Review Article

Antiviral treatment of COVID-19: a clinical pharmacology narrative review

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ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) in December 2019 in China, has become a pandemic in March 2020. Repurposing old and relatively safe drugs becomes an advantageous option to obtain the urgently needed effective treatment. Repurposing chloroquine, hydroxychloroquine, oseltamivir, lopinavir/ritonavir, and favipiravir, and the use of investigational drug remdesivir for treatment of COVID-19, are reviewed from the clinical pharmacology perspective, particularly its efficacy and safety. Limited clinical studies of chloroquine, hydroxychloroquine, favipiravir, and remdesivir showed some efficacy in COVID-19 treatment with tolerable adverse effects. Potential serious adverse effect of chloroquine and hydroxychloroquine is cardiac arrhythmia. Oseltamivir has no documented activity against SARS-CoV-2, while lopinavir/ritonavir showed limited efficacy in COVID-19. Currently, there is no sufficient evidence to recommend any specific anti-COVID-19 treatment. The decision to use these drugs during the COVID-19 pandemic must be based on careful consideration of the potential benefits and risks to the patient.

KEYWORDS COVID-19, favipiravir, hydroxychloroquine, lopinavir, oseltamivir, remdesivir

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new strain of coronavirus that causes acute respiratory infections known as coronavirus disease 2019 (COVID-19).[1] SARS-CoV-2 is a positive-sense, single-stranded RNA virus belongs to the genus *Betacoronavirus* with ~79% similarity with SARS-CoV, and ~50% similarity with Middle East respiratory syndrome corona virus (MERS-CoV).[1] The virus first emerged in December 2019 in Wuhan, China, and on March 11, 2020 World Health Organization (WHO) declared COVID-19 as a pandemic.[1,2] The clinical manifestations of COVID-19 vary; most have mild and self-limiting airway disorders (81%), but a small proportion of patients (5%), generally those with a decreased immune system, are elderly, or have certain comorbidities, can experience progressive severe pneumonia, multiple organ failure, and death.[3]

Up until now, there has been no specific treatment for COVID-19.[3] Several old drugs that have been used for other indications, or new drugs that are still under trials, are being studied in various parts of the world. The gold standard to determine the efficacy and safety of a drug is a good quality randomized controlled

trial (RCT). However, in the context of an outbreak, performing RCT is quite challenging; a randomization process to determine who receives or not receives the experimental drugs might not be acceptable by the severely ill patients. As of this writing, reports on the results of RCTs of drugs used for COVID-19 are limited. Most of the research are still ongoing. The efficacy and safety of several drugs are obtained from preliminary tests on a small number of patients, some with an open-label and non-randomized designs. Since robust data on the efficacy and safety of the drugs used for management of COVID-19 are still lacking, medical associations construct treatment recommendations for patients with COVID-19 that may vary between countries. Clinical pharmacology deals with the use of medicines in humans. It is underpinned by the basic science of pharmacology, with added focus on the implementation of pharmacological principles and methods in humans. The aim is to improve patient's care by promoting safe and effective use of medicines, and assessing the efficacy and safety of new medications. In this article, we aimed to review the clinical pharmacological aspects, namely, the mechanism of actions, pharmacokinetics, safety profile (adverse drug reactions, precautions, and potential drug-drug interactions), as well as the efficacy of several potential antivirals for treatment of COVID-19.

