Review Article

Early Pharmaceutical Treatment Modalities for COVID-19 Patients in the Beginning of the Pandemic

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Abstract

Coronavirus is a family of RNA viruses that come from the genus beta coronavirus, this virus is distributed in many species like, birds, humans and other mammals. Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus. In most infected people with COVID-19 virus, the symptoms will appear as mild to moderate respiratory, symptoms and most of them can recover without needing specific treatment. On the other hand, older people and those with fundamental medical, problems such as, cardiovascular disease, diabetes, chronic respiratory disease and cancer are more likely to develop a serious illness and require special care and treatment.

Keywords: Antiviral, COVID-19, supportive agents, treatment

Introduction

Viruses can be defined as tiny parasites that live obligatorily inside living cells. They can be deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) type, depending on their genomic material.[1] The coronavirus subfamily is an enveloped, single-strand RNA virus that belongs to the Coronaviridae family and is divided into four groups of viruses (alpha, beta, gamma, and delta).[2]The related viral order and families are illustrated in Figure 1. Till December 2019, it had been found that six forms of viruses from this family can affect human resulting in various diseases. Fortunately, four of them cause mild infections in humans; however, serious illnesses that may be fatal were noticed with the remaining two forms. They are severe acute respiratory syndrome (SARS) coronavirus, and Middle East respiratory syndrome (MERS) coronavirus.[3] At the end of 2019, an outbreak of patients who suffered from acute respiratory infection was recorded in Wuhan, a business city in China. The underlying cause was a new version of beta group of a positive sense corona virus named later as SARS coronavirus 2 (SARS-CoV-2) and the resulted disease as coronavirus disease-2019 (COVID-19).[4]

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Infection by coronavirus starts by binding S protein which envelopes virus to a receptor named as angiotensin-converting enzyme-2 that found on the host cell and results in fusing this virus with the host cell membrane before penetrating the cell membrane and ending up inside the host cell.[5,6] It is a serious illness that resulted more nearly affected more than 4 million victims with nearly 300, 000 deaths worldwide. The virus spreads from one person to another, especially between people in close contact with one another (within about 6 ft), through droplets produced by infected patients, mainly during coughing or sneezing. It also may be possible that a person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes.[7]

The major symptoms of COVID-19 vary from asymptomatic or mild symptoms to severe respiratory

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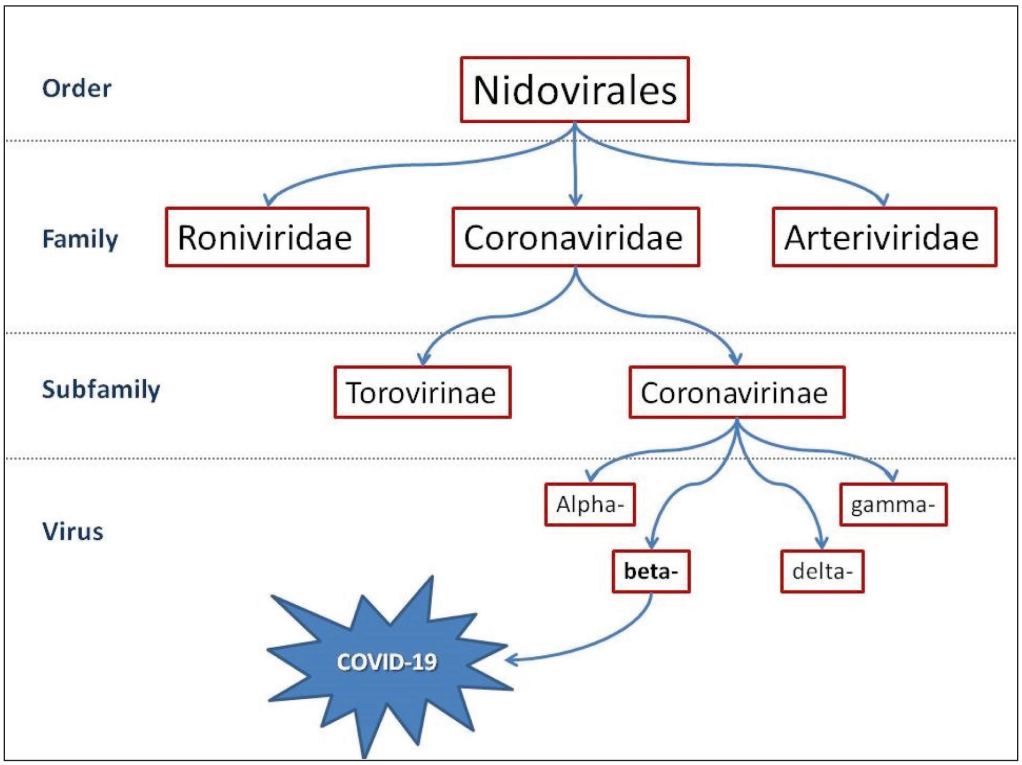

