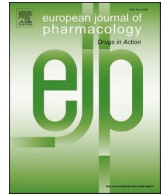




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## A review of medications used to control and improve the signs and symptoms of COVID-19 patients

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### ABSTRACT

In December 2019, an unprecedented outbreak of pneumonia associated with a novel coronavirus disease 2019 (COVID-19) emerged in Wuhan City, Hubei province, China. The virus that caused the disease was officially named by the World Health Organization (WHO) as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to the high transmission rate of SARS-CoV-2, it became a global pandemic and public health emergency within few months. Since SARS-CoV-2 is genetically 80% homologous with the SARS-CoVs family, it is hypothesized that medications developed for the treatment of SARS-CoVs may be useful in the control and management of SARS-CoV-2. In this regard, some medication being tested in clinical trials and in vitro studies include anti-viral RNA polymerase inhibitors, HIV-protease inhibitors, anti-inflammatory agents, angiotensin converting enzyme type 2 (ACE 2) blockers, and some other novel medications. In this communication, we reviewed the general characteristics of medications, medical usage, mechanism of action, as well as SARS-CoV-2 related trials.

### 1. Introduction

COVID-19 is an emerging infection caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Cao et al., 2020). The virus was first detected in Wuhan, China, in December 2019, and soon affected a large number of people (Cao et al., 2020; Lian et al., 2020). The official total number of infected cases in China on April 15, 2020, reached 82,295, with 3342 deaths (Azman and Luquero, 2020). Since then, the virus has spread rapidly to other parts of the world, with a total of 23,130,443 infected cases and 803,374 deaths worldwide by August 22, 2020, 08:04 GMT (Khairat et al., 2020).

Given the unknown biology of the virus and its high rate of

transmission, there has been a concerted global effort to understand the various pathological dimensions of the disease (Shereen et al., 2020). This include isolation of the virus, identification of its genetic sequence, and the search for appropriate pharmaceutical treatment options (Feng Tan, 2020).

Other similar human coronaviruses previously identified in the last two decades are the Middle East Respiratory Syndrome Virus (MERS-CoV, 2015) and SARS-CoV (2003) (Rabaan et al., 2020). The SARS-CoV was transmitted from an unknown host, perhaps a bat, to a civet cat, and then to a human, the first victim of which was reported in China (Kuehn, 2013; Lu et al., 2015). These viruses target the lower respiratory system first by attaching to the pulmonary epithelial cells, and then delivering

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their nucleocapsid and stealing the cellular machinery to replicate in the cytoplasm (Lung et al., 2020). The virus also affects other organs including the gastrointestinal tract (Gu et al., 2020), the brain (Wu et al., 2020), the kidney (Cheng et al., 2020), the liver (Fan et al., 2020) and the heart (Tan and Aboulhosn, 2020).

Genetically, SARS-CoV and SARS-CoV-2 are 80% homologous (Yi et al., 2020) and they both belong to the Coronaviridae family with characteristic enveloped single-stranded and positive-strand ribonucleic acid (RNA) structure (Ciotti et al., 2020).

The SARS family contains 14 binding amino acids residues, out of which 8 amino acids are specifically conserved for SARS-CoV-2. On this basis, it is believed that drugs used in the management of SARS-CoV patients may be somewhat effective in the management and treatment of COVID-19 patients. Hence, the main focus of COVID-19 therapy has so far been based on drug repurposing strategy (Chatterjee et al., 2020).

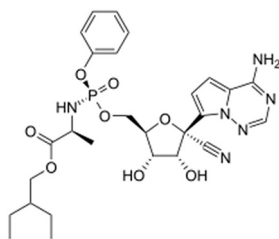
The SARS-CoV-2 replication cycle involves are six steps: viral entrance, replication machinery translation, replication, structural proteins translation, virion assembly and release. SARS-CoV-2 attaches to host cells via plasma membrane fusion and for this angiotensin-converting enzyme 2 (ACE2) is known to serve as a virion receptor. Some inhibitors such as griffithsin prevent the virus entry via binding to the receptor glycoproteins. SARS-CoV-2 can also be taken up into endosomes based on activation of spike proteins by cathepsin L. Lyso-somotropic agents such as bafilomycin A1 or ammonium chloride which block the pH dependent cysteine protease could limit viral entry. Also, some the transmembrane serine protease 2 (TMPRSS2) which activates the spike proteins can be targeted by anti-TMPRSS2 antibody (Hoffmann et al., 2020; Shirato et al., 2018). In the translation step, RNA-dependent RNA polymerase play an important role and can be targeted by drugs such as favipiravir. Furthermore, the virus RNA replication which is mediated by the kinase signaling pathway could be inhibited by saracatinib (Lin et al., 2017; Shin et al., 2018). RNA-dependent RNA polymerase accounts for RNA replication of S1, S2, envelope and membrane structural proteins, and the RNAs translated by ribosomes on endoplasmic reticulum cytosolic surface. Then, nucleocapsids from genomic RNA, remain in the cytoplasm and fuse with virion precursor to be transported to the cell surface from the ER through the Golgi Apparatus in small vesicles. Virions are then released to infect other cells and induce the host inflammatory response (McKimm-Breschkin, 2013).