SARS-CoV-2: life cycle and potential drug's site of actions

SARS-CoV-2 is a *Betacoronavirus* that belongs to the Coronaviridae family of the order Nidovirales. It is a single-stranded RNA virus that has at least four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). SARS-CoV attachment to the host cell is initiated by interactions between the S protein and its receptor, the angiotensin-converting enzyme 2 (ACE2).[4] Then, an-acid-dependent cleavage of S protein by type II transmembrane serine protease, followed by fusion of the viral and the host cellular membrane (generally occurs within acidified endosomes), enables the virus to gain access to the cell cytosol. Inside the host cell, viral polyproteins are synthesized, and further encode the replicase-transcriptase complex. By utilizing its RNA-dependent RNA polymerase (RdRp), the virus synthesizes its RNA. Structural proteins are then synthesized, followed by assembly and release of the new viral particles.[4] Potential antiviral targets the steps of the viral life cycle (Figure 1). The clinical pharmacology characteristics of several potential antivirals used in COVID-19 are summarized in Table 1.
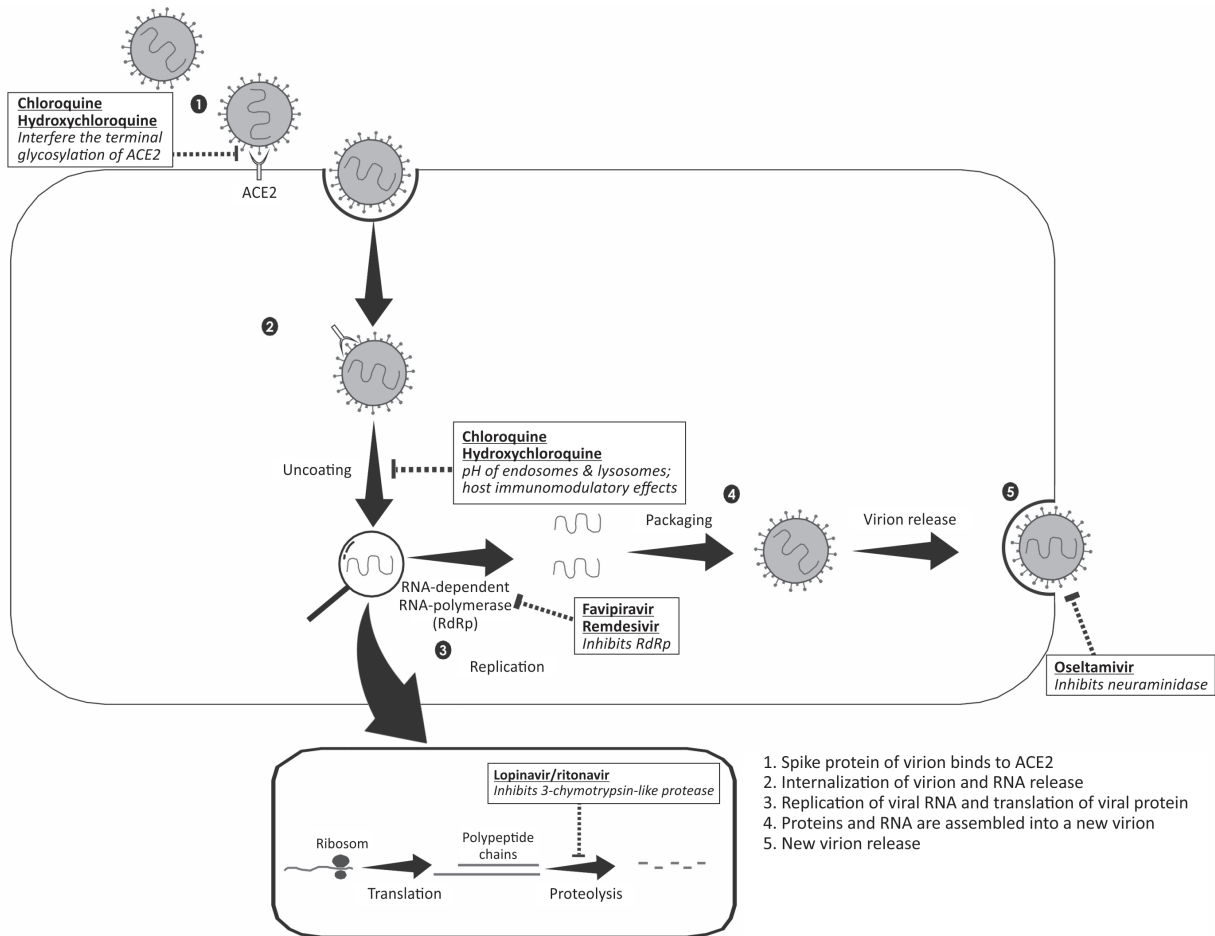
Chloroquine

Chloroquine, a synthetic 4-aminoquinoline, has been known since 1934 as an effective, antimalarial substitute of quinine.[5] Characteristics of chloroquine as an antimalarial are well known, but data about their efficacy and safety for the treatment of COVID-19 is limited. In Indonesia, chloroquine is no longer recommended as the first-line antimalarial drug due to widespread resistance problems. Currently, chloroquine is also used in the management of autoimmune diseases such as rheumatoid arthritis and lupus erythematosus.[5] Many *in vitro* studies have shown that chloroquine has the potential of broad-spectrum antiviral activity, including SARS-CoV.[6,7]