Figure 1: Tree of COVID-19 family

illness like, pneumonia and acute respiratory distress syndrome (ARDS) with rapidly progressive fever, fatigue, cough, myalgia, and difficult breathing that may end with leukopenia and ARDS. Additionally, 20% of patients with COVID-19 need admission to intensive care units, and the mortality among hospitalized patients is just above 13.9%.[8]

Accordingly, the aims from this review are to highlight the current drugs that used early in the beginning of COVID-19 pandemic and to illustrate evidences supporting the use of these drugs in managing this pandemic illness.

Antiviral agents

The mandate for antiviral therapeutics is urgent particularly with escalating numbers deaths globally. This will significantly reduce hospital admission period and subsequent mortality. Attempts for treating SARS-CoV (in 2003) and MERS-CoV (in 2012) were conducted. Therefore, coronavirus-specific therapeutics (antivirals) have been advanced into clinical trials. Currently, many antiviral compounds used to treat other diseases re-prescribed for COVID-19 patients.[9]

Chloroquine and hydroxychloroquine

These drugs are used extensively as antimalarial agent with immunomodulatory effect.[10] Hydroxychloroquine is a derivative of chloroquine with less toxicity; nevertheless, both drugs exhibit their activity as antiviral drugs by using different mechanisms. In nature, the chloroquine occurs as weak alkaline and it has ability to change the endosome pH. It can inhibit viral invasion to the cells by using endosome pathway. They have been used in treating patient with Zika virus[11]and Borna virus disease.[12]These viruses use acidic endosome for activating and entering inside host cells and by preventing the acidification of endosome these drugs inhibit entry of virus inside host cells.[13]

Another mechanism for these drugs against viral infection is by inhibiting gene expression of the virus where chloroquine inhibits gene replication of certain viruses such as, human immunodeficiency virus (HIV) in CD4 + T cell. Chloroquine and hydroxychloroquine alter acidity of vesicle and cause inhibition for many enzymes such as acid hydrolases. These enzymes are curtailed for post-translational modification of newly synthesized protein.[14] With COVID-19, there are other mechanisms for these drugs may be suggested, one of these mechanisms is that the drugs capable of reducing viral replication through dropping terminal glycosylation of angiotensin-converting enzyme-2 receptor (ACE2) that was found on Vero E6 cells and prevent binding of this virus to the receptor.[15] While other mechanism suggest that drug interfere with virus and try to acidify lysosome and result in inhibition of cathepsins that which need for acidic PH for cleavage of COVID-19 spike protein, that is, a requirement for the formation of the autophagosome.[16]

In accordance with the "New Coronavirus Pneumonia Diagnosis and Treatment Program (trial version 6)"

issued by the National Health and Health Commission in China, the recommended dosage of chloroquine phosphate is 500 mg tablets used BID daily and it taken for 10 days.[17] However, the minimum course of hydroxychloroquine treatment should be continuing to at least 5 days.[18]

Remdesivir

It is a prodrug of nucleotide analogue that is, metabolized inside the cell to the analogue of adenosine phosphate. Remdesivir is considered as RNA-dependent RNA polymerases inhibitor with a wide range of activity against different types of virus families such as, Filoviruses (Ebola).[19] Moreover, it is active against coronaviruses with divergent RNA-dependent RNA polymerases.[20,21] These coronaviruses include (SARS-COV and MERS).[22-24] Remdesivir is a phosphoramidate prodrug of a 1'-cyano-substituted nucleotide analogue.[25] It is a triphosphate form of remdesivir (RDV-TP) which is similar to adenosine triphosphate and is used as a substrate for numerous of viral RNA-dependent RNA polymerase (RdRp) enzymes or complexes.[26]