To date, the drugs used for COVID-19 include anti-viral RNA polymerase inhibitors (Shah et al., 2020), HIV-protease inhibitors (Adepoju, 2020), anti-inflammatory agents (Russell et al., 2020), angiotensin converting enzyme type 2 (ACE 2) blockers (Yang and Meng, 2020), convalescent plasma (Roback and Guarner, 2020), RNA antisense technologies (Xu et al., 2020), monoclonal antibodies (Shanmugaraj et al., 2020) and Chinese traditional medicines (Li et al., 2020b).

## 2. RNA polymerase inhibitors

### 2.1. Remdesivir

#### 2.1.1. Chemical structure



#### 2.1.2. Background

Remdesivir is an antiviral drug of the nucleotide analogs class

(Al-Tawfiq et al., 2020). It is an analogue of adenosine, which disrupt the RNA chain of virus and causes termination in pre-mature form (Shannon et al., 2020). The Gilead Sciences Company has been manufacturing it for treating Ebola virus and Marburg virus diseases (Grein et al., 2020). Subsequent researches have shown that the drug is effective against other single stranded RNA viruses (Gordon et al., 2020), including respiratory syncytial virus (Tchesnokov et al., 2019a), Junin virus (De Clercq, 2019), Lassa fever virus (Shannon et al., 2020), Nipah virus (Lo et al., 2019), Hendra virus (Ko et al., 2020), and the coronaviruses (including MERS (de Wit et al., 2020) and SARS viruses (Ko et al., 2020b)). Recent studies have been focusing on this drug to assess its effectiveness for SARS-CoV-2 infection. Based on its efficacy on patients infected with other coronaviruses (Agostini et al., 2018b), it was provided to physicians for treating an American patient (Snohomish County, Washington, 2020) infected with SARS-CoV-2 and also submitted to China for more investigations in different phases of clinical trials.

#### 2.1.3. Research

- SARS-CoV-2: The Gilead Company stated that remdesivir is already proven to be effective against SARS-CoV and MERS animal models. On this basis, in January 2020, the Company started to test it against SARS-CoV-2 in a small group of infected patients in collaboration with Chinese medical authorities (Grein et al., 2020).
- Veterinary applications: GS-441524, the active form of remdesivir, had been shown to be effective in coping with coronavirus caused feline infectious peritonitis. It has not been approved by FDA for this purpose, however, but has been available in social markets since 2019. It is claimed that a pill of the drug can eliminate feline coronavirus from infected cats (Pedersen et al., 2019).
- Ebola virus: Remdesivir was tested in clinical trials for its effects on West African Ebola Virus epidemic of 2013–2016. Then, it was administered in one patient who was in early stage of disease. The result of trials were promising. So, researchers conducted trials in emergency setting that started in 2018 up to the middle of 2019 when Congolese health officials noticed that monoclonal antibody treatments such as mAb114 and REGN-EB3 was more effective in infected patients with Ebola virus. However, its safety as anti-Ebola therapy has been approved (Warren et al., 2016).

#### 2.1.4. Mechanism of action

Remdesivir is a prodrug and its active form, GS-441524, is a metabolic byproduct. GS-441524 as an adenosine nucleotide analog disrupts the activity of RNA-dependent RNA polymerase and escape of viral exoribonuclease. It also causes RNA chain termination, mutation and decline in RNA production of virus. Ebola virus RNA-dependent RNA polymerase is suppressed by the drug via RNA chain termination. In 2018, a report published that mutations in mouse hepatitis virus RNA replicase causes partial resistance to remdesivir, however, these mutations make the viruses less effective in pathogenicity (Agostini et al., 2018a; Tchesnokov et al., 2019b).

#### 2.1.5. Trials

Remdesivir had been administrated in a 35 years old male patient who was diagnosed with COVID-19 in Snohomish County, Washington. The patient suffered from developing pneumonia and persistent fever on seventh day of hospitalization. The next day after therapy, the patient showed clinical improvement with negative oropharyngeal swab, although nasopharyngeal swab persist positive. There was no side effect of remdesivir administration for this patient (Jacobs et al., 2016). Also, previous case reports on the treatment of other viruses by remdesivir declare no side effects (Dörnemann et al., 2017). Remdesivir had been prescribed for the first 12 patients in the United States (Kujawski et al., 2020). All of them complained of transient gastrointestinal symptoms and their laboratory tests showed aminotransferase elevation. Also,

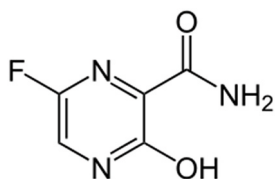
there are ongoing clinical trials in China and United States. Two trials have been registered in China that implemented on severe disease and mild-moderate disease. Also, the Gilead Company gave the drug (eIND) to hospitalized and under mechanical ventilation patients with confirmed SARS-CoV-2 infection. Exclusion criteria for this compensation include multi-organ failure, receiving vasopressors for hypotension, liver disease defined as ALT >5 x ULN, or renal impairment defined as CrCl <30 ml/min or receiving dialysis or continuous veno-venous hemofiltration. Clinical trials and in vitro studies suggested that remdesivir is an effective drug for the treatment of infected patient with SARS-CoV-2. The results of the Gilead trial showed that 5-day treatment with remdesivir could lead to significant improvement in the clinical signs and symptoms of SARS-CoV-2 patients when compared with standard care treatment alone. Remdesivir generally was tolerable in the treatment groups and the most adverse effects were nausea, diarrhea and headache.

