

Review Article

Treatment of coronavirus disease 2019: a comprehensive review

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Abstract

The new type of Coronavirus (SARS-CoV-2) is a highly contagious pathogen that causes severe acute respiratory syndrome and can be transmitted from human to human. COVID-19, which has been declared as a pandemic by the world health organization and is infected with more than 50 million people, is also responsible for the death of more than 1 million people. There is no sufficient data from randomized clinical trials that any potential treatment improves outcomes in COVID-19 patients. Chloroquine and hydroxychloroquine, antivirals such as favipiravir, lopinavir/ritonavir, immunomodulatory agents tocilizumab, siltuximab, and sarilumab, and anti-inflammatory drugs such as steroids are used for the treatment of COVID-19. Repurposing drugs can provide new treatment options faster than discovering new drugs due to the known safety profiles of existing drugs. On the other hand, there are new drug and vaccine trials for COVID-19. Many researchers, governmental or non-governmental institutions having clinical trials for COVID-19 drugs and vaccines. In this comprehensive review, we investigate the clinical features, management, and treatment of COVID-19 and possible adverse effects and important information related to drugs used for COVID-19. For future preparedness and readiness, new laws and legislations should be constituted. Besides, emergency teams and budgets should be prepared as well.

Keywords: COVID-19, SARS-CoV-2 Pandemic, Social Isolation, Pharmacotherapy, Pharmaceutical care, Turkey

Background

In December 2019, a novel coronavirus that caused a severe coronavirus disease emerged first in Wuhan, China [1]. It probably originated from bat-derived coronaviruses that spread to humans through an unknown intermediate mammal host [2]. This virus has been identified as a new enveloped RNA betacoronavirus [1]. The novel betacoronavirus is similar to Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Considering phylogenetic similarity with SARS-CoV, it has been named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and in the months that followed, it has spread worldwide, causing the current pandemic [2,3]. WHO announced on January 30 that the SARS-CoV-2 epidemic was a Public Health Emergency of International Concern (PHEIC) [1].

Viruses have four major structural proteins: spike (S), envelope (E), nucleocapsid (N), membrane (M) [4]. S glycoprotein is on its surface, and SARS-CoV-2 mainly infects ciliated bronchial epithelial cells and type II pneumocytes through the S glycoprotein that binds to the angiotensin-converting enzyme 2 (ACE2) surface receptor. When S

glycoprotein binds to ACE2, the cell surface-associated transmembrane serine two proteases (TMPRSS2) and cathepsin trigger trimer S protein cleavage. S glycoprotein contains S1 and S2 subunits. While S1 determines host diversity and facilitates viral binding to target cells, S2 mediates the fusion of viral and cellular membranes and provides a viral entry with endocytosis [5]. As soon as the virus enters the cell, viral polyproteins encoding the replicase-transcriptase complex are synthesized. The virus then synthesizes RNA with RNA-dependent RNA polymerase. Structural proteins are synthesized and lead to the release of viral particles. Non-structural proteins that share homology with other novel coronaviruses (nCoVs) (e.g., 3-chymotrypsin-like protease, RNA-dependent RNA polymerase) are promising drug targets. Viral entry and immune regulation pathways are also among the additional drug targets [2]. In this study, we try to summarize the clinical features of COVID-19 and possible ups and downs of the treatment options for COVID-19. There is a vast amount of drug and vaccination clinical trials to treat COVID-19.

Methods

Study design

This study has been structured as a comprehensive review. Treatment guidelines, clinical studies, systematic reviews, and case studies were included in our study. The current English and Turkish literature published in PubMed, Medline, Web of

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Science, EMBASE, Türkiye Atif Dizini search engines reviewed.

To minimize bias, information collected from each study included: (1) design and characteristics of study; (2) clinical feature and possible effects on COVID-19; (3) the type of outcome measure.

Clinical findings, symptoms, and diagnosis of COVID-19

COVID-19 symptoms are generally nonspecific. While most common symptoms are fever and cough, common symptoms are fatigue, myalgia, dyspnea, altered sense of smell/taste, anorexia, sputum production/expectoration, sore throat [1,6,7]. Gastrointestinal symptoms, confusion, dizziness, headache, rhinorrhoea or nasal congestion, haemoptysis, chest pain, conjunctivitis, cutaneous manifestations (e.g. Maculopapular rash), bronchial breath sounds, tachypnoea, tachycardia, cyanosis, crackles/rales on auscultation are rare [7].

The incubation period in COVID-19 is within 14 days after exposure. The average incubation period is four days (interquartile range, 2–7 days) [8]. The positive result of a high-throughput sequencing, positive result of an RT-PCR assay for respiratory samples (e.g., nasopharyngeal swab), or a positive result of anti-SARS-CoV-2 IgM/IgG may help to confirm the diagnosis of COVID-19 [9]. RT-PCR may tend to present the negative result at an average of 5.1 days. It is recommended to repeat the test 3 days after a negative result [10]. Gene sequencing is pricey and very time-consuming. Serological tests can be used for rapid screening in the clinics because they can have resulted in 15 minutes [1]. Laboratory values that suggest COVID-19 disease include lymphopenia, prolonged prothrombin time (PT), eosinopenia, increased lactate dehydrogenase (LDH), increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased D-dimer, increased neutrophils, increased C-reactive protein (CRP) and increased troponin [10]. Radiological findings have been shown to vary depending on the initial medical intervention, patient's age, disease progression, immune status, and comorbidity [6]. When chest computed tomography (CT) for patients with novel coronavirus pneumonia is used, typical imaging features such as patchy bilateral shadows, subsegmental areas of ground-glass opacity, or consolidation are observed. Changes in imaging reflect the severity of the disease [11]. It may be recommended for suspected COVID-19 patients or those with a negative RT-PCR test. Abnormal chest-CT may do not mean that a patient does not have COVID-19. However, regular chest CT is not specific to determine the diagnosis of COVID-19. A chest X-ray is required for patients with suspected pneumonia and shows unilateral-bilateral lung infiltrates [7]. Currently, the diagnosis of COVID-19 is especially based on epidemiological history, clinical features, laboratory detection, and chest imaging [9].

According to published guidelines in China, disease severity was classified into mild, moderate, severe, and critical: -

- 1) Mild type: Asymptomatic or some upper respiratory tract infection symptoms are mild, no pneumonia manifestations.
- 2) Moderate type: Similar clinical symptoms and pneumonia manifestations can be seen in imaging [12].
- 3) Severe type: Disease progression with danger signs; when any of these criteria exist: respiratory rate ≥ 30 breaths/min; oxygen saturation $\leq 93\%$ at a rest state; arterial partial pressure

of oxygen (PaO₂)/oxygen concentration (FiO₂) ≤ 300 mmHg. Patients with $> 50\%$ lesions progression within 24 to 48 hours in lung [13].

4) Critical type: Shock or organ failure that requires intensive care [12].

Prevention and control

Currently, there is no vaccine or approved specific therapy for COVID-19; thus, prevention is vital to control it. People can reduce their chances of being infected with several basic methods. However, some factors make the prevention process more difficult. People with the infection do not necessarily show the symptoms, but they still can spread the virus. SARS-CoV-2 has a long incubation period. In some situations, transmission can occur even after clinical recovery. These are some of the factors that make prevention difficult [14].