Additionally, the RDV-TP was shown to have ability to inhibit RNA-dependent RNA polymerases of respiratory syncytial virus (RSV)[26] and Nipah virus (NIV).[27] All these viruses are non-segmented negative-sense RNA viruses. The RDV-TP is a non-obligate chain terminator. It contains a 3'-hydroxyl group and may form with the next incoming nucleotide a phosphodiester bond. Similarly, as established for RdRp enzymes from RSV, Ebola virus (EBOV), NIV and MERS, the chain termination delay provides a possible mechanism of action.[28,29]

A study by Dyer[30] in 2019 showed that when remdesivir used to treat patient with EBOV disease in early stage of infection, the mortality rate reach to 33%, while its mountains to 75% or more in non-treated patients with EBOV infection. Other study in Wuhan Institute of Virology proved that remdesivir had activity against COVID-19 in Vero E6 cell and suggested that the mechanism behind this drug is post-entry stage of host cells.[31] Furthermore, a study by Zhou *et al.*[32] proved that remdesivir was able to inhibit viral infection efficiently in human cell line (human liver cancer Huh-7 cell), also it sensitive to COVID-19. Recently, the use of this drug in combination with chloroquine exhibit highly potentials for controlling COVID-19 infection in *in vitro* study.[31] Currently, several clinical trials for prescribing remdesivir in treatment of COVID-19 are on-going in National Institutes of Health in United States and South Korea as phase 3 by administration 200 mg of remdesivir intravenously as initial dose on the first day, followed by 100 mg per day as maintenance dose up to 10 total treatment days, the primary outcome was defined up to 28 days.[33]

Oseltamivir

It is a drug used for treating influenza type A and B.[34] Oseltamivir is absorbed rapidly from the gastrointestinal tract as a prodrug form (oseltamivir phosphate) then it converted into active metabolite by hepatic esterase enzyme.[35] The antiviral role of it occurs by binding to/and inhibiting of the active site of neuraminidase enzymes. These enzymes were found on all types of influenza viruses where they were crucial for releasing progeny virions from infected host cells.[36]

Hence, oseltamivir reduces the replication of virus resulting in limitation load of virus in addition to the host infection course. Although, the active site of neuraminidase is highly preserved but this drug has activity against all subtypes of neuraminidase enzymes *in vitro*.[37] These subtypes of enzyme include neuraminidase of human seasonal viruses, avian viruses and pandemic virus such as new emergent pandemic (H1N1) 2009 virus.[38] This drug is highly selective for influenza neuraminidase and shows little or no activity against neuraminidases of other viruses, bacteria.[39] Furthermore, oseltamivir and beside its antiviral function, it plays a role in preventing and reducing symptoms that occur with flu virus such as, stuffy nose, cough, sore throat, fever. Regarding dosage and duration, it is given twice daily for 5 days to treat viral infection and once daily for 42 days as prophylaxis.[34] In China, oseltamivir has been used for COVID-19 patients solely or in combination with other drugs such antibiotics and corticosteroids[40,41] or with chloroquine and favipiravir.[42]

Lopinavir/ritonavir

It is a co-formulation of lopinavir and ritonavir (anti-HIV drugs). Aspartyl protease is the enzyme that encoded by the pol gene of the HIV and causing cleavage of the precursor polypeptides in HIV, so it plays important role in replication cycle of this virus. Lopinavir and ritonavir act as HIV protease inhibitors; therefore, they are used in combination in HIV therapy. Although corona viruses encode different types of protease enzymes, for example, the cysteine protease, evidence demonstrates that lopinavir and ritonavir inhibit corona viral 3CL1pro protease.[43,44] Various, *in vivo* and *in vitro*, studies done on SARS and MERS showed a controversial effect for lopinavir/ritonavir combination against these viruses.[31,45] De Wilde *et al.*[46] in *in vitro* study found that combination of lopinavir and ritonavir is less effective than remdesivir against strain of SARS and MERS. While other studies indicated some of success in usage of this combination for treating patients with MERS infection and COVID-19 infection.[47,48] Likewise, this combination has been with interferon β-1α, this interferon act as inhibitor to the multiplication of SARS and MERS in cell cultures.[49] Lopinavir/ritonavir combination was involved in a clinical trial in patients with mild and moderate COVID-19, it showed a little benefit

