin-like protease (CL^{pro}) and Papain-like protease (PL^{pro}). PL^{pro} cleaves the N-terminal region while $3CL^{pro}$ cleaves the C-terminal region of the viral precursor protein. The

$3CL^{pro}$ of Sars-Cov-2 which is 96% similar to that of Sars-Cov is an ideal target for the Sars-Cov-2 inhibition target [47-50]. If we successfully block the synthesis of this enzyme, the result will be the formation of defective harmless viruses.

2.3 RNA-dependent RNA polymerase (RdRp).

The genomic replication and transcription of Coronaviruses take place in the infected cell's cytoplasmic membrane and depends on the viral RNA-dependent RNA-polymerase (RdRp) [51-54]. This enzyme is the most valuable broad-spectrum antiviral target for adenosine nucleoside analogs drugs such as remdesivir [55]. RdRps are class of nucleic acid polymerase having unique characteristics compared to other catalytic enzymes [56-58]. In order to successfully work, the chain terminating nucleotide analog needs viral RdRps to recognize and bind to the active form of the inhibitor into the growing RNA strand [59]. So, the successful inhibition of RdRps by nucleoside analogs is essential step in the blocking viral replication and transcription [60].

2.4 Importin (IMP) α and β1.

Positive strand RNA viruses replicate inside the nucleus of the infected host cells [61-63]. In order to be infective, Sars-Cov-2 must pass its genomic contents into the cell nucleus. And to penetrate into the cell nucleus, the viral protein needs a special transport mechanism to carry it into the host's cell nucleus. RNA virus's protein needs to bind to Importin (IMP) as a transporter in order to penetrate into host cell's nucleus [64]. Importin (IMP) is a nucleocytoplasmic transport protein needed by coronaviruses to cross in and out the cell nucleus [65]. To cross into human's cell nucleus, coronaviruses need importin α as well as importin β1 subtypes [66, 67]. The successful blocking of fusion between viral protein and importin is essential step in hindering the ferrying of viral genome into the cell nucleus [68]. This will prevent the viral replication and hence lower the viral load. Any drug with higher affinity to importin than viral genome will be of greater importance. In this review we will discuss the broad spectrum anti-parasitic agent, Ivermectin as one of the drugs which can compete with viral protein to bind to the importin.

2.5 Immune mediators.

Once transmitted to human, Sars-Cov-2 reaches the epithelial cells in the respiratory tracts. Here, they replicate and mitigate and moves down to bind the alveolar epithelial cells in the lungs. More replication takes place here which in turn triggers strong immune response called Cytokine Storm [6, 69]. This happen when the Sars-Cov-2 genomic contents trigger innate and adaptive immune system to cause the so-called Cytokine Releasing Syndrome. This causes massive release of cytokines which causes mild to severe pulmonary edema and respiratory distress [70, 71]. In older patients and those with underlining chronic diseases, pulmonary edema and respiratory distress reported to be the causes of large number mortality [71-73]. Hence the use of immunomodulators is essential in the prevention of number of mortalities in the COVID-19 affected individuals. In this review we discuss the use of tocilizumab as an important candidate to tackle the cytokine storm.

3. Drugs investigated for treatment of COVID-19

3.1 Tocilizumab: An IL-6R Antagonist

Pathological studies done on people suffered from COVID-19 shows bilateral diffuse alveolar injury with cytomyxoid fibroma exudate [70]. Another study also shows evident desquamation of pneumocytes, hyaline membrane formation and pulmonary edema [74]. This signifies that these patients had cytokine storm secondary to Cytokine Releasing Syndrome (CRS). 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 [70, 74]. 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 [11, 75]. 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 [76]. This in turn activates the cytokines such as IL-6 which binds to the IL-6 receptors in the target cells. The result is Cytokine 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 [23, 76]**.** The evident clinical trial 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 reveals bilateral multiple ground-glass opacities and pneumatocele. His laboratory studies show increased serum IL-6. The patient was given intravenous Tocilizumab 8mg/kg once a day and the symptoms disappeared and the laboratory studies showed the decreased level of IL-6 within 10 days [70]. 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 [77]. Mihai and colleagues report 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 [78]. In a study reported from Barcelona, 58 Covid-19 patients were given tocilizumab and other received tocilizumab in combination with corticosteroids. Some survived but 8 patients (13.8%) died of COVID-19. In his report, Campins L *et al*., advises that the timing on when to initiate the immunomodulators to the Covid-19 patients is vital [79] and Galvan-Roman JM and his colleagues suggest that the patients with baseline IL-6 Level of greater that 30 pg/ml will need invasive mechanical ventilation (IMV) [80]. When administered earlier to COVID-19 patients, Tocilizumab can prevent the affected patients from needing mechanical ventilation and hence increasing the survival rate of the COVID-19 patients [81].

Tocilizumab, apart from being effective in fighting the cytokine storms with good efficacy, it also has superiority status in safety too [82].