People should take precautions to avoid being exposed to the virus [15]. There are several recommendations about prevention, but the most important one is careful about personal hygiene. Hands should be washed with soap and water for at least 20 seconds; alcohol-based hand sanitizers, which contain at least %60 alcohol, also can be used. It is recommended to avoid touching eyes, nose, and mouth. Moreover, people should maintain at least 1 meter distance from others, especially individuals with symptoms [16]. It is also recommended to avoid going to crowded places because, in these places, people are more likely to come into close contact with each other, so maintaining physical distance is more difficult [17]. People should cover their nose and mouth with a tissue or inner side of their elbow when they cough or sneeze [18]. These are simple but crucial recommendations in order to reduce the transmission of the infection.

People should stay at home and isolate themselves from other people, even with minor symptoms such as cough, headache, and mild fever. If patients have more severe symptoms such as difficulty breathing and fever, they should follow health authorities' directions. People with either mild or severe symptoms should wear a medical mask to leave their houses [17]. Patients with chronic comorbidities or older than 65 age are in the high-risk group. Thus, even though they do not have any symptoms, they stay at home as far as possible to reduce the risk of being infected [16].

Health care workers are also at high-risk because they frequently contact infected patients. It is crucial to protect health care workers; otherwise, patients cannot be treated, and transmission of infection to other patients become easier [14]. Therefore, health care workers who contact COVID-19 patients require full personal protective equipment. Prior to performing procedures that generate aerosol, health care workers are recommended to use N95 and FFP2 masks [15,16].

Potential therapeutic agents for COVID-19 treatment

There is no sufficient data from randomized clinical trials that any potential treatment improves outcomes in COVID-19 patients. Moreover, no prophylactic treatment has been recommended [2]. The current treatment consists of antiviral, supportive, and symptomatic treatment, which are decided to depend on the patient's clinical condition. Supportive treatments are fever and pain management, oxygen treatment, fluid intake, and antibiotic treatment in the presence of an additional

bacterial infection [19]. Table 1 and Table 2 summarizes the properties of potential therapeutic agents for the treatment of COVID-19.

Chloroquine and hydroxychloroquine

Chloroquine (CQ) has been described as a possible broad-spectrum antiviral drug, and it is used for the prevention and treatment of malaria treatment of chronic inflammatory diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis [2,20]. It has an antiviral effect against various RNA viruses such as rabies virus, hepatitis virus, and HIV [20]. Chloroquine and its hydroxy derivative, hydroxychloroquine (HCQ), act by preventing glycosylation at the host receptor, increasing the endosomal pH, and inhibiting the proteolytic process, so they block viral entry into the cells [2]. Chloroquine has an in vitro effect against SARS-CoV-1 and MERS-CoV [21]. There is no high-quality evidence for the therapeutic efficacy of chloroquine/ hydroxychloroquine in SARS or MERS [2]. In vitro, chloroquine and hydroxychloroquine activity have been reported in infected Vero E6 cells against SARS-CoV-2 [21]. Numerous clinical trials are examining the efficacy and safety of chloroquine and hydroxychloroquine. Several researchers have proposed chloroquine and hydroxychloroquine in the treatment of COVID-19 because of the similarities to SARS-CoV infection [22]. However, these agents' efficacy and safety for treatment and prevention are not established [21][23]. Now, there are more than 80 trials worldwide investigating the use of chloroquine, hydroxychloroquine as monotherapy, or in combination with other agents [24]. Due to their mechanisms of preventing viral entry and evidence of efficacy, chloroquine and hydroxychloroquine have also been suggested as potential therapeutic agents for prophylaxis against the COVID-19. However, there are limited data available about this situation, so usage of CQ and HCQ as prophylactic agents is not recommended except in the context of a clinical trial [25].

Chloroquine and hydroxychloroquine are well tolerated in patients with malaria and SLE [2]. Even though they have similar activity, hydroxychloroquine has fewer toxicities and drug-drug interactions than chloroquine due to the hydroxyl group in its structure [26]. Nevertheless, both agents can cause serious adverse effects [2]. They cause cardiac adverse effects such as QTc prolongation, Torsade de Pointes, ventricular arrhythmia, and cardiac deaths. The incidence of QTc prolongation is greater for chloroquine than hydroxychloroquine. Concomitant use of medications that cause QTc prolongation such as antiarrhythmics, antipsychotics, antifungals, macrolides, and fluoroquinolones should be avoided and preferred only if necessary. Baseline and follow-up ECG are recommended when there are potential drug interactions with concomitant medications (e.g., azithromycin) or underlying cardiac diseases [2,27].

In patients with a clinical condition that also causes QTc prolongation, azithromycin should not be used in treatment [28]. The other adverse effects include hypoglycemia, rash, nausea, retinopathy, and bone marrow suppression. The incidence of nausea may be reduced with divided daily doses. Retinopathy and bone marrow suppression generally occur in the long-term use of CQ and HCQ [27].

The hemodynamic complications usually occur with excessively high doses. However, QTc prolongation may occur with the standard doses even there are no concomitant electrolyte abnormalities such as hypomagnesemia and hypokalemia [29]. Moreover, the risk of hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency is high with the use of CQ. There is no evidence about hemolysis for the use of HCQ. Thus, hydroxychloroquine is a preferred agent be used in patients with G6PD deficiency [27]. The use of these agents in a pregnant woman is generally considered safe [2].

Currently, the use of hydroxychloroquine and chloroquine in patients with COVID-19 is controversial. NIH COVID-19 Treatment Guidelines Panel does not recommend chloroquine or hydroxychloroquine for the treatment of COVID-19 in hospitalized patients. The Panel also does not recommend using these agents in non-hospitalized patients except in a clinical trial [30]. Furthermore, FDA has revoked the Emergency Use Authorization for HCQ and CQ. One of the reasons for this decision is recent data from a randomized controlled trial that showed no evidence of benefit in mortality with hydroxychloroquine treatment in patients with COVID-19 [23].

Azithromycin

Azithromycin is a macrolide antibiotic used in the treatment of various infections such as respiratory, skin, and soft-tissue infections. Currently, azithromycin is being used off-label in patients with COVID-19, but its efficacy and safety for this indication have not been proven yet [31]. According to the study carried out by Garret et al. [29], azithromycin was shown to reinforce the effects of hydroxychloroquine. In this study, patients with COVID-19 were divided into three groups. Six patients were treated with the combination of hydroxychloroquine and azithromycin, 14 patients have treated with hydroxychloroquine as monotherapy, and the third group was 16 control patients with COVID-19. On day 6, all of the patients treated with the combination therapy exhibited a virological cure.

On the other hand, the virological cure percentage exhibition was 57.1% in patients treated with hydroxychloroquine monotherapy and 12.5% in the control group. Therefore, it is considered that the use of hydroxychloroquine and azithromycin combination might be an efficient treatment for COVID-19 [32]. Nevertheless, additional studies are needed to assess the efficacy and safety of this therapy. Furthermore, there are concerns associated with hydroxychloroquine and azithromycin combination because both drugs can cause QTc prolongation. Thus, it is recommended to be careful and monitor patients treated with the hydroxychloroquine and azithromycin combination [21][23]. The risk of QTc prolongation is higher in elderly patients with cardiac comorbidities, patients those taking concomitant QT-interval prolonging drugs, and patients with electrolyte abnormalities [28].