for improving the clinical outcome.[20] On the other hand, a trial was done on patients with severe COVID-19 showed no benefit of lopinavir/ritonavir beyond standard care.[47] Lastly, a clinical experience suggested a success to a certain degree of lopinavir/ritonavir combination against COVID-19 when ribavirin (see next) is added and with or without interferon.[50,51]

Favipiravir

Favipiravir Avigan™ (Fujifilm Toyama Chemical Co., Tokyo) also known as T-705 (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), is a substituted pyrazine compound. Favipiravir was discovered through screening chemical library for antiviral activity against influenza virus by Toyama Chemical Co., Ltd (Japan). It has a potent antiviral activity against RNA of influenza virus by inhibiting RdRp enzymes that are essential for viral genome transcription and replication without affecting RNA or DNA synthesis of the host cell. This enzyme, unlike other polymerase, that the mutation rate is high and leads to generating variability of RNA viruses.[52,53] Favipiravir (T-705) was used in many virus conditions as it had effectiveness against EBOV, influenza H1N1 virus in 2009 and Lassa fever.[54,55] In China and Japan, a randomized clinical trial for adult patients with COVID-19, using favipiravir (1600 mg twice for first day followed by 600 mg twice daily for 10 days) showed a significant improvement in latency of pyrexia and cough and when its effect compared with arbidol, the clinical recovery rate did not significantly improve at 7 days.[40] In a single clinical trial, favipiravir was used in combination with oseltamivir and chloroquine; It found that the drug gives half-maximum response EC50 of 61.88 μM against SARS-CoV-2 and also has low toxicity (EC50 > 400 μM).[56]

Supportive agents

These agents are used in conjunction with antiviral agents to increase strength of immune system or reduce symptoms that occur with COVID-19 and these include:

Azithromycin

It is a macrolide bacteriostatic antibiotic which inhibits protein synthesis and it indicated in many respiratory, urogenital, dermal and other bacterial infections.[57,58] Many pre-clinical and clinical studies revealed that macrolide antibiotics can down-regulate the inflammatory response, reduce production of cytokines and stimulate immunoglobulin antibodies generation.[59]

The main reason behind mortality and morbidity in patients with respiratory viral infection is excess cytokines release and activation of inflammatory cascade.[60,61] Macrolide antibiotic, especially azithromycin, can work through two mechanisms; first, it is effective in reducing symptoms like fever and minimizing complications such as pneumonia which is probably occur by decreasing plasma interleukin-4 (IL-4), IL-8 and chemotaxin (eotaxin).[62-64] Secondly, azithromycin can display antiviral action on bronchial epithelial cells and it is found that it has ability to reduce exacerbations of chronic obstructive pulmonary disease (COPD) by exhibit anti-inflammatory and antiviral activities through affecting the expression of cytokine.[65] A study in France suggested that a combination of hydroxychloroquine with azithromycin can be effective against COVID-19 infections. This small number clinical study showed a 100% viral clearance in nasopharyngeal swabs in six patients after 5 to 6 days of the combination of hydroxychloroquine and azithromycin. Meanwhile, the rate of viral clearance was (57.1%) when hydroxychloroquine used alone and only 12.5% in patients who did not receive hydroxychloroquine.[66]

Convalescent plasma transfusion therapy

It is a traditional adaptive immunotherapy, that collected from donor after recovery from the infection and development of antibodies, this therapy was successfully applied in the last two decade to treatment numerous infectious diseases as SARS, MERS, H1N1 pandemic in 2009 and EBOV that showed safety and satisfactory efficacy.[67,68] In severe cases of COVID-19, transfusion of convalescent plasma improved the clinical symptoms and paraclinical criteria within several days as mentioned in some studies and these needed evaluation in clinical trials.[68,69]