• **Mechanism of action**

Chloroquine elevates the endosomal pH, thus, interferes with the viral-host cell fusion that needs acidic environment. It inhibits the glycosylation of cellular receptors of SARS-CoV, the ACE2.[6,7] Chloroquine effectively reduces the number of infected cells on primate (Vero E6) cell culture infected with SARS-CoV.[6] The inhibition of SARS-CoV infection occurred in the presence of 1–10 µM chloroquine, which are plasma concentrations achievable during the prophylaxis and treatment of malaria (varies between 1.6 to 2.5 µM), hence are well tolerated by patients.[6] In Vero E6 cell culture infected with the SARS-CoV-2, the 90% effective concentrations (EC_{90}) of chloroquine was reported to be 6.90 µM.[7]

• **Pharmacokinetics**

Chloroquine is well absorbed in oral administration and widely distributed into tissues, including the liver, spleen, kidney, lungs, also to the brain and spinal cord. Sixty percent of chloroquine is bound to plasma protein. The peak level is reached within 3–5 hours. Chloroquine is metabolized to the active metabolites of desethylchloroquine and bis-desethylchloroquine by the cytochrome P450 2C8 (CYP2C8), CYP2D6, and CYP3A4 enzymes. Chloroquine (±50%) and its metabolites are excreted in the urine. Chloroquine half-life is long, from several days to weeks, with the terminal half-life ranges from 30 to 60 days.

Figure 1. The schematic life cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and targets of selected potential antiviral drugs

- **Adverse drug reactions**

Chloroquine safety profile is obtained mainly from its use as an antimalarial drug. The drug is safe when administered according to the recommended regimen. However, its margin of safety is narrow, a single-dose of 30 mg/kg body weight (BW) may lead to death.[5] Acute adverse effects are more common when chloroquine is administered too fast by the parenteral route. Cardiovascular adverse effects include hypotension, vasodilation, myocardial dysfunction, arrhythmia, and cardiac arrest. Overdose may cause central nervous system effects such as confusion, convulsions, and coma. Ototoxicity and retinopathy mostly occur in long-term use (at the use of daily doses >250 mg, with cumulative doses of more than 1 g/kgBW).[5]

Chloroquine should be used with caution in patients with hypoglycemia or diabetes mellitus. Life-threatening hypoglycemia may occur in patients with or without antidiabetic medications.[5] Moreover, chloroquine can cause cardiac arrhythmias due to

prolongation of the QT interval. Caution must be given when it was administered to other drugs with the potential to cause prolongation of the QT interval, such as some antibiotics (macrolides and quinolone), antiarrhytmics (amiodarone and quinidine), antidepressants (amitryptyline and sertraline), and antiemetics (ondansetron and metocloperamide).[5]

- **Clinical study of chloroquine in COVID-19**

Until recently, there has been no clinical research article publication related to chloroquine use in COVID-19. Published articles are mostly in the form of narrative, editorial, expert consensus, for which clinical trial data cannot be accessed. Various RCTs to demonstrate the efficacy and safety of chloroquine use in COVID-19 are still ongoing.[8]

Gao et al[9] reported in a narrative letter that based on data from more than 100 patients included in multicenter clinical trials conducted in China, chloroquine phosphate shows a superiority compared to a control treatment in inhibiting the