Lopinavir and Ritonavir

Lopinavir and Ritonavir are HIV protease inhibitors, and they suppress the cleavage of a polyprotein into multiple functional proteins and inhibit 3C-like protease [20,33]. They are mainly used in the treatment of human immunodeficiency virus-1

(HIV-1) [33]. The combination of lopinavir and ritonavir has in vitro activity against SARS-CoV-1 and MERS-CoV. Also, in vitro activity of this combination against SARS-CoV-2 has been reported in infected Vero E6 cells [21]. According to recent randomized controlled trials, the average time from symptom onset to initiation of treatment was 13 days. In the SARS-CoV-1 experience, treatment was effective if treatment started early [34,35]. Therefore, the use of lopinavir/ritonavir may be useful in the early stages of SARS-CoV-2 infection and mild disease conditions [34].

Lopinavir/ritonavir combination has been of interest for the treatment of COVID-19 [36]. There is limited data about lopinavir/ritonavir for the treatment of COVID-19, and most of the studies about the combination are mostly case reports and small, retrospective, non-randomized cohort studies. Therefore, it is difficult to determine the effect of Lopinavir/ritonavir in SARS-CoV-2 infection [2]. According to available data, there is no advantage over standard care for SARS CoV-2 [25]. Cao B et al. compared lopinavir/ritonavir's efficacy with standard care in 199 hospitalized patients with severe COVID-19. According to this open-label randomized controlled trial's results, there are no differences between combination treatment and standard care. Additionally, adverse events are more common in patients receiving lopinavir/ritonavir, but serious adverse events are common in the standard care group [36]. Although additional randomized controlled trials (RCTs) of lopinavir/ritonavir are ongoing, the current data suggest a limited role for lopinavir/ritonavir in COVID-19 treatment [2].

Lopinavir/ritonavir combination may cause adverse effects. Nausea, vomiting, and diarrhea are the common adverse effects of this agent. Hepatotoxicity is the other adverse effect of the combination treatment [27]. According to a recent randomized clinical trial, 50% of patients who receive lopinavir/ritonavir treatment caused adverse effects, and 14% of patients discontinued therapy because of the gastrointestinal adverse effects [2]. When this combination is used, adverse effects and drug interactions should be monitored [25] because lopinavir/ritonavir is an inhibitor of CYP3A4, so that it may cause important drug interactions.

Lopinavir/ritonavir can be used in pregnant women. However, this combination's oral solution contains 42% alcohol and 15.3% propylene glycol, so the use of this preparation is not recommended in pregnancy. Once-daily use of lopinavir/ritonavir is also not recommended in pregnancy. Lopinavir/ritonavir is approved for the treatment of HIV in infants, children, and adolescents. However, there is no data on lopinavir/ritonavir's efficacy to treat COVID-19 in pediatric patients [27].

Umifenovir

Umifenovir, known as also Arbidol, is an antiviral agent that is approved in China and Russia for influenza treatment and prophylaxis. The FDA does not approve it, so it is not available in the US [16]. It has in vitro activity against SARS-CoV-1 and SARS-CoV-2 [21]. There is an increasing interest in umifenovir because of its action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope [2].

Umifenovir can be found in some guidelines for the treatment of COVID-19. This agent's efficacy for the treatment has not been established yet [21][23]. There are ongoing randomized

clinical trials to evaluate the efficacy of umifenovir for the treatment of COVID-19 [2].

Remdesivir

Remdesivir, known as GS-5734, is a monophosphate prodrug and has a broad spectrum of antiviral effects against Ebola and other RNA viruses [2,5]. Remdesivir inhibits RNA-dependent RNA polymerase, and also its active triphosphate form can compete with ATP binding to the polymerase by interfering with viral RNA synthesis. Relatively complete data are available on its safety and human pharmacokinetics [33]. It has been shown that remdesivir has activity against SARS-CoV and MERS-CoV in vitro and animal models. In vitro activity of remdesivir against SARS-CoV-2 has been reported in infected Vero E6 cells [21]. Several studies recommend that a combination of remdesivir with specific monoclonal antibodies may be an ideal option for the treatment of COVID-19 [37]. It has been expected that the possibility of toxicity is low with the use of remdesivir since it is highly selective to viral polymerases. It has a long intracellular half-life, so once-daily administration of remdesivir can be possible [34]. It is the most promising drug currently being investigated for COVID-19 [21]. The use of IV remdesivir provides significant improvement for the first COVID-19 case in the US. After that, a trial has been initiated to investigate the efficacy and safety of remdesivir in hospitalized COVID-19 patients. In a cohort study of hospitalized severe COVID-19 patients, an improvement was observed in 36 of 53 patients [25]. Moreover, reports of case studies suggested that the use of remdesivir may be beneficial in patients with severe COVID-19 [38].

Remdesivir can cause adverse effects such as nausea, vomiting, diarrhea, elevation in serum transaminase levels, and prothrombin time elevation. Patients with an eGFR<50 ml/min are not included in some clinical trials because remdesivir formulation contains sulfobutylether-beta-cyclodextrin sodium that is cleared renally. In pregnant and pediatric patients, the efficacy and safety of remdesivir for COVID-19 treatment have not been evaluated [27].

Favipiravir

Favipiravir, also known as T705, is a guanosine analog. It converts into its active phosphoribosylated form in cells and inhibits RNA-dependent RNA polymerase. It has a broader antiviral spectrum because of its mechanism of action and inhibitory activity on a wide range of RNA viruses such as flavivirus, poliovirus, rhinovirus, and is a broad-spectrum drug [25,39]. Favipiravir is an antiviral agent that has already been used in the clinic to treat patients with Ebola and Lassa viruses, and it is used for influenza treatment in Japan [36,40]. In vitro studies have shown that favipiravir inhibits SARS-CoV 2 in Vero E6 cells [25]. Due to these reasons, favipiravir considered a potential candidate for the treatment of COVID-19 [41]. Favipiravir has in-vitro activity against SARS-CoV-2, but it has shown its antiviral activity with a high concentration compared to chloroquine or remdesivir [42].

There are limited clinical experience reports that support favipiravir for the treatment of COVID-19 [2]. Thus, additional reports are necessary to determine efficacy for treatment and identify the optimal dosage and treatment duration [21]. In a randomized clinical trial that was carried out by Cao B, et al.

[91], the efficacy and safety of favipiravir and umifenovir have been investigated in 240 hospitalized patients with COVID-19. According to the trial results, the 7-day clinical recovery rate was 55.86% in the umifenovir group, and the rate was 71.43% in the favipiravir group. The time for fever reduction and cough relief was significantly shorter in the favipiravir group, but no difference was observed in oxygen therapy or non-invasive mechanical ventilation rate. Furthermore, the most common adverse effects were abnormal liver function tests, psychiatric, gastrointestinal symptoms, and elevation in serum uric acid levels. There is a need for additional randomized clinical trials about the efficacy and safety of favipiravir for the treatment of COVID-19 [25,36].