The plasma collected from donor, who confirmed with infectious disease (COVID-19) and subsequence negative test for SARS-CoV-2, the symptoms resolved at least for 14 days after recovery and the ABO blood groups system compatible plasma of 200–250 mL (400 mL of convalescent plasma in total), antibody titer >1:1000, transfused in the same day to critical ill patients with continuously received other steroids and antiviral drugs, the viral load decrease gradually within several days.[69] The antiviral action of convalescent plasma mediated by direct neutralizing the virus infection via binding the antibody to pathogen (i.e., virus) result in inhibiting pathogens' entry and amplification in addition to antibody effect in complement activation, cytotoxicity and phagocytosis. Furthermore, the plasma from recovery donor has immunomodulation of hypercoagulable state.[70,71]

Tocilizumab

Tocilizumab (Actemra) is one of interleukin antagonists with a monoclonal antibody that inhibits binding of IL-6 to its receptors and prevents IL-6 signal transduction to inflammatory mediators B and T cells.[72] It is used in treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis.[73]

In critical ill patients with COVID-19, an excessive immune response and cytokine storm with highly elevated IL-6 level can be designated.[74,75] The usage of tocilizumab as

a humanized IL-6 receptors antibody in treating COVID-19 patients showed a successful result particularly in those who have multiple myeloma.[76]

Chinese clinical trial demonstrated that a dose of 4–8 mg/kg (initially single dose 400 mg intravenous infusion) infused over 1 h as initial dose for critical COVID-19 patient resulted in rapid reduction in fever and oxygen supplementation within several days from using tocilizumab and the same dose repeated after 12 h as maximum single dose 800 mg when the symptoms are not improved.[77] The same dosage protocol with maximum dose (800 mg initial intravenous infusion) and if the symptoms not improved or worsen in sever ill patient with COVID-19, one additional dose may be used in US/Global randomized, placebo-controlled trial.[78]

Vitamin C

Vitamin C (ascorbic acid) is one of the important antioxidants that improves endothelial function, reduces oxidative stress production and prohibit inflammatory cascade.[79] It involves in collagen biosynthesis through hydroxylation reaction and facilitation the transport of iron. Furthermore, it has a therapeutic role when given in a high dose in many diseases like, cancer, atherosclerosis and viral infection.[80] The oral supplementation of vitamin C in common cold was studied, since it reduced symptoms duration and decreased the common cold incidence in severely physical stress individual.[81] High dosage of Vitamin C (injectable) is used in treating sepsis since it has a physiological role beside anti-inflammatory action. It recovers vasopressor synthesis, improves immune cell function and epigenetic immunological modification.[82] Vitamin C level decreases during infection thus the patients require increasing the level of vitamin C (according to severity of infection) by administrating high doses to improve the immune state. In COVID-19 pneumonia, immune effector cells hyperactivity caused lung injury.[83] China initiated phase 2 randomized controlled trials in patient in intensive care unit with COVID-19 pneumonia to evaluate intravenous vitamin C in a dose of 12 g every 12 h for 7 days. The dose of vitamin C (12 g) diluted to total volume of 50 mL by sterile water for injection and infused on a rate of 12 mL/h. It has been noticed that, intravenous vitamin C administration in high dose rather than physiological concentration act as pro-oxidant to immune cells.[84] The beneficial influence of vitamin C injection in sepsis can be showed in several meta-analysis studies. The intravenous dosage of vitamin C is not constant as it varies among studies; in CITRIS-ALI study, the dose of vitamin C was 50 mg/kg every 6 h for 4 days while vitamins study suggested the effect of vitamin C at a dose of 1.5 g every 6 h until resolution the shock or up to 10 days.[85,86] Additional studies are strongly indicated for vitamin C dose adjustment and duration in sepsis generally and in COVID-19 specifically.[86]

Glutathione

It is an endogenous antioxidant, can be obtained from diet and through dietary supplements as well. It is crucial in enhancing the immunity via protecting immune cells through antioxidant mechanism and also it is essential for both innate and adaptive immunity.[87] According to Kuppner *et al.*[88] 2003, glutathione is important for T-lymphocytes proliferation, phagocytic activity of neutrophils in addition to the function of dendritic cell. Glutathione was used in trial for treating COVID-19 in USA. Administration of 2 g of intravenous glutathione results in improvement in patient's dyspnea (due to COVID-19 pneumonia) within 1 h from starting medication. In addition, repeating the dose of both 2000 mg of oral and intravenous glutathione result in further relief in respiratory symptoms. The trial suggested that oral and intravenous glutathione, glutathione precursors (N-acetyl-cysteine) and alpha lipoic acid may represent a novel treatment modality for blocking NF-κB and addressing "cytokine storm syndrome" and respiratory distress in patients with COVID-19 pneumonia.[89]