Four clinical trials are also enrolling patients in the United States. The first trial (NCT04302766) is implementing enrollment on Department of Defense-affiliated staff who suffered from SARS-CoV-2 infection. The detail of inclusion and exclusion criteria as well as primary outcome is not available. The second trial (NCT04292899) is a phase III trial that compare the effectiveness of remdesivir in the 5th and 10th day of administration in severely ill patients with SARS-CoV-2 infection.

They defined their primary outcome as proportion of normalized fever patients and oxygen saturation at the 14th day of the study. The third trial (NCT04292730) is also a phase III trial that compare the standard care of moderate SARS-CoV-2 infected patients on the 5th and 10th day of treatment with remdesivir. The inclusion and exclusion criteria for this trial are same as NCT04292899. The primary outcome defines the proportion of discharged patients up to the 14th day of hospitalization. The fourth trial (NCT04280705) is a placebo-controlled clinical trial. The primary outcome define as percentage of subjects reporting each severity rating by day 15 (death, hospitalized/ventilated or ECMO, hospitalized/HFNC, hospitalized/on O<sub>2</sub>, hospitalized/not on O<sub>2</sub>, not hospitalized/limited activity, not hospitalized/no limitations).

## 2.2. Favipiravir

### 2.2.1. Chemical structure



### 2.2.2. Background

Favipiravir is an antiviral drug and also known as T-705, Avigan, Favipira and Favilavir. With activity against RNA viruses, it is being developed by Toyama Chemical (Japan) (Du and Chen, 2020; Shiraki and Daikoku, 2020). It is a derivative of pyrazinecarboxamide as well as other antiviral drugs including T-1105 and T-1106 (Zhu et al., 2018). Experimental studies had shown that favipiravir was effective against influenza viruses (Pascua et al., 2019), yellow fever virus (Furuta et al., 2013), foot and mouth disease virus (Furuta et al., 2009b), West Nile virus (Escribano-Romero et al., 2017), arenaviruses (Veliziotis et al., 2020), bunyaviruses (Scharton et al., 2014) and alphaviruses (Delang et al., 2014), enteroviruses (Furuta et al., 2013), Rift Valley fever (Borrego et al., 2019) and other flaviviruses (Segura Guerrero et al., 2018).

### 2.2.3. Research

- Ebola virus: Some experimental studies are suggesting that favipiravir may be helpful for treating Ebola virus infected patients (Madelain et al., 2020). Its efficacy on Ebola infection in human is however not very clear (Bixler et al., 2018). During west Africa Ebola virus outbreak, one study reported that favipiravir was effective in improvement of an Ebola infected nurse (Trompiz et al., 2014). The results of a clinical trial that was conducted in Guéckédou, Guinea (December 2014) showed a decline in mortality rate in Ebola infected patients in low to moderate levels of the disease but with no effect on severe form (Fink, 2015; Grobusch-mp, 2015).
- SARS-CoV-2: Since February 2020, favipiravir has been studied in drug repurposing program for the treatment of SARS-CoV-2 pandemic (Li and De Clercq, 2020). The results showed that favipiravir seemed to be effective in improvement of COVID-19 patients (March 2020, Wuhan and Shenzhen, China). Then, one study conducted to compare favipiravir with lopinavir and found that it made reduction in viral clearance time to four days when compared to control group (eleven days) and improvement in CT scans result (Cai et al., 2020).

### 2.2.4. Mechanism of action

Favipiravir is a selective viral RNA-dependent RNA polymerase inhibitor. Some studies demonstrated that favipiravir induces transcription mutations in RNA and lead to a lethal phenotype of virus. The active form of favipiravir, favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP), which is a metabolic byproduct, is also available as oral and intravenous formulations. Studies demonstrated that hypoxanthine guanine phosphoribosyltransferase (HGPRT) plays a key role in its activation. Also, it had been shown that favipiravir neither suppress the synthesis of RNA or DNA in mammalian cells, nor is toxic to them. Favipiravir was approved in Japan (2014) for its ability in coping with influenza pandemic. However, other studies did not support its effectiveness in human airway cells and this led to doubts about its effectiveness against influenza infections (Baranovich et al., 2013; Furuta et al., 2009a; Guedj et al., 2018; Jin et al., 2013; Naesens et al., 2013; Smeets et al., 2009; Yoon et al., 2018).

### 2.2.5. Trials

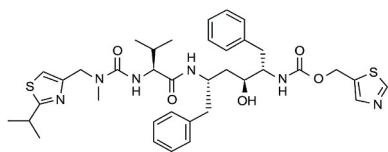
Favipiravir was approved by China officials for the treatment of influenza on March 2020. Then, the drug was approved for use against SARS-CoV-2 infection in clinical trials (Baden and Rubin, 2020). The first trial (NCT04310228) is a multicenter randomized trial that combines favipiravir (3200 mg/day) with tocilizumab (400 mg/day) and assesses the efficacy of the drug combination when compared with individual drugs alone. The primary outcome is defined as clinically cure rate. The second trial (NCT04336904) is a phase III clinical trial that was designed for evaluation of favipiravir safety in moderate type of SARS-CoV-2 infection. The third trial (NCT04303299) has similar design. The results of the investigations on 80 SARS-CoV-2 infected patients showed that favipiravir is the most potent antiviral agents when compared to other drugs in this group, and was without significant adverse effects on treated patients (Dong et al., 2020).