High doses of favipiravir should be used with caution due to lack of safety data, and it is contraindicated in pregnancy. In addition, if favipiravir is used with paracetamol, the recommended maximum daily dose of paracetamol is 3 g [21].

Immunomodulatory agents

An increase of pro-inflammatory factors in COVID-19 disease can cause a cytokine storm. This condition worsens the prognosis of COVID-19 [12]. Thus, all patients with severe COVID-19 should be screened for hyper inflammation because immunosuppressive therapy could affirmatively affect mortality [43]. Interleukin 6 (IL-6) measurements can help identify the severity of the disease [44]. Tocilizumab, siltuximab, and sarilumab are monoclonal antibodies, and each of them has different pharmacological properties. They inhibit the IL-6 receptor and are used for the treatment of rheumatological conditions [12,45]. Tocilizumab has been approved by the FDA to treat cytokine release syndrome, which results in excessive cytokine production and may consequently rapid multiple organ damage [12,37]. Tocilizumab may be beneficial for COVID-19 patients who can develop such an uncontrolled immune response [7,21].

There is an uncontrolled, retrospective cohort study, including 21 hospitalized patients with COVID-19. According to this study results, tocilizumab therapy provided clinical improvement in oxygenation, systemic inflammation, and respiratory function [27]. Also, there are no adverse reactions reported in this study [46]. However, this study has limitations such as small sample size and lack of a control group [27]. Thus, there is a need for additional studies to assess the efficacy of tocilizumab and other IL-6 antagonists. In accordance with this purpose, numerous studies of tocilizumab, sarilumab, and siltuximab are ongoing in different countries [45].

Tocilizumab should not be used in pregnancy, neutropenia, active tuberculosis, active hepatitis B or C, allergy, and hypersensitivity. Liver function tests and thrombocyte count should be monitored during treatment. Patients with a history of diverticulitis should be monitored due to gastrointestinal perforation risk [28].

Corticosteroids

Corticosteroids reduce proinflammatory cytokines. They have anti-inflammatory and also antifibrotic properties [12,47]. The use of corticosteroids for the treatment of COVID-19 is controversial. SARS-CoV-2 infection may cause acute lung injury and acute respiratory distress syndrome (ARDS) due to increased inflammatory responses. Corticosteroids can be useful

in these cases as anti-inflammatory agents. However, corticosteroids also delay viral clearance and increase the risk of secondary infection [16][2]. Therefore, prior to the corticosteroid therapy in COVID-19 patients, the risks and benefits should be assessed carefully [21]. In patients with COVID-19, recommendations about corticosteroids' use depend on various factors such as the severity of illness, indication, and underlying medical conditions. These factors vary from patient to patient, so each patient should be assessed individually [27]. WHO, CDC, NIH, and IDSA generally do not recommend the routine use of corticosteroids in patients with COVID-19 unless corticosteroids are indicated for other reasons such as exacerbation of asthma, COPD, or septic shock [21].

Immunoglobulin therapy

Passive immune treatment includes whole convalescent blood, convalescent plasma, human immunoglobulin, and monoclonal or polyclonal antibodies [12]. The use of convalescent plasma or hyperimmune immunoglobulin is rational since antibodies produced by recovered patients may help immune clearance of infected cells and free virus [2]. Various convalescent blood products have been developed to treat infectious diseases. On the other hand, these are difficult and expensive to produce in emergencies [12]. Currently, plasma collected by apheresis is the preferred treatment [12]. The mechanism of action has resulted in cell cytotoxicity, phagocytosis, and direct neutralization of the pathogen by binding the transfused antibodies to the pathogen [26]. Convalescent plasma has been used previously for SARS-CoV-1, MERS, Ebola, and H1N1 influenza, and successful results have been reported [34]. In a case study associated with COVID-19, a severely ill patient was treated with convalescent plasma from six donors. While anti-SARS-CoV IgG titers from the convalescent plasma were high, anti-SARS-CoV IgM titers were weak [48].

However, this approach has several disadvantages, including the difficulty of scaling for the widespread use and the risk of transmission of other diseases from the plasma of recovered patients. In addition, antibodies in plasma are usually at a lower concentration, which may not be sufficient for therapy. The company of Regeneron in the USA is about to present two antibodies that can synthetically be produced for the treatment of COVID-19, and clinical studies would be started later. These antibodies would be useful for prophylaxis and treatment in particularly high-risk groups [35]. The US-FDA has approved the use of convalescent plasma for patients with severe or immediately life-threatening COVID-19. Efficacy and safety of convalescent plasma for the treatment of COVID-19 have not been established yet [49].

Other agents

Inhaled nitric oxide (iNO) has been known as an efficient and selective pulmonary vasodilator. It also has an antimicrobial effect. Because of these factors iNO is used to treat respiratory diseases such as pulmonary hypertension and ARDS. It has a relatively good safety profile and maybe a promising candidate in treating severe COVID-19 patients, as it alleviates lung damage [12]. The Surviving Sepsis Campaign has recommended a trial of the inhaled pulmonary vasodilator in COVID-19 patients with severe ARDS and hypoxemia who have mechanically ventilated despite optimized ventilation and

other recovery strategies. Inhaled epoprostenol, which is naturally occurring prostaglandin and inhaled nitric oxide, are two pulmonary vasodilators that have been investigated commonly [26]. Based on a randomized controlled trial with an experience with inhaled epoprostenol, it has been observed that the mean pulmonary artery pressure decreased, and oxygenation improved in patients with ARDS. However, additional data related to inhaled epoprostenol is needed in the treatment of ARDS [21,26].

Vitamin C is a potent antioxidant agent since it can neutralize free radicals, prevent, and reverse cellular damage. Vitamin C, which is known to be effective against influenza, is an effective antiviral agent. Some hospitals have been reported administering high doses of vitamin C as supportive treatment to infected patients. In China, it has been observed that the oxygenation index of 50 moderate-severe patients who received high doses of vitamin C was improved, and all patients eventually recovered and discharged. Doses were administered with IV infusion over 8–10 hours among 2 and 10 g per day. The NIH panel stated that 1.5 mg/kg vitamin C is safe and does not cause side effects [26].

Colchicine is an agent with anti-inflammatory and antifibrotic properties, and it is often used for the treatment of gout. Colchicine has been shown to reduce inflammation in cardiac myocytes in some COVID-19 patients with myopathy. There are several ongoing studies to investigate the effect of colchicine in a cytokine storm [26].

Concomitant use of certain drugs in patients with COVID-19

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (ARBs)

SARS-CoV-2 has some similarities with SARS-CoV and MERS-CoV in terms of their mechanisms. According to the findings from several studies with the SARS-CoV, it has been considered that angiotensin-converting enzyme 2 (ACE2) acts as a co-transporter for the virus to enter the lungs [50]. Similar to the SARS-CoV, SARS-CoV-2 also enter the lungs after the binding to ACE2 [51]. ACE2 is an enzyme and a receptor on cell surfaces for SARS-CoV and SARS-CoV-2 and is expressed in the lung, heart, kidney, and testis [52]. It is a homologue of ACE1, an important therapeutic target in cardiovascular diseases (CVD) [51]. ACE1 converts the angiotensin I to angiotensin II. Angiotensin II causes an increase in blood pressure. The ACEI inhibit angiotensin I to angiotensin II conversion and widely used in CVD. The effects of ACE2 is not as clear as ACE1, and there is no specific treatment involving ACE2 [50,51]. However, it has been known that ACE2 degrade the angiotensin II to angiotensin (1-7), so it affects the renin-angiotensin system significantly by antagonizing the role of angiotensin II [53].