Corticosteroid

It is known that corticosteroid is an anti-inflammatory drug that inhibits the synthesis of cyclooxygenase-2. Moreover, corticosteroid reduces phospholipase A2 in the lipid membrane which is responsible for inhibition in arachidonic acid production. Consequently, a down production of prostaglandin will be noticed. Besides, corticosteroid has immunomodulatory properties.[90] The use of corticosteroid in patients with SARS, MERS and influenza showed no survival benefit or possible harm as delay viral clearance, increase risk diabetes; psychosis and avascular necrosis. Because of that, there is restriction in prescribing corticosteroids COVID-19 patients with exception in patients suffer from asthma, COPD or similar diseases to reduce symptoms.[91]

Methylprednisolone is the most important corticosteroid and it was recommended in a retrospective study for COVID-19 patients with pneumonia who developed ARDS because of reduction mortality.[92] This was probably via improving in clinical symptoms such as fever and hypoxia and shorten disease course. The suggested dose of methylprednisolone was 1–2 mg/kg daily for 5–7 days.[93]

In Chinese hospital, regimen of low to medium dose of methylprednisolone 0.5–1 mg/kg daily or equivalent reduced the mortality by lowering oxygen index less than 300 mm Hg.[94] Methylprednisolone is already used as a combination with oseltamivir, antibiotic and oxygen therapy for patients with COVID-19 pneumonia during influenza season.[95]

Recombinant human angiotensin-converting enzyme-2 (rhACE2)

Angiotensin-converting enzyme-2 (ACE2) is the functional receptor for SARS-CoV *in vitro*[96] and *in vivo*.[97] This receptor is very important for entry of virus to the host and also for its replication. The ACE2 is not only receptor for virus entry but also it has a role in protection lung from injury because SARS-CoV binds to this receptor and cause deregulation to the protection pathway of lung.[97] Alveolar epithelial type II cells contain about 83% of ACE2 expression. Consequently, these cells can reserve as reservoir for viral invasion.[98] ACE2 receptor expression has been found in other non-pulmonary tissue such as, heart, kidney, endothelium and intestine.[99,100] The soluble recombinant human angiotensin-converting enzyme-2 (rhACE2) may have the ability for inhibiting entrance and replication of SARS-CoV-2 in cellular and embryonic cell-derived organoids by factor 1000–5000 times.[101] It has been suggested that administration of rhACE2 result in directing substrates away from released enzyme ACE and this will cause reduction in serum level of angiotensin II and prevent further activation of ACE2 receptor.[102]

rhACE2 was developed by biologist for treatment acute lung injury, ARDS and pulmonary arterial hypertension. In China, clinical trials are underway now to evaluating the biological and physiological role of rhACE2 in COVID-19 pneumonia, especially with ARDS.[103]

Anticoagulant

Recent evidence indicates that hypercoagulable state was developed in patients with COVID-19.[104-106] These coagulation abnormalities include thrombotic disseminated

Table 1: Dose of antiviral and supportive agents used for treatment of the coronavirus disease-19