Table 1. Pharmacology of selected potential antiviral in COVID-19

Agent	Adult dose	Adverse reactions	Precautions	Contraindications	Special population	Drug-drug interactions
CQ phosphate[5–10]	500 mg CQ (300 mg base) every 12 to 24 hours, 5 to 10 days depends on severity	Gastrointestinal: nausea, vomiting, abdominal discomfort. Cardiovascular: hypotension, cardiomyopathy, cardiac arrhythmia, cardiac arrest, ECG changes (including prolonged QRS and QTc intervals), Torsade de Pointes. CNS: confusion, convulsion. Hematology: bone marrow supression, hemolysis (rare). Others: pruritus, hypoglycemia, myopathy, retinal toxicity, and hepatic & renal toxicity. Monitoring: Hematology: full blood count, serum electrolytes, blood glucose, renal function. Cardiovascular: ECG. Hepatic: liver enzymes. Optic: visual acuity, fundoscopy, visual field examination. Muscular: neuromuscular function evaluation	Use with caution in patients with cardiac disease, QT prolongation, history of ventricular arrhythmia, bradycardia, uncorrected potassium or magnesium imbalance	Hypersensitivity to 4-aminoquinoline compounds, retinal or visual field changes of any etiologies	Pregnancy: category C, allowed if benefit outweighs risks	Drugs with potential to cause QT interval prolongation: quinolone antibiotics (levofloxacin, moxifloxacin), macrolides (azithromycin, erythromycin), amiodarone. Antacids and kaolin: decrease the serum concentration of CQ/HCQ. Separate administration of antacids & CQ/HCQ by at least 4 hours. Antidiabetic agents: CQ/HCQ may enhance the hypoglycemic effect of hypoglycemia associated agents. Digoxin: CQ/HCQ may increase digoxin serum concentration. Antiepileptics: increased risk of convulsions
HCQ[5,11–15]	400 mg QD, 5 to 7 days, depends on severity	Similar to CQ, less common	Severe hypoglycemia has been reported in patients with/ without concomitant use of antidiabetic agents	Hypersensitivity to HCQ & other 4-aminoquinoline compounds	Pregnancy: category C, allowed if benefit outweighs risks	Similar with CQ
Oseltamivir[4,16–20]	75 mg BID, 5 days	Nausea, vomitus, abdominal discomfort (frequency 5–10%)	Anaphylaxis reactions and serious skin reactions including toxic epidermal necrolysis and Steven-Johnson syndrome have been reported	Hypersensitivity to any component of oseltamivir	Pregnancy: category C, allowed if benefit outweighs risks	Caution with concomitant use of drugs with narrow therapeutic index

Table 1. (continued)

Agent	Adult dose	Adverse reactions	Precautions	Contraindications	Special population	Drug-drug interactions
LPV/RTV[21–28]	400/100 mg QD, 10 days	Frequency >10%: diarrhea, nausea, vomiting, abdominal pain, increased serum ALT, rash, hyperlipidemia Frequency 1–10%: headache, elevated LFTs, neutropenia, weakness	Altered cardiac conduction: use with caution in patients with underlying heart disease, preexisting conduction system abnormalities, ischemic heart disease or cardiomyopathies. Avoid use in combination with QTc or PR interval prolonging drugs or in patients with hypokalemia or congenital long QT syndrome. Preexisting hepatitis: frequent monitoring of liver function is required. Diabetes: blood glucose monitoring. Use with caution in patients with increased triglycerides; pancreatitis has been observed	Hypersensitivity to any component of LPV/RTV	Pregnancy: category C, allowed if benefit outweighs risks. Lactation: no data	Substrate and inhibitors of CYP450, P-gp, UGT1A1: LPV/RTV may increase serum concentrations of domperidone, simvastatin, apixaban, rivaroxaban, quetiapine, ticagrelor, diminish antiplatelet effect of clopidogrel. Amiodarone, clarithromycin: enhance QT-prolongation effect Rifampicin: decrease LPV serum concentration
Favipiravir[28–32]	Loading dose: 1,600 mg BID on day 1, followed by 600 mg BID (day 2 to 5)	Frequency ≥1%: diarrhea, inrease of AST and ALT, triglyceride, blood uric acid, decrease of leucocytes. Frequency 0.5–1%: nausea, vomitus, abdominal discomfort, glucosuria. Frequency <0.5%: decrease of serum potassium	Caution in patients with gout; favipiravir may increase plasma uric acid. Females of childbearing potential: pregnancy test negative before treatment initiation, appropriate contraception use is advised up to 7 days after the end of treatment. Breastfeeding woman: stop breastfeeding during treatment with favipiravir. Men with partner of childbearing potential: use of condoms is advised up to 7 days after the end of favipiravir treatment	Hypersensitivity to any componentof favipiravir	Contraindicated for women who is pregnant or planning to be pregnant (teratogenic & embryotoxic). Children: not recommended based on findings in the toxicity studies in juvenile animals (degeneration & necrosis of hepatocytes, papillary muscle in the heart, degeneration of skeletal muscle fiber, and gait disturbance)	Cautious when concomitantly given with: • CQ or HCQ (favipiravir inhibits CQ & HCQ metabolism by CYP2C8) • Pyrazinamide (increase plasma uric acid) • Oseltamivir (favipiravir inhibits oseltamivir deesterification) (clinical significancies are unknown)

Table 1. (continued)