This association between the ACE2 and SARS-CoV-2 has questioned the use of ACE inhibitors and ARBs since these drugs could lead to increased expression of ACE2. The increased expression of ACE2 may ease the viral entry to cells and increase the risk of becoming infected [54]. American Heart Association (AHA), American College of Cardiology (ACC), Heart Failure Society America (HFSA), and European Society of Cardiology (ESC) recommend continuing treatment with ACE inhibitors or ARBs. Furthermore, these agents have an

important role in patients with hypertension and those with heart failure and proteinuria. Thus, particularly in high-risk patients, discontinuation of treatment could lead to more severe and adverse health outcomes such as uncontrolled hypertension, renal function impairment, and cardiac decompensation (12,21). It has been considered that the use of ACE inhibitors and ARBs in COVID-19 might be beneficial due to its potential anti-inflammatory effects. Induced ACE2 activity causes an increase in conversion of angiotensin II to angiotensin (1-7), and this final peptide can produce anti-inflammatory activity. However, it is not sure whether the anti-inflammatory activity is harmful or beneficial in SARS-CoV-2 infection [55].

As a consequence, there is insufficient data about the effects of ACE inhibitors and ARBs in patients with COVID-19. It is recommended that patients treated with ACE inhibitors or ARBs for cardiovascular disease should continue these medications [27].

Non-steroid anti-inflammatory drugs (NSAIDs)

In France, four patients with COVID-19 and no underlying health problems have developed serious complications after using NSAIDs. Therefore, in mid-March 2020, it was recommended that ibuprofen should not be used in patients with COVID-19 for symptomatic relief [56,57]. Additionally, it has been proposed that ibuprofen can increase the expression of ACE2 [58]. Currently, there is no sufficient evidence in order to recommend against the use of ibuprofen and other NSAIDs in patients with COVID-19, and patients may need NSAIDs for symptom relief if paracetamol is inadequate. Nevertheless, regular use of NSAIDs is not recommended as a first-line drug option, and paracetamol is the preferred antipyretic agent in patients with COVID-19 [21,67].

Corticosteroids

Corticosteroids are generally not recommended in patients with COVID-19 unless indicated for another condition such as exacerbation of asthma or COPD. Patients received oral corticosteroid therapy before the SARS-CoV-2 infection should continue their treatment. Similarly, inhaled corticosteroids used daily to treat asthma, and COPD should not be discontinued in patients with COVID-19 [21,27].

Anticoagulants

According to the preliminary reports, hemostatic abnormalities occur in patients with COVID-19 [60]. The endothelium has an essential role in haemostasis regulation, but this regulation is generally disrupted during viral infections [61]. It is one of the reasons for hemostatic abnormalities in patients with COVID-19. Mild thrombocytopenia and increased D-dimer levels associated with worse clinical outcomes are instances of hemostatic abnormalities in COVID-19 patients [60].

The International Society for Thrombosis and Haemostasis (ISTH) and American Society of Hematology (ASH) recommend prophylactic dose low molecular weight heparin (LMWH) to all hospitalized COVID-19 patients, including non-critical ill patients. Unless they have contraindications for LMWH such as active bleeding and platelet count < 25 x 10⁹/L [62]. Also, WHO interim guidance statement recommends the use of once-daily LMWH or twice daily subcutaneous unfractionated heparin (UFH) as thromboprophylaxis. Some

clinicians use a higher dose or therapeutic dose parenteral anticoagulant in COVID-19 patients. However, additional studies are necessary to evaluate this situation. LMWHs can be more advantageous over UFH due to the once-daily dosing regimen [60]. LMWH or UFH is generally preferred in hospitalized patients' thromboprophylaxis because they have shorter half-lives, can be administered intravenously or subcutaneously, and have fewer drug-drug interactions in comparison to oral anticoagulants. Patients who receive anticoagulant or antiplatelet agents for underlying conditions should continue their treatment [27].

Statins

Statins have the function of reducing endothelial dysfunction; in this way, they affect ACE2 [27]. Furthermore, these lipid-lowering agents have anti-inflammatory and immunomodulatory effects. Therefore, with statins, lung injury caused by the body's immune response may be controlled [63]. Patients with COVID-19 who are on use statins for a CVD should continue not to disrupt statin [27]. Discontinuation of statin therapy may be recommended in patients who may develop severe rhabdomyolysis. Drug interactions may occur with concomitant use of statins and medications used for the treatment of COVID-19 [21].

Comorbidities in COVID-19 – diabetes mellitus and hypertension

According to various studies, diabetes and hypertension are highly prevalent comorbidities among patients with COVID-19 [50]. Also, it has been reported that SARS-CoV-2 may cause injury to other organs such as the heart, liver, and kidneys in addition to pneumonia. Thus, especially in older patients with underlying comorbidities paying full attention in the treatment of original comorbidity is necessary [64,65].

Various mechanisms may explain the susceptibility of patients with diabetes in SARS-CoV-2 infection. Decreased pulmonary function, including a reduction in forced vital capacity and forced expiratory volume, decreased viral clearance and T cell function, and aggravated inflammation are instances of these mechanisms that generally occur due to hyperglycemia [65–67]. Therefore, in patients with diabetes controlling blood glucose is crucial, and these patients should be monitored closely.

Hypertension is another comorbidity and common disease, particularly in older. Patients with hypertension are also in high-risk groups for COVID-19. Moreover, there is an important issue with the medications of patients with hypertension. ACE inhibitors and ARBs are widely used drugs for the treatment of hypertension. However, there are conflicting considerations available about the use of them in patients with COVID-19. Thus, patients with hypertension can be confused and unwilling about the continuation of treatment. Health care providers should ensure that these patients continue their treatment because discontinuation of treatment could lead to uncontrolled hypertension, which is more dangerous in COVID-19 [12].

Patients with hypertension or/and diabetes should be aware that uncontrolled blood pressure or blood glucose levels may increase the severity of COVID-19. Thus, they should receive their medications properly, maintain a healthy lifestyle, and

follow health authorities' recommendations about prevention and control [68,69].

Healthcare professionals have a great responsibility for patient education. Especially clinical pharmacists who use all their pharmaceutical knowledge for the benefit of patients can improve health status by ensuring proper medication use [92].

Managing symptoms of COVID-19

There are various symptoms of COVID-19, such as fever, cough, difficulty breathing. The presence and severity of symptoms vary from one patient to another. In addition to antiviral and investigational drugs mentioned above in detail, there are also drugs and recommendations for managing COVID-19 symptoms. In managing the symptoms, several factors should be considered, such as the patient's underlying conditions and other drugs used by the patient. There are several methods listed below that can be applied to manage symptoms:

- Firstly, simple non-medication remedies such as honey can relieve cough, but it is not safe for children under the age of 1. The short term use of codeine linctus or tablets and morphine sulfate oral solution may be considered if coughing is distressing in patients with COVID-19. Patients should be informed about the constipation effect of codeine and morphine.
- Generally, paracetamol is the recommended agent for the management of fever. There is no recommendation against the use of NSAIDs, but paracetamol is generally preferred antipyretic in patients with COVID-19. Also, patients should drink enough water to avoid dehydration.
- Breathing and relaxation techniques, ventilating the room frequently can help manage difficulty breathing in patients with COVID-19 [70].