## 3. Protease inhibitors

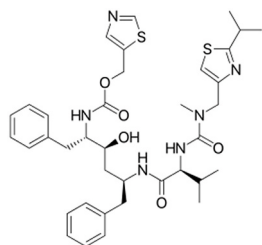
### 3.1. Lopinavir/ritonavir

#### 3.1.1. Chemical structure

##### 3.1.1.1. Ritonavir



### 3.1.1.2. Lopinavir



### 3.1.2. Background

Lopinavir/Ritonavir is an antiretroviral drug combination used to treat HIV/AIDS. Often ritonavir low dose is used as a part of highly active antiretroviral therapy. Lopinavir inhibit SARS-CoV replication via suppressing the main viral protease (Cao et al., 2020). Chu et al., investigated the effects of lopinavir (4 mg/ml) and ribavirin (50 mg/ml) on SARS-CoV (Chu et al., 2004). They found that ribavirin along with lopinavir have more anti-retroviral effects on SARS-CoV when compared to each drug alone. They used combination lopinavir/ritonavir, ribavirin, and corticosteroids for SARS-CoV infected patients without acute respiratory distress syndrome (ARDS). Patients who received lopinavir/ritonavir were compared with patients receiving ribavirin and corticosteroids. The first group showed significant reduction in ARDS development or death at the 21st day of the medication. Another study in the same center showed significant reduction in intubation, steroid use and mortality in patients administered lopinavir/ritonavir when compared to patients not receiving the treatment. The result showed that lopinavir/ritonavir combination was beneficial when administered at the time of SARS-CoV infection diagnosis (Que et al., 2003). Also, one study showed that lopinavir had antiviral activity against SARS-CoV in vitro with the half maximal effective concentration in Vero E6 cells was close to that found in the serum of HIV-infected patients (Sheahan et al., 2020). A clinical trial evaluated the effects lopinavir/ritonavir in addition to interferon- $\beta$  against MERS-CoV infected patients and showed no significant differences when compared to lopinavir/ritonavir alone (Chan et al., 2015). In vitro studies further showed that lopinavir/ritonavir plus interferon- $\beta$  did not have significant effects on virus titer and lung status in MERS-CoV infected mice (Sheahan et al., 2020a). Animal studies found that lopinavir/ritonavir had beneficial effects on pathological and clinical features of MERS-CoV infection. Also, it is used for hepatitis C treatment (Molto et al., 2007). Some of the reported side effects include gastrointestinal problems (nausea, vomiting, and diarrhea), loss of appetite, and in some serious cases, allergic reactions, arrhythmias, pancreatitis, and liver problems (Bongiovanni et al., 2004).

### 3.1.3. Research

- HIV/AIDS: Ritonavir is the second FDA approved drug for the treatment of HIV. It was originally designed to suppress HIV protease. Mechanistic studies found that ritonavir also inhibits CYP3A4 which is now known as the main mechanism of the drug's action. Currently, it is used in the treatment of HIV in a co-administration program of anti-retroviral drugs (Clevenbergh et al., 2002; Walmsley et al., 2002).
- SARS-CoV-2: Even though there is no in vitro study that proved the efficacy of lopinavir/ritonavir for SARS-CoV-2, the persuasive results

of studies on lopinavir/ritonavir effects on SARS-CoV and MERS-CoV led to the lopinavir/ritonavir consideration in SARS-CoV-2 treatment in China. The prescribed doses for adult and adolescent are 400 mg/day and 10 mg/kg body weight for no more than 10 days (Lim et al., 2020).

### 3.1.4. Mechanism of action

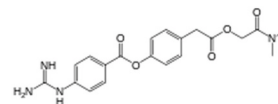
Ritonavir is one the pseudo-C2-symmetric small molecule inhibitors family and act as a HIV protease inhibitor. Ritonavir specifically inhibits a metabolic enzyme, cytochrome P450-3A4 (CYP3A4). Mainly expressed in the intestine and liver, CYP3A4 metabolizes and removes protease inhibitors and xenobiotics (small and foreign molecules same as drugs or toxins) from the body. Ritonavir binds to CYP3A4 and inhibits it leading to a decrease in antiretroviral break down and increase in other antiretroviral drugs bioavailability and their serum levels (Zeldin and Petruschke, 2004).

### 3.1.5. Trials

One study reported the status of 6 infected patients with SARS-CoV-2 in Korea and China (Xu et al., 2020). The result showed that lopinavir/ritonavir led to a decrease in virus titer and improved clinical symptoms. Another study by Young et al., was based on 18 patients (Young et al., 2020): 5 patients received lopinavir/ritonavir alone, of which 3 patients experienced mechanical ventilation requirement reduction and 2 patients had viral titer clearance. Four patients had serious complications however. Another report in China showed patients' general information who administered lopinavir/ritonavir with other adjuvant therapies, but they did not mention the patients' clinical status. Cao et al., also implemented a clinical trial to compare the lopinavir/ritonavir 800/200 mg/day with other SARS-CoV-2 infected patients under standard care (Cao et al., 2020). The result showed no significant difference in clinical features, viral load and mortality rate of the two groups. Interpretation of the study results is difficult due to trials variation in medication type, medications initiation, different levels of disease severity and lack of control groups for comparison.