Agent	Adult dose	Adverse reactions	Precautions	Contraindications	Special population	Drug-drug interactions
Remdesivir[33–40]	Loading: 200 mg IV drip for >30 min, followed by 100 mg given by 3 hours drip, for 9–13 days	Gastrointestinal disturbance, increase of liver transaminases	• Clinical safety data in patients with liver and renal disease are not yet available • Monitoring of renal function is required, if eGFR decreases ≥50%, consider to discontinue the drug • Monitoring of liver function: remdesivir may transiently increases liver transaminases	Not recommended in patients with moderate to severe renal dysfunction	Clinical trial data on use in pregnant and breastfeeding women are not yet available. Animal study showed remdesivir effects of in animal fetus renal development. Special precaution should be exercised for use in these populations	Data on remdesivir interactions with other drugs is not known yet. Caution in concomitant use with strong CYP450 inducers or inhibitors

COVID-19=coronavirus disease 2019; CQ=chloroquine, ECG=electrocardiography; QTc=corrected QT; CNS=central nervous system; HCQ=hydroxychloroquine; QD (*quaque die*)=once a day; BID (*bis in die*)=two times a day; LPV/RTV=lopinavir/ritonavir; ALT=alanine aminotransferase; LFT=liver function test; CYP450=cytochrome P450; P-gp=P-glycoprotein; UGT1A1=uridine diphosphate glucuronosyltransferase family 1 member A1; AST=aspartate aminotransferase; CYP2C8=cytochrome P450 2C8; eGFR=estimated glomerular filtration rate

exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course, without the occurrence of severe adverse reactions. However, data from this study cannot be accessed.

A multicenter collaboration group from the Department of Science and Technology of Guangdong Province published the consensus of experts in China on February 20, 2020, recommending chloroquine phosphate tablets, at a dose of 500 mg two times a day (BID) for 10 days for patients with a diagnosis of mild, moderate, and severe SARS-CoV-2 pneumonia, provided there are no contraindications to the drug.[10] The consensus stated to conduct blood tests to monitor for anemia, thrombocytopenia, leukopenia, serum electrolyte disturbances, and/or liver and kidney dysfunction. Routine electrocardiography is also recommended to monitor the possibility of QT interval prolongation or bradycardia, as well as the patient's history to determine the potential for visual and/or mental disorders. The panel recommends avoiding coadministration of other drugs that are known to prolong QT intervals, such as antimicrobial quinolones, macrolides, ondansetron, and various antiarrhythmic, antidepressant, and antipsychotic drugs.[10]

The Centre for Infectious Disease Control - The Netherlands recommends the use of chloroquine for severe COVID-19 that requires hospital treatment and oxygen therapy or is treated in the intensive care unit. However, due to the lack of supporting evidence, the document also states that treating patients with optimal supportive care alone is still a reasonable choice. The recommended dose of oral chloroquine for adults is: at the first day, initial dose is 600 mg, then 300 mg in the next 12 hours, followed by 300 mg BID on day 2 to 5. It is recommended to stop treatment on day 5 to reduce the risk of adverse effects, since the drug has a long half-life (>30 hours).[8]

Hydroxychloroquine

Hydroxychloroquine is a chloroquine derivative with many similar characteristics, however it has a better safety profile, especially in long-term use.[5]

• **Mechanism of actions**

The mechanism of action of hydroxychloroquine in COVID-19 is unclear, allegedly similar to chloroquine,

through inhibition of fusion and uncoating of the virus, lysosomal alkalinization, inhibition of virus interaction with ACE2 receptors, and as an immunomodulator.[11]

• **Pharmacokinetics**

Hydroxychloroquine is absorbed rapidly during oral administration and is widely distributed to tissues. The bioavailability is 67–74%, and the peak level is reached in 3.3 hours. Hydroxychloroquine is metabolized by the CYP2C8, CYP2D6, and CYP3A4 enzymes into desethylhydroxychloroquine and bis-desethylchloroquine.[12] Hydroxychloroquine and its metabolites are excreted slowly through the kidneys, with the terminal half-life of 40–50 days.[5]

• **Adverse effects**

Mild and transient headache, dizziness, gastrointestinal complaints (diarrhea, anorexia, nausea, abdominal cramps, and vomiting) and hypoglycemia may occur during treatment with hydroxychloroquine. Heart problems such as prolonged QT intervals and arrhythmia may occur during acute or chronic use. Myopathies, neuropathy, and permanent retinal damage may occur in long term use.[5] Concomitant use of chloroquine or hydroxychloroquine with medications that extend the QT interval increases the potential for cardiac arrhythmia.