Drug-vaccine studies for COVID-19

An overview of drug studies

Repurpose drugs can provide new treatment options faster than the discovery of new drugs, as the safety profiles of existing drugs already exist. For this purpose, bioinformatics' use to analyze the interactions of drugs with the proteins of the target organism is a method for effectively selecting drugs against SARS-CoV 2 [71]. Until now, researchers have suggested more than 30 drugs (remdesivir, favipiravir, indinavir, raltegravir, darunavir/cobicistat, saquinavir, etc.) with possible effects against COVID-19 [37]. General corticosteroids and established antiviral drugs, including neuraminidase inhibitors (oseltamivir, zanamivir, peramivir, etc.), acyclovir, ganciclovir, and ribavirin have found unacceptable for use in general clinical practice, and these are not recommended for the prevention and treatment of COVID-19 [72].

There is currently a large global trial known as Solidarity, supported by the World Health Organization (WHO). These trials include four repurposed drugs as potential therapeutic agents: chloroquine and hydroxychloroquine, remdesivir, lopinavir, and ritonavir combination with or without interferon [12,73]. As of April 21, 2020, more than 100 countries are working together to find effective therapeutics in the shortest possible time. Enrolling patients in one randomized trial will

facilitate the rapid comparison of unproven treatments worldwide, and while randomized clinical trials usually take years, time spent will decrease by percent 80. On 4 July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the hydroxychloroquine and lopinavir/ritonavir arms of the trials [73]. A record of international clinical trials can be found on the WHO website and at ClinicalTrials.gov. At present, the evidence needed for the efficacy and safety of treatments against COVID-19 will be provided by randomized controlled trials. Thus, we will determine whether the benefits of most treatments outweigh the harms [25]. While searching for the "COVID-19" term on the "Clinicaltrials.com" website, there are a total of 3176 studies; 1649 of them are recruiting. Among these, 913 studies are interventional (clinical trials), and among these are 378, 205, 46 studies in phase 2, phase 3, phase 4, respectively [74]. Drugs that are included in clinical studies mainly are antiviral drugs, immunotherapy drugs (such as Interferon, Immunoglobulin, etc.), antimalarial drugs (such as chloroquine, hydroxychloroquine, chloroquine phosphate), glucocorticoids, traditional Chinese medicine interventions, and others (such as vitamin C, vitamin D, polymyositis injection, zinc sulfate, acetylcysteine, etc.) [19].

Besides, the FDA has issued guidance for investigation of convalescent plasma in the United States for COVID-19. It is essential to establish protocols for collecting, preparing, and applying apheresis-collected convalescent plasma in response to the current pandemic [12]. Clinical trials are ongoing in China to evaluate the use of convalescent serum for treatment [75].

Vaccine Development for COVID-19

Based on the small SARS-CoV-1 vaccine studies in phase 1, these studies' results with an inactivated virus vaccine and a spike-based DNA vaccine are promising as they induced neutralizing antibody titers and were safe. It is thought that cross-protection can be provided against SARS-CoV-2 with some neutralizing monoclonal antibodies isolated against SARS-CoV-1, such as CR3022. Vaccines developed against MERS-CoV targeting the MERS-CoV S protein are in preclinical and clinical development. However, MERS-CoV vaccines are not thought to induce potent cross-neutralizing antibodies due to the phylogenetic distance between the two viruses [75]. For the development of CoV vaccines, most of these targets are spike (S) glycoprotein that elicited neutralizing-antibodies and T-cell responses [76].

The effect of vaccines' protection may depend on various factors such as the selected vaccination platform, antigens, animal models, and ways of vaccination. Different ways of vaccination could also help to develop effective vaccines for coronaviruses [77]. Candidate vaccines are in development, but it may take at least 12 to 18 months [78]. Thirty-three vaccine candidates are currently approved for human testing through clinical trials, including mRNA and DNA platform vaccines, adenovirus vector vaccines, and inactivated virus vaccines [79]. Nine of them are in the Phase 3 clinical trial (Table 3). Generally, DNA-based, and protein-based vaccines have been the main approaches for developing stable and effective vaccines with less innate immunogenicity [78]. In addition, mRNA-based vaccines are safer, efficient, and easier to manufacture, and unlike traditional vaccines made from an

inactivated pathogen or small subunits of living pathogen, synthesis of this vaccine does not require viruses [78,80]. Recently, various DNA vaccine platforms have been developed to promote vaccines' efficacy by using electroporation to deliver plasmids encoding antigens and diverse immune responses and adding adjuvants to promote immune responses. In this context, Inovio Pharmaceuticals and International Vaccine Institute is developing a DNA vaccine (INO-4800) against COVID-19, and the vaccine is in clinical phase I/II stage [79,81] ChAdOx1-S COVID-19 vaccine, which entered the phase 3 clinical study developed by the University of Oxford in partnership with AstraZeneca, consists of the S protein sequence of SARS-CoV-2 and a non-replicating adenovirus vector. Adenovirus-based vectors cover respiratory, and GI epithelium, the two major sites in which SARS-CoV-2's ACE-2 receptor is expressed, and these are relatively safe in children and individuals with underlying disease due to its non-replication in the host [80]. On March 16, 2020, phase 1 clinical trial of novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine has been started jointly by Moderna and the Vaccine Research Center at the National Institutes of Health [78], and this vaccine is currently in phase 3 clinical trial. The immunogenicity and efficacy of the inactivated SARS-CoV vaccines were detected in experimental animals [82].

Currently, there are six candidate inactive vaccines in the clinical evaluation stage [79]. Preclinical trials have been started for some of the SARS-CoV-2 vaccine candidates [75]. 143 candidate vaccines are in the preclinical phase [79]. Additional vaccine approaches in the preclinical stage include DNA vaccines, live attenuated vaccines, inactivated virus vaccines, recombinant-protein based vaccines, and viral-vector-based vaccines. It is difficult to predict which of these platforms will be more successful or faster because all of them have advantages and disadvantages [75].

Conclusion

COVID-19 had a massive impact on every aspect of life. Healthcare workers and researchers are working hard either to treat or find a permanent solution to this pandemic. With preventive measures, the number of new cases will be kept reduced. There are several medicine options frequently used for COVID-19. However, these drugs are not absolute and have many side effects. Many of these drugs may not be familiar to the physician and require a clinical pharmacist's professional support. A healthcare professional team containing physicians, pharmacists, nurses, physiotherapists, etc. needs to collaborate. Interdisciplinary plans should be created to obtain the most relevant results. COVID-19 is the first pandemic of the 21st century and tested the global health system's readiness under a pandemic. It revealed some of the strengths of the health system while showing us the parts that required improvement. After the COVID-19 pandemic, we will have the opportunity to analyze these weaknesses and take the necessary measures to ensure the health system's better performance under future pandemics. Future preparedness is another important issue to prevent catastrophic outcomes of a pandemic. Emergency protocols, teams, guidelines, and budget should be ready for future pandemics. Besides healthcare workers, these teams should contain different occupational professionals.