## 3.2. Camostat

### 3.2.1. Chemical structure



### 3.2.2. Background

Camostat is a serine protease inhibitor. Since serine protease enzymes play a variety of roles in the body, camostat has a diverse range of uses. Camostat was recognized as a protease inhibitor in the 1980s (Japan) and due to most of the data on it have been published in Japanese, very little information is available outside Japan. In Japan, camostat is used for chronic pancreatitis since 1985 in a dose of 600 mg/day. It has also been used in the treatment of postoperative reflux esophagitis since 1994 in a dose of 300 mg/day. In a trial with 900 mg/day, camostat showed edema and urticaria as side effects, while camostat therapy at a dose of 600 mg/day showed no significant side effects (Uno, 2020).

### 3.2.3. Mechanism of action

Camostat mesilate is a TMPRSS2 inhibitor that suppress the SARS-CoV spread and pathogenesis in an infected mouse model. Studies also showed that SARS-CoV-2 needs TMPRSS2 for entry into host cells (Bittmann et al., 2020). In one study using SARS-CoV-2 isolated from infected patient, Camostat was shown to block the virus entry into lung cells (Bittmann et al., 2020).

### 3.2.4. Research

Camostat is used in the treatment of some cancers. Some studies also showed that camostat is effective against viral infections in addition to inhibiting fibrosis in the liver or kidney diseases or pancreatitis (Midgley et al., 1994; Okuno et al., 2001).

### 3.2.5. Trials

There are six clinical trials in phase I and II stages. One of these trials is designed to investigate the camostat mesylate effects on SARS-CoV-2 associated coagulopathy, myocardial injury, duration of hypoxia or intubation the length of intensive care unit and hospital stay, and mortality rates (NCT04435015). Another trial has been designed to assess the effects of combination therapy of hydroxychloroquine and camostat (Foipan) on clinical features and improvement of SARS-CoV-2 infected patients (NCT04338906). Other trials are designed to evaluate the effects of camostat on SARS-CoV-2 replication in early stages (NCT04353284), patients improvement (NCT04321096), safety and tolerance evaluation of combination of camostat and hydroxychloroquine, and to compare with hydroxychloroquine combined with azithromycin (NCT04355052) and treatment of infected patients (NCT04374019).

## 4. Anti-inflammatory agents

### 4.1. Anti-interleukin 6 (IL-6) agents (tocilizumab)

#### 4.1.1. Chemical structure



#### 4.1.2. Background

Interleukin-6 is an inflammatory cytokine secreted by monocytes and macrophages. Increased levels of IL-6 leads to inflammatory diseases such as cytokine-release syndrome. So, anti-IL-6 agents are helpful in the treatment of inflammatory diseases such as rheumatoid arthritis. Tocilizumab is the first approved drug in this class and first used in treatment of large-cell lung carcinoma. In vivo and in vitro studies demonstrated that tocilizumab could reduce tumor growth in ovarian cancer (De Luna et al., 2020; Mihai et al., 2020).

#### 4.1.3. Research

- Cancer: Anti-IL6 drugs such as tocilizumab had been tested in patients with ovarian cancer. Anti-IL-6 antibody reduced IL-6 signaling in cell culture and animal models of the disease. But, there is no favorable effect of medication in a phase II clinical trial on patient with severe form of ovarian cancer. Recent studies showed that anti-IL6 agent's administration resulted in suppression of the signal transducer and activator of transcription and led to activation of the epidermal growth factor receptor pathway. Inhibition of this pathway results in improvement in cancer patients (Ando et al., 2014; Tanaka et al., 2018).
- SARS-CoV-2: Hyperinflammatory states such as elevated serum levels of IL-6, has been shown in severe SARS-CoV-2 infection and leads to increased mortality in patients. National Health Commission of China planned to use tocilizumab in the treatment of SARS-CoV-2

infected patients. China approved tocilizumab for its anti-inflammatory effects in March 2020, however there is no data on its effectiveness or detail due to only 21 patients had been used in the study (Bennardo et al., 2020; Cellina et al., 2020; De Luna et al., 2020; Luo et al., 2020; Michot et al., 2020; Mihai et al., 2020; Zhang et al., 2020a, 2020c).

#### 4.1.4. Mechanism of action

Tocilizumab as an anti-IL-6 receptor monoclonal antibody binds to both soluble and membrane-bound IL-6 receptors, and suppress the IL-6 associated pathways (Jones et al., 2010).