Name of drug	Mechanism of action	Dose and duration of drug
Hydroxychloroquine	Antiviral act by inhibiting replication of virus	- 200 mg 3 time daily for 10 days[106] - 200 mg 3 time daily for 6 days[16] - 400 mg twice daily in first day then 200 mg twice daily for 4 days[114] - 800 mg in first day then 400 mh/day for 4 days[115]
Remdesivir	Antiviral act by inhibiting RNA-dependent RNA polymerase	- 200 mg IV as initial dose then 100 mg IV daily for 10 days[33,116]
Oseltamivir	Antiviral act by inhibiting neuraminidase enzyme	- 75 mg twice daily for 5 days[18,117]
Lopinavir/ritonavir	Antiviral act by inhibiting HIV protease enzyme	- 400 mg/100 mg twice daily (5–10 days)[118] - 400 mg/100 mg twice daily for 14 days[48]
Favipiravir	Antiviral act by inhibiting RNA-dependent RNA polymerase	- 1600 mg twice daily at first day then 600 mg twice daily for 10 days[58] - 1800 mg twice daily at first day then 600 mg twice daily for 14 days[119]
Azithromycin	Supportive therapy act as antiviral and anti-inflammatory	- 500 mg daily in first day then 250 mg daily for next 4 days[66] - 500 mg daily for 5 days[120] - 500 mg daily for 3 days[121]
Convalescent plasma transfusion therapy	Supportive therapy has antiviral and immunomodulatory effect	- 1–2 units ~200–400 mL as a maximum dose in 7 mL/kg as single IV infusion[69-122]
Tocilizumab	Supportive therapy act as anti-inflammatory and immunosuppressant agent (IL-6) inhibitors	- 8 mg/kg in 100 mL 0.9% saline solution given IV not less than 1 h (maximum single daily dose 800 mg)[78] - 400 mg as initial single dose through IV drip[83] - 162 mg SC *2 dose/12 h[121]
Vitamin C	Supportive therapy act as antioxidants and immunosuppressant agents	- 15 g IV for 4 days[85] - 12 g/12 h. IV infusion pump 12 mL/h. for 7 days[84] - 10 g given IV[123]
Glutathione	Supportive therapy act as antioxidants and immunosuppressant agents	- 2 g/h. IV then repeat use 2000 mg of oral or IV[89]
Corticosteroid (methylprednisolone)	Supportive therapy act as anti-inflammatory agents and immunosuppressant agent	- 1 mg/kg/day IV for 7 days[124] - 1–2 mg/kg/day for 5–7 days[93,125]
Recombinant human an angiotensin-converting enzyme inhibitor-2(rhACE2)	Supportive therapy act by inhibiting entry and replication of virus	- 0.4 mg/kg IV twice daily for 7 days[126,127]
Anticoagulants	Supportive therapy act by reducing the thrombotic complications that developed in patients with COVID-19	- Low molecular weight heparin or fractional heparin at dose 5000 units SC (2–3) times daily by depending on creatinine clearance[112] - Enoxaparin (40–60 mg/daily)[110]

IV: intravenous, SC: subcutaneous, g: gram, mg: milligram, Kg: kilogram, h: hour, mL: milliliter

intravascular coagulation, venous thrombo-embolism, micro-vascular thrombosis of pulmonary vasculature and elevated level of D-dimer and fibrinogen.[104,105,107]

American Society of Hematology and International Society for Thrombosis and Haemostasis suggested that early administration of anticoagulant in patient with sever COVID-19 infection results in improvement in patient outcomes and decrease the thrombotic complication.[108,109] They recommended that all hospitalized patients with COVID-19 should receive a prophylactic dose of low molecular weight heparin (LMWH), except when there is contraindication such as active bleeding (platelets count < 25×10^9 cell/L) or fibrinogen level <0.5 g/l L.[109-111]

Reduced-dose of LMWH or unfractionated heparin (UFH) in dose 5000 units subcutaneously 2–3 times daily in patients with creatinine clearance less than 30 mL/min[112] while the Fondaparnux is used in patient with history of heparin induce thrombocytopenia.[113] Although the bleeding is uncommon in COVID-19 patients, but the standard risk factors for bleeding should be considered and patients should be assessed to balance the risk of bleeding with risk of thrombosis.[113]

Finally, recent data showed that prophylactic dose of LMWH or UFH is associated with a reduced 28-day mortality in patients with severe COVID-19 who exhibit a sepsis-induced coagulopathy or have very high level of D-dimer levels (>6-fold than upper limit of normal).[110,128]

Results

Despite the large number of drugs that have been and still are suggested to treat patients with COVID-19 [Table 1], no definitive therapy has been found yet.

Conclusion

The main purpose from all current management protocols is to reduce complications and support patient till spontaneous recovery rather than eradicating the virus. Moreover, further studies are mandatory to find antiviral drug against this virus.

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Conflicts of interest

There are no conflicts of interest.

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