Table 1 Properties of select proposed drugs for treatment of COVID-19

Agent/ Class	Target/Clinical Use	FDA-Approved Indications	Contraindications	Rationale	References
Chloroquine phosphate (Aralen/generic) Antimalarial	<ul style="list-style-type: none"> • It blocks viral entry by inhibiting proteolytic processing and endosomal acidification and glycosylation of host receptors. • It provides additional immunomodulatory effects with autophagy, lysosomal activity, inhibition of cytokine production in host cells. 	<ul style="list-style-type: none"> • Malaria • Extra-intestinal amebiasis 	<ul style="list-style-type: none"> • Hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of formulation. • Presence of retinal or visual field changes of any etiology (unless benefit outweighs risk) 	<ul style="list-style-type: none"> • Efficacy and safety of chloroquine for treatment or prevention of COVID-19 not established. • NIH indicates insufficient clinical data for the use of chloroquine 	[2,21,83]
Hydroxychloroquine sulfate (Plaquenil/generic) Antimalarial	<ul style="list-style-type: none"> • Its mechanism of action is the same as chloroquine. 	<ul style="list-style-type: none"> • Lupus erythematosus • Malaria • Rheumatoid Arthritis 	<ul style="list-style-type: none"> • Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative or any component of the formulation 	<ul style="list-style-type: none"> • Efficacy and safety of hydroxychloro-quine for treatment or prevention of COVID-19 not established. • Additional data required on the combination of azithromycin and hydroxychloroquine. 	[2,21,84]
Lopinavir/ritonavir (Kaletra) HIV Proteaz İnhibitörleri	<ul style="list-style-type: none"> • 3CL protease 	<ul style="list-style-type: none"> • HIV İnfection 	<ul style="list-style-type: none"> • Hypersensitivity to lopinavir/ ritonavir or any of its ingredients, including ritonavir. • Co-administration with drugs highly dependent on CYP450 3A. • Co-administration with potent CYP450 3A inducers. 	<ul style="list-style-type: none"> • Its effectiveness in the use of COVID-19 treatment with other antivirals or alone haven't exactly established. 	[2,21,85]
Umifenovir (Arbidol) Antiviral	<ul style="list-style-type: none"> • S protein/ACE2, membrane fusion inhibitor 	<ul style="list-style-type: none"> • Not approved by FDA 	<ul style="list-style-type: none"> • Known hypersensitivity to umifenovir 	<ul style="list-style-type: none"> • Included in some guidelines for the treatment of COVID-19. • There are limited data on its use in the treatment of COVID-19. 	[2,21,83]
Remdesivir Antiviral	<ul style="list-style-type: none"> • RNA polymerase inhibitor 	<ul style="list-style-type: none"> • Not approved by FDA • Investigational antiviral agent 	<ul style="list-style-type: none"> • Exclusion criteria based on specific protocols 	<ul style="list-style-type: none"> • It is the most promising direct-acting antiviral currently being researched for COVID-19. • Efficacy and safety of remdesivir for treatment of COVID-19 not established. • NIH indicates insufficient clinical data for the use of remdesivir 	[21,86]
Favipiravir Antiviral	<ul style="list-style-type: none"> • RNA polymerase inhibitor 	<ul style="list-style-type: none"> • Not approved by FDA • Not commercially available in the US 	<ul style="list-style-type: none"> • Exclusion criteria based on specific protocols. • Favipiravir is contraindicated in women with known or suspected pregnancy, and measures should be taken to prevent 	<ul style="list-style-type: none"> • Efficacy and safety of favipiravir for treatment of COVID-19 not established. 	[2,21,83,87]

			pregnancy during medication.		
Tocilizumab (Actemra) Disease-modifying Anti-rheumatic Drug	• IL-6 inhibition-reduction in cytokine storm	•Cytokine release syndrome, severe or life-threatening •Giant cell arteritis •Polyarticular juvenile idiopathic arthritis •Rheumatoid arthritis •Systemic juvenile idiopathic arthritis	• Known hypersensitivity to tocilizumab or any components of the formulation. Caution in patients with neutropenia (<500 cells/ μ L) or thrombocytopenia (<50 000/ μ L)	• In China, tocilizumab can be used for treating severely or critically ill COVID-19 patients with extensive lung lesions and high IL-6. • NIH reports insufficient clinical data for use of tocilizumab.	[21,83,88]

Table 2 Practical Information on Potential Therapeutic Agents for Treatment of COVID-19

Drug	Dosing	Administration	Dose adjustments in renal and hepatic improvement	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Special Populations	References
Chloroquine Phosphate	Suggested dose in Emergency Use Authorization (EUA) (now revoked) for adults and adolescents weighing 50 kg or more: 1 g orally once daily on day 1, then 500 mg orally once daily for 4-7 days of total treatment based on clinical evaluation.	It may be administered with food to decrease GI adverse effects. Crushing tablet is not preferred, but if needed may be crushed and mixed with applesauce or similar foods.	No dosage adjustments necessary in patients with eGFR \geq 10 ml/minute. In patients with eGFR<10 ml/minute, dose should be administered 50% of the usual dose only for long-term use, but no changes are necessary in short-term use. No dose adjustments necessary in hepatic impairment.	QTc prolongation, Torsade de Pointes, AV block, ventricular arrhythmia Gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal cramps. Hypoglycemia Hemolysis Myopathy Retinal toxicity Neuropsychiatric effects Allergic reaction	Complete Blood Count (CBC), liver function tests, serum creatinine (SCr), blood glucose, potassium, magnesium. Baseline ECG. It is recommended to perform G6PD testing. Chloroquine should not be used in patients with G6PD deficiency.	CYP2D6 and CYP3A4 substrate. The risk of QTc prolongation increase with the concomitant use of other QTc prolonging agents.	If benefit outweighs risks it may be used in pregnant women.	[2,27,89]
Hydroxychloroquine sulfate	400 mg orally twice daily on day 1, then 200 mg orally twice daily on days 2-5. Suggested dose in EUA(now revoked) for hospitalized adults and adolescents weighing 50 kg or more: 800 mg once daily on day 1, then 400 mg once daily for 4-7 days of total treatment based on clinical evaluation.	Crushing tablets is not recommended by manufacturer. But in patients unable to swallow tablets, it has been recommended that tablets may be crushed and mixed with a small amount of applesauce, or compounded into an oral solution.	No dosage adjustments are recommended in kidney or hepatic impairment, it should be used with caution in this patients.	QTc prolongation, Torsade de Pointes, AV block, ventricular arrhythmia. Gastrointestinal effects such as nausea, vomiting, diarrhea, abdominal cramps. Hypoglycemia Myopathy Retinal toxicity Neuropsychiatric effects Allergic reaction	Complete Blood Count (CBC), liver function tests, serum creatinine, blood glucose, potassium, magnesium. Baseline ECG.	CYP2D6, CYP3A4, CYP3A5 and CYP2C8 substrate. The risk of QTc prolongation increase with the concomitant use of other QTc prolonging agents.	If benefit outweighs risks it may be used in pregnant women.	[2,27,84]
Azithromycin	500 mg orally once daily on day 1, then 250 mg orally once daily on days 2-5.	It may be taken without regard to food.	No dosage adjustment necessary in renal impairment. Even though it is predominantly hepatically eliminated, there is no dosage adjustment provided in manufacturer's	Gastrointestinal symptoms. Hepatotoxicity	Baseline/follow-up ECG. Liver function tests, serum creatinin, potassium, magnesium.	If it is used with the QTc prolonging drugs such as hydroxychloroquine, the risk of QTc prolongation increase.	There is no certain recommendations for the use in pregnancy.	[27,90]