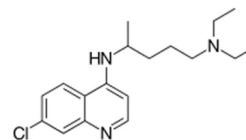
#### 4.1.5. Trials

One study employed 21 patients who were first under standard care program for a week and then under tocilizumab administration. At the end of the first week of standard care program, the IL-6 serum levels were  $132.38 \pm 278.54$  pg/ml (normal < 7 pg/ml). After administration of tocilizumab, the results showed significant improvement of fever, C-reactive protein, lung opacities and decrease in mechanical ventilation requirement. At present, tocilizumab is one the most important medication options for severe condition of SARS-CoV-2 infection with elevated IL-6 serum levels. According to the 7th edition of the National Health Commission of the People's Republic of China COVID-19 Diagnosis and Treatment Guide, the recommended dose is 4–8 mg/kg or 400 mg standard dose twice a day. There are currently 14 clinical trials on this drug all over the world the result of which is yet to be published (Jones et al., 2010). Another study with 89 patients showed lower mortality and rapid improvement in CRP and lymphocyte counts in addition to clinical indices (Formina et al., 2020).

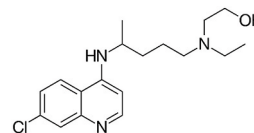
### 4.2. Chloroquine and hydroxychloroquine

#### 4.2.1. Chemical structure

##### 4.2.1.1. Chloroquine



##### 4.2.1.2. Hydroxychloroquine



#### 4.2.2. Background

Chloroquine is a 4-aminoquinoline class of drug and originally designed and used for the treatment of malaria. Also, it is used for amebiasis, rheumatoid arthritis, and lupus erythematosus due to its anti-inflammatory properties. At present, it is used for the treatment of SARS-CoV-2 infection. Chloroquine has some side effects including: appetite loss, muscle problems, skin rash, gastrointestinal problems, and in some cases serious side effects such as seizures, vision problems and muscle damages (Moore, 2020).

#### 4.2.3. Research

- SARS-CoV-2: There is some evidence of chloroquine use for SARS-CoV-2 infection. Earlier in vitro studies demonstrated that chloroquine had inhibitory effects on SARS-CoV and MERS-CoV at a dose of 1–8.8  $\mu$ M. In one in vitro study, Wang et al. showed that chloroquine