3.2 Chloroquine/Hydroxychloroquine: The Glycosylation inhibitor

Known for many years for its role as treatment and prophylaxis against malaria, the 9-aminoquinoline known as chloroquine possesses great efficacy in curing viral infections by inhibiting the viral replication processes [83, 84]. This is done by altering the required PH Level inside the target cells [85]. Viruses such as coronaviruses, flaviviruses and retroviruses need certain levels of PH in some steps of their replication [86]. By altering the PH within the target cells, Chloroquine and Hydroxychloroquine reported to have good ability in inhibiting 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 [87]. Chloroquine can reduce the terminal glycosylation of the angiotensin converting enzyme 2 (ACE2) receptor on Vero E6 Cells and impedes the binding of SARS-Cov-2 to the ACE 2 receptor. This interferes with the viral replication [88, 89].

In a study conducted in China, chloroquine demonstrates 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 [9]. 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 [90]. 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 [91].

3.3 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 [92]. 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 [6]. CHM can alleviate or prevent the respiratory infections by inhibiting respiratory pathogens [92, 93]. In combination with western medicine, CHM can be used effectively in treating COVID-19 patients [93].

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 [94]. 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 they report good results [95].

3.4 Lopinavir/Ritonavir: The Protease inhibitors

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 [4, 96]**.** 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 [97]. Lim and colleagues studied the viral load of beta-coronavirus and reported that there were no coronavirus titers reading after administering lopinavir/ritonavir to the affected individual [98]. But Cao and colleagues concluded that, Ritonavir-lopinavir combination has no benefits beyond standard care in treating COVID-19 adult patients [99].

3.5 Remdesivir: An adenosine nucleotide analogue.

Remdesivir is a 1'-cyano-substituted adenosine nucleotide inhibitor that has broad-spectrum antiviral activity against RNA Viruses [59, 100]. Its triphosphate form, remdesivir triphosphate (RDV-TP) has similar structure to adenosine triphosphate (ATP) which is used as substrate of various viral RNA-dependent RNA polymerase (RdRp) enzyme [101, 102]. Since it is nucleotide analogue, RDV-TP blocks the chain termination in RNA viruses hence inhibit the viral replication [100, 103]. Since it is nucleoside analogue, Remdesivir can inhibit the viral RNA polymerases which in turn can block the activity of SARS-CoV-2 [10, 84, 100]

Mulangu and colleagues report a 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 [104]. In vitro study including primary human epithelial cells culture, Remdesivir, a nucleotide prodrug, GS-5734 shows that it can inhibit the replication of SARS-Cov and MERS-Cov [105].

In patients hospitalized for severe COVID-19, Remdesivir was administered and yielded a good result after 36 out of 53 (68%) patients had shown good clinical improvement [106]**.**

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 show good result with no any adverse effect recorded [107].

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 [11]. 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 [11]. Remdesivir which possesses 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 [4]. In some study, remsedivir show superiority over placebo in the treatment of Covid-19 patients with mild to severe lower respiratory tract symptoms [108, 109] and early administration of remdesivir in animal model study has good result in blocking viral replication [110].

3.6 Ivermectin: Broad spectrum anti-parasitic agent**.**

Used for many years as prophylaxis for parasitic disease in Africa, the FDA-approved broad spectrum anti-parasitic agent, Ivermectin has shown an anti-viral activity against wide range of viruses [111-115]. Ivermectin acts on SARS-Cov2 by restricting the penetration of viral protein into the host cell nucleus [116]. This nuclear transport inhibition is done by blocking the binding of viral protein to Importin (IMP) superfamily of transporters of α and β1 types [67, 116, 117]. This means Ivermectin binds to the Importin to prevents the binding of the viral protein to the Importin and this will cause a decreased infection due to higher antiviral response [118]. In a clinical trial by Ahmed and his colleagues, five-day use of ivermectin results in an earlier clearance of the virus [119]. This means the use of Ivermectin with or without other drugs may block the viral replication and lower the viral load, and hence reduce the duration of illness and can block the transmission too [120, 121]. Because Ivermectin possesses an ability to lower the viral load, it might be the drug of choice in combination with other drugs in the fight against SARS-CoV-2 infection.