			labeling. It should be used with caution due to potential for hepatotoxicity					
Lopinavir/Ritonavir	400 mg/100 mg orally twice daily for 10-14 days.	Tablets may be taken with or without food; oral solution must be administered with food.	Dose adjustments are not necessary in renal or hepatic impairment. But it should be used with caution in hepatic impairment.	Nausea, vomiting, diarrhea. Pancreatitis, hepatotoxicity, cardiac conduction abnormalities.	HIV antigen/antibody testing at baseline. Liver function tests. Monitoring ECG may be considered when given with other QTc prolonging drugs.	Lopinavir: CYP3A4 inhibitor and substrate, Ritonavir CYP3A4 and CYP2D6 substrate and inhibitor. Thus, lopinavir/ritonavir has high drug-drug interaction potential.	The combination may be used in pregnant women. It is recommended avoiding use of oral solution in pregnancy because of the ethanol content.	[2,27,85]
Remdesivir	200 mg IV on day 1, then 100 mg IV daily on days 2-5 (or 10)	IV infusion over 30-120 minutes. Flushing line at least 30 mL normal saline after remdesivir infusion is recommended.	The use of remdesivir is not recommended in patients with eGFR<30 ml/min. The formulation contains cyclodextrin, and this excipient may accumulate in patients with kidney impairment. There are no dosage adjustments provided for patients with hepatic impairment, but it is recommended against use of remdesivir If ALT or AST is>5 times ULN.	Reversible elevations in serum transaminases, Renal injury, Gastrointestinal symptoms, Mild PT prolongation without INR change.	Renal and hepatic function Monitor for infusion reactions.	It has not significant effects on CYP enzymes. It is considered that strong induction of P-glycoprotein reduce remdesivir levels. Thus, the use of remdesivir with inducers of P-glycoprotein is not recommended.	Safety of remdesivir in pregnancy not known yet, so it is not recommended in pregnant women currently.	[2,27,86]
Favipiravir	1600 mg twice daily on day 1, then 600 mg twice daily for a total duration of 7 to 14 days.	Favipiravir tablets can be crushed or mixed with liquid.	There is limited data about dose adjustments in renal and hepatic impairment.	Diarrhea, nausea and vomiting, decreased appetite, hyperuricemia, decreased neutrophils, increased serum transaminases.	CBC, hepatic panel, the level of uric acid.	It is a CYP2C8 and aldehyde oxidase inhibitor and metabolized by aldehyde oxidase and xanthine oxidase.	The use of favipiravir in pregnancy is contraindicated.	[2,27,87]
Umifenovir	200 mg orally 3 times daily for no more than 10 days.	There is no specific recommendations about its administration. Its bioavailability is 40%.	Dosage adjustment in renal impairment is not necessary. There are no specific recommendations for hepatic impairment.	Gastrointestinal symptoms, increased transaminases, allergic reactions.	Hepatic panel.	It is metabolized by CYP3A4, so monitoring is recommended with concomitant use of strong inducers or inhibitors of CYP3A4.	It should not be used in children under the age of 2.	(2,21,27)
Tocilizumab	The first dose is 4-8 mg/kg. The recommended dose is 4 mg, diluted to 100 ml with 0.9% normal saline. In patients with unadequate response, additional dose can be administered after 12 hour. The maximum number	The dose is diluted to 100 ml with 0.9% normal saline. The infusion time should be more than 1 hour. It should not be infused with other agents in the same IV line.	No dosage adjustments necessary in mild and moderate renal impairment. It has not been studied in severe renal impairment. No dose adjustments recommended in hepatic	Elevations in serum transaminases, injection site reactions, infections, hematologic effects, infusion related reactions.	Liver function tests, trombocyte and neutrophil counts, monitor for infusion reactions and infections.	According to the in vitro data, IL-6 decrease the mRNA expression for several CYP450 isoenzymes.	It should not be used in pregnancy.	[2,27,46,88]

	of administration is two and maximum dose of single dose is 800 mg.		impairment. Initiation of therapy in patients with active hepatic disease or in rheumatoid arthritis and giant cell arteritis patients with baseline ALT or AST>1.5 x ULN is not recommended					
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Table 3. Nine candidate vaccines in phase 3 clinical trial for COVID-19

Platform	Type of candidate vaccine	Developer	Clinical Stage			
			Phase 1	Phase 1/2	Phase 2	Phase 3
Non-Replicating Viral Vector	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	ChiCTR2000030906 Study Report		ChiCTR2000031781 Study Report	NCT04526990
RNA	LNP-encapsulated mRNA	Moderna/NIAID	NCT04283461 Interim Report		NCT04405076	NCT04470427
Inactivated	Inactivated	Wuhan Institute of Biological Products/Sinopharm		ChiCTR2000031809 Interim Report		ChiCTR2000034780
Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm		ChiCTR2000032459		ChiCTR2000034780
Inactivated	Inactivated	Sinovac		NCT04383574 NCT04352608		NCT04456595 669/UN6.KEP/EC/2020
Non-Replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca		PACTR202006922165132 2020-001072-15 Interim Report	2020-001228-32	ISRCTN89951424 NCT04516746
RNA	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer		2020-001038-36 ChiCTR2000034825 Study Report		NCT04368728
Non-Replicating Viral Vector	Adeno-based (rAd26-S+rAd5-S)	Gamaleya Research Institute	NCT04436471 NCT04437875			NCT04530396
Non-Replicating Viral Vector	Ad26COV S1	Janssen Pharmaceutical Companies		NCT04436276		NCT04505722 (not yet recruiting)

Inc: Incorporated, LNP: Lipid nanoparticle, NIAID: The National Institute of Allergy and Infectious Diseases

Abbreviation

COVID-19: Coronavirus Disease-2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; ACE: Angiotensin Converting Enzyme; NIH: National Institutes of Health; WHO: World Health Organization; FDA: Food and Drug Administration; CDC: Centers for Disease Control and Prevention; IDSA: Infectious Diseases Society of America; ARDS: Acute Respiratory Distress Syndrome; NSAIDs: Non-steroidal Anti-inflammatory Drugs; LMWH: Low Molecular Weight Heparin; UFH; Unfractionated Heparin.

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Availability of data and materials

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Authors' contributions

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writing, reviewing, editing, and approving the manuscript in its final form. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

We conducted the research following the Declaration of Helsinki. However, Review Articles need no ethics committee approval.

Consent for publication

Not applicable

Competing interest

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