**Table 1**  
Under study medications for SARS-CoV-2 treatment.

Medication	Description
Allogeneic natural killer (NK) cells (Wang et al., 2020)	A novel FDA-approved drug in phase 1 and 2 trial, with activities of NK cells, such as some receptors activation that bind to viral antigens on cells that infected with virus. Trials number: NCT04323514, NCT04280224.
Amgen collaborating with Adaptive Biotechnologies (Prime)	Discovery/development of fully human neutralizing antibodies targeting SARS-CoV-2.
Anakinra (Wampler Muskardin, 2020)	Antagonist of IL-1 receptor that suppress cytokine storming. Trials number: NCT04339712, NCT04324021, NCT02735707, NCT04330638, NCT04341584.
Antibodies (Casadevall and Pirofski, 2020)	Isolated more than 500 antibodies from SARS-CoV-2 infected patients for improvement of patients.
Anti-SARS-CoV-2 polyclonal hyperimmune globulin (Walls et al., 2020)	Hypothesized the usefulness for severe infected patients.
Arbidol (Umifenovir) (Zhu et al., 2020)	Antiviral drug for SARS-CoV-2 treatment without available clinical trial data. Trials number: NCT04286503, NCT04260594, NCT04273763.
AT-001	Aldose reductase inhibitor found to protect against oxidative damages.
Aviptadil (Jahangir et al., 2020)	A synthetic peptide that acts as vasoactivator and inhibits inflammatory cytokine such as IL-6 production. Trials number: NCT04311697.
Baricitinib (Richardson et al., 2020)	Inhibitor of janus kinase family enzyme. Trials number: NCT04340232, NCT04320277, NCT04345289, NCT04321993.
Bevacizumab (Rosa and Santos, 2020)	A monoclonal antibody that is human specific and synthesized by genetic engineering. Bevacizumab prevents the binding of vascular endothelial growth factor (VEGF) association with Flt-1 and KDR receptors. Trials number: NCT04305106, NCT04344782, NCT04275414.
Brilacidin (Philippidis, 2020)	Defensin like agent that disrupts the pathogen membrane that results in cell death
CEL-SCI Corporation (Philippidis, 2020)	A type of immunotherapy by peptide technology of ligand antigen epitope presentation system for SARS-CoV-2 viral titer reduction.
CD24Fc (Jahangir et al., 2020)	A biological immunomodulator that reduces inflammatory cytokines. Trials number: NCT04317040.
CM4620-IE	An inhibitor of Calcium release-activated calcium channel and suppress the channel overactivation which can lead to pulmonary inflammatory complications. Trial number: NCT04345614.
Convalescent plasma (Syal, 2020)	Past studies found that convalescent plasma SARS-CoV, MERS-CoV, Ebola, and H1N1 influenza of infected patients who had recovered of infection were useful in prevention and treatment of infection. Effectiveness and safety of SARS-CoV infected patients' convalescent plasma is not clear yet. Trials number: NCT04345679, NCT04343755, NCT04342182, NCT04343261, NCT04333355, NCT04338360, NCT04345523, NCT04344535, NCT04344015, NCT04340050, NCT04332380, NCT04332835, NCT04327349, NCT04334876, NCT04292340, NCT04345289, NCT04333251, NCT04344977, NCT04342195, NCT04323800.
Corticosteroids (Kakodkar et al., 2020)	Steroid hormones excrete of adrenal cortex Trials number: NCT04345445, NCT04329650, NCT04273321, NCT04344288.
Darunavir/cobicistat (Spezzani et al., 2020)	HIV-1 protease inhibitor Trial numbers: NCT04252274.
Dexamethasone (Ledford, 2020)	Corticosteroid medication. Trial numbers: NCT04325061, NCT04395105, NCT04347980, NCT04344730.
Disulfiram (Dong et al., 2020)	A therapeutic agent that inhibits alcohol metabolism with demonstrated effects on SARS-CoVs proteases.
Eculizumab (Campbell and Kahwash, 2020)	Monoclonal IgG antibody of human that acts against membrane attack complex formation. Trial numbers: NCT04288713.
Galidesivir (BCX4430) (Elfiky, 2020b)	RNA polymerase inhibitor Nucleoside with antiviral activity that showed promising effects on Ebola and SARS-CoV.
Gimsilumab (Conigliaro et al., 2019)	Monoclonal antibody with anti-inflammatory effects against GM-CSF production and may have favorable effects in SARS-CoV-2 treatment.
Griffithsin (Li and De Clercq, 2020)	A protein derived of red algae with inhibitory effects on HIV action and SARS-CoV.
Ifenprodil (Engel Jr and Pitkänen, 2020)	N-methyl-d-aspartate receptor inhibitor and reduces inflammation.
Inhaled therapy	Inhaled formulation of dry powder for improvement of respiratory complications of SARS-CoV-2 infection.
Intranasal vazegepant	Inhibitor of Calcitonin gene-related peptide receptor and down regulate the inflammatory status.
Ivermectin (Patri and Fabbrocini, 2020)	Anti-parasite drug Trials number: NCT04343092.
IVIG (Alhazzani et al., 2020)	Intravenous immunoglobulin. Trials number: NCT04261426, NCT04264858, NCT04344977, NCT04324021, NCT04341116, NCT04333368.
Monoclonal antibodies (Shanmugaraj et al., 2020)	Trials numbers: NCT04341116, NCT04342195.
Nelfinavir (Adem et al., 2020)	Protease inhibitor of HIV
Niclosamide (Xu et al., 2020)	Bioavailable chlorinated salicylanilide, with anthelmintic and potential antineoplastic activity Trials number: NCT04345419
Nitazoxanide (Srivatsan Padmanabhan)	Antiviral agent Trials number: NCT04343248, NCT04345419, NCT04341493.
Nitric oxide (Ling et al., 2020)	Trials number: NCT04305457, NCT04337918, NCT04306393, NCT04312243, NCT03331445, NCT04285801, NCT04338828.
Oseltamivir (Velavan and Meyer, 2020)	Antiviral medication Trials number: NCT04255017, NCT04261270, NCT04303299, NCT04338698.
REGN3048 (Philippidis, 2020)	Human specific monoclonal antibody and effective in MERS-CoV treatment. Trials number: NCT03301090.
Ribavirin/interferon (Elfiky, 2020)	Antiviral agent against hepatitis C and some viral hemorrhagic fevers Trials number: NCT04276688.
Danoprevir/Ritonavir/Interferon (Yu et al., 2020)	Antiviral agent against HIV/AIDS Trials number: NCT04291729
Sarilumab (Clerkin et al., 2020)	IL-6 receptor inhibitor for rheumatoid arthritis treatment. Trials number: NCT04341870, NCT04327388, NCT04324073, NCT04345289, NCT04321993, NCT04322773.
Sofosbuvir (Elfiky, 2020b)	Antiviral drug against hepatitis C, SARS-CoV.
Statins (Driggin et al., 2020)	Cholesterol lowering drugs Trials number: NCT04343001.

(continued on next page)

Table 1 (continued)

Medication	Description
TAK-888 (Schilling, 2020)	SARS-CoV-2 antibody derived of infection recovered patients.
TZLS-501 (Philippidis, 2020)	Anti-IL6 receptor in human.
Vascular leakage therapy (Clerkin et al., 2020)	Affects the angiotensin-Tie2 pathway to improve endothelial function.
Virus Biotechnology and NIH (Baig et al., 2020)	Developing human monoclonal antibodies against SARS-CoV-2.
Vitamin C (Carr, 2020)	Trials number: NCT04323514, NCT04335084, NCT04344184, NCT04342728, NCT04334967, NCT04264533, NCT04328961, NCT04334512, NCT04326725, NCT03680274.
Vitamin D (McCartney and Byrne, 2020)	Trials number: NCT04335084, NCT04344041, NCT04326725, NCT04334005.
Xuebijing (Li et al., 2020a)	Chinese herbal medicine extract infusion formulation given at 100 ml IV twice daily, suggested as a “may consider” treatment for severe and critical cases in the National Health Commission of the People’s Republic of China: the COVID-19 Diagnosis and Treatment Guide, 7th Edition. This previously demonstrated improved mortality in patients with severe community acquired pneumonia in China.65

displayed an  $EC_{50}$  of 1.13  $\mu$ M at 48 h in Vero E6 cells against SARS-CoV-2 infection. These promising findings supported the oral use of 500 mg chloroquine twice a day during SARS-CoV-2 outbreak. Gao et al. reported that chloroquine phosphate may be useful in the management and treatment of SARS-CoV-2 infected patients, due to the improvement of pneumonia, lung imaging findings, virus titer, and decline of disease course in more than 100 patients with SARS-CoV-2 infection. Also, no adverse event was reported in the study. Further studies reported that hydroxychloroquine (hydroxychloroquine is hydroxylated compound of chloroquine) have better acceptability than chloroquine. One study by Biot et al., assessed and compared the hydroxychloroquine and chloroquine inhibitory activity against SARS-CoV. The results showed that chloroquine had better effect when compared to hydroxychloroquine with  $EC_{50}$  of  $6.5 \pm 3.2 \mu$ M and  $34 \pm 5 \mu$ M, respectively. Physiologically based pharmacokinetic modelling showed a loading dose of hydroxychloroquine as 400 mg (Biot et al., 2006; Yao et al., 2020).