Proposed Treatment strategies for hospitalized and outpatient Sars-Cov-2 positive individuals

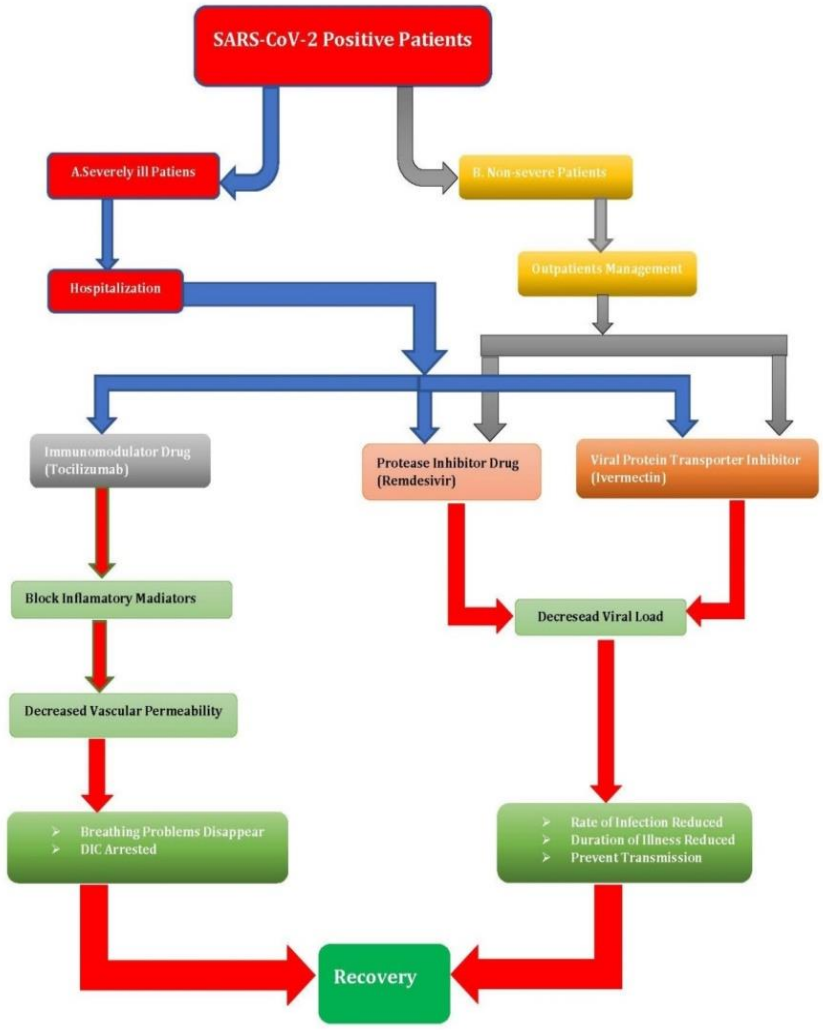

Fig 1: Proposed Treatment strategies for hospitalized and outpatient Sars-Cov-2 positive individuals whereby: A. Severely ill patients will require hospitalization and concomitant administration of tocilizumab, remdesivir and ivermectin and B. Non-severe patients will be given an outpatient management with only Remdesivir and Ivermectin

Table 1: Proposed doses for drugs investigated for the treatment of COVID-19 in clinical trials

Drug	Class	Mechanism Of Action	Dosage	Reference
Tocilizumab	Immunomodulator	Suppression of the activity of IL-6 in the target cells.	8mg/Kg Intravenously. Start Dose or 400mg Iv Start.	[70, 77]
Chloroquine/ Hydroxychloroquine	Quinoline	Inhibiting the viral replication by altering the PH within the cells.	400mg Twice In The First day followed by 200mg twice a day for four days	[9]
Astragalus polysaccharide	Chinese Herbal Medicine (CHM)	Inhibit the expression of two early viral proteins, Zta and Rta		[92, 93]
Lianhua qingwen granules	Chinese Herbal Medicine (CHM)		6g three times a day(incombination with western medicine)	[94, 95]
Lopinavir/ Ritonavir	Antiviral (Protease inhibitors)	Blocking the protein required for virus replication.	Lopinavir 800mg once a day Ritonavir 200mg once a day	[99]
Remdesivir	Antiviral (Nucleoside analogue)	Inhibit the viral RNA polymerases	200mg Intravenously once in the first day 100mg once a day for 9 days.	[11]
Ivermectin	Broad Spectrum antiparasitic agent	Restriction of Penetration of Viral Protein into host cells	12mg once a day for five days	[119]

4. CONCLUSION

Since Tocilizumab, Remdesivir and Ivermectin have shown high antiviral activities against SARS-CoV-2 than other drugs discussed in this review, it is highly recommended that these three 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) and hence prevent respiratory failure. 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. Ivermectin can block the entrance of the viral protein to the host cell nucleus which results in the lower rate of infection. Lower infection rate will reduce the duration of illness or hospitalization and prevent transmission. Tocilizumab, Remdesivir and ivermectin are recommended for the severely-ill patients because the goal will be to tackle the cytokine storm and lower the viral load at the same time. But Remdesivir and Ivermectin is recommended for the non-severe patients since they can be taken orally in outpatients setting. In non-severe patients, the goal is to limit the viral replication and prevent transmission. Chloroquine and hydroxychloroquine have good antiviral activity but many studies show that they have more severe side-effects compared to other drugs under trials. Hence, we don't recommend the use of CQ and HCQ in the fight against Sars-Cov-2 infections.

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