#### 4.2.4. Mechanism of action

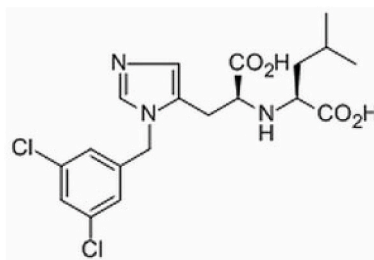
Antiviral effects of chloroquine may be related to its effects on endosomal and lysosomal pH. Since virus release needs low pH, chloroquine consumption leads to impaired endosomal or lysosomal virus release. So, the virus cannot release its genetic material into the cell and replicate (Fredericksen et al., 2002; Savarino et al., 2003).

#### 4.2.5. Trials

Gautret et al. reported the initial results of their study on 200 mg hydroxychloroquine three times a day administration in SARS-CoV-2 infected patients (20 hydroxychloroquine and 16 control) (Gautret et al., 2001). The results showed that hydroxychloroquine is significantly more effective to get rid of infection when compared to standard care protocol. Six patients also received a combination of hydroxychloroquine and azithromycin. The result showed that this combination is more effective than hydroxychloroquine alone. So, it seems that azithromycin may potentiate the effect of hydroxychloroquine against SARS-CoV-2 infection (Gautret et al., 2020). Gao et al., also reported significant improvement without adverse events for therapy with hydroxychloroquine (Gao et al., 2020). Another trial was conducted in Wuhan, China, on 62 patients with PCR-confirmed SARS-CoV-2 infection. Half of them were randomly assigned to receive 200 mg hydroxychloroquine sulfate orally and twice daily. The result showed that the time to clinical recovery was significantly reduced in hydroxychloroquine receiving group. Recently, some studies with inconsistent results were published. In a large population trial in hospitalized patients, emergency use of chloroquine and hydroxychloroquine showed no beneficial effects on mortality, clinical signs and recovery speed (Boulware et al., 2020). These controversial results made the US Food and Drug Administration (FDA) to withdraw the emergency use of chloroquine and hydroxychloroquine approve (Food and Administration, 2020).

## 5. Angiotensin converting enzyme type 2 (ACE 2) blockers

### 5.1. Chemical structure



### 5.2. Background

Angiotensin-converting enzyme 2 (ACE2) is a cell membrane’s attached enzyme of the lungs, arteries, heart, kidney, and intestines cells. ACE2 catalyses the angiotensin II hydrolysis into angiotensin (1–7). Recently, it was proven that ACE2 serves as the entry point into cells for some coronaviruses, including SARS-CoV, and SARS-CoV-2 (Zhang et al., 2020b).

### 5.3. Research and mechanism of action

- SARS-CoV-2: Several studies reported that SARS-CoV-2 entry into target cells utilise ACE2 receptors (Zhang et al., 2020b). There is also a significant correlation between SARS-CoV-2 infections with other co-morbidities including hypertension, cardiovascular disease, and diabetes (Yang et al., 2020). There is a hypothesis that medications that lead to increase in ACE2 expression could potentially increase susceptibility to SARS-CoV-2 infection. Also, ACE2 catalysis the conversion of angiotensin 2 to angiotensin 1-7 and vasodilates vessels and lowers angiotensin 2 receptor binding which leads to protect lungs from injury (Peng et al., 2005).

### 5.4. Trials

In a study by Vaduganathan et al., it was found that ACE2 administration in patients with lung injury may be beneficial in SARS-CoV-2 infected patients with stable condition, and the use of it for patients with comorbidities in not recommended. On the other hand, some studies suggested that ACEIs increases the gene expression of ACE2, and other experimental studies vice versa. There are two clinical trials employed to evaluate the safety and efficacy of losartan in SARS-CoV-2 infected patients (Vaduganathan et al., 2020).

## 6. Other medications

Other potential medications for SARS-CoV-2 infection are listed in



Table 1.

## 7. Conclusion

Medicinal management of SARS-CoV-2 infected patients is conducting to control and treat infection and prevention of progression to critical illness. Each medication listed in the present review has beneficial effects along with some adverse effects and the results remain inconclusive due to daily changes in outcome. Due to the rapid progression of the disease and an increase in viral load, the authors suggest that rapid initiation of medication will be useful in high-risk patients. However, there is a concern about the unclear adverse effects of medications. In this regard, clinicians must follow releasing literature. So, authors suggest that clinicians and institutions release their experiences of treatment of COVID-19 to the medical community.

## Author contributions

All authors contributed equally to this work.

## Declaration of competing interest

The authors state that there are no disclosures associated with this study.

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