• **Clinical studies of hydroxychloroquine in COVID-19**

In vitro study using SARS-CoV-2-infected Vero cells showed that hydroxychloroquine (EC_{50} = 0.72 µM) inhibits the virus more potent than chloroquine (EC_{50} = 5.47 µM) as anti-SARS-CoV-2, so the effective dose needed is lower.[13] A preliminary, open-label, non-RCT by Gautret et al[14] in France involving 36 positive COVID-19 patients (both asymptomatic or with symptoms of upper and lower respiratory tract infections) compared hydroxychloroquine sulphate therapy 200 mg three times a day (n = 16) during 10 days with symptomatic supportive therapy (n = 26). On day 6, more patients in hydroxychloroquine group (70%) had virologic clearance measured by airway swabs, compared to 12.5% in supportive therapy group. Additional azithromycin given to six patients in this study reportedly showed a synergistic effect with hydroxychloroquine in virologic clearance.[14] The clinical and safety outcomes are not reported in this study. Considering the small sample size, the lack of

reports of clinical and safety outcomes, and biases that might occur due to the open, non-randomized design, the results of this study should be interpreted carefully. Different results were obtained from a preliminary study by Chen et al[15] which involved a total of 30 COVID-19 patients to compare the efficacy of 400 mg hydroxychloroquine daily for 5 days with conventional treatment alone. On day 7, the COVID-19 nasopharyngeal virologic swabs were negative at 13 cases (86.7%) in the hydroxychloroquine group, and 14 cases (93.3%) in the control group ($p>0.05$). The duration of hospital stays and time to reach normal body temperature also did not differ significantly between the two groups. Adverse effects of diarrhea and abnormal liver function were comparable in the hydroxychloroquine and control groups (26.7% *versus* 20%, $p>0.05$).[15]

More than 10 clinical trials of hydroxychloroquine for COVID-19 treatment are still ongoing. Some countries released recommendations for the use of hydroxychloroquine for COVID-19 treatment based on existing *in vitro* and preliminary (pre-published) research results.[15]

Oseltamivir

Oseltamivir is available in the form of oseltamivir phosphate, a prodrug that is metabolized by plasma and hepatic esterase to the active form of oseltamivir carboxylate.[16,17] Oseltamivir is approved for the treatment and prevention of influenza types A and B, and available only in oral dosage form.[16,17]

• **Mechanism of actions**

Influenza viruses need a neuraminidase enzyme to release the newly formed viruses from the infected cells at the end of the replication process.[16] Oseltamivir carboxylate, the active metabolite of oseltamivir, interacts with the neuraminidase, leads to a conformational change within the enzyme's active site, and inhibits its activity. Inhibition of neuraminidase results in viral aggregation at the surface of the cell and decreases virus spread within the respiratory tract.[16,17]

• **Pharmacokinetics**

Oseltamivir is well and rapidly absorbed after oral administration. It is immediately converted by plasma and hepatic esterase to the active metabolite oseltamivir carboxylate. The elimination half-life of

the drug is 1–2 hours for oseltamivir and 6–10 hours for oseltamivir carboxylate. The drug is excreted through the kidneys, and dose adjustment is needed in impaired kidney function.[16,17] Doses given for the treatment of influenza types A and B are 75 mg BID for 5 days (adults) and 3 mg/kg BID for 5 days (children).

- **Adverse effects**

The safety profile of oseltamivir is good. The most common adverse effects are nausea, abdominal discomfort, and sometimes emesis (occurring in 5–10% of patients).[18] This drug is safe to use in pediatrics for over one year. Its use in pregnant women is not recommended, except when in the judgment of the physician, the benefit outweighs the possible hazard.[18]

- **Clinical study of oseltamivir in COVID-19**

The *in vitro* activity of oseltamivir against SARS-CoV-2 has not been documented. Unlike influenza viruses, coronaviruses do not have neuraminidase.[4,17] After replicating inside the host cell, the virus needs the help of viral protein E and the exocytosis to escape.[4,17] Oseltamivir might have no role against COVID-19. Oseltamivir was given empirically during the initial outbreak of COVID-19 in China before the discovery of the causative virus SARS-CoV-2 and since it occurred during the peak time of the influenza season.[19,20] Several studies that include oseltamivir as comparison group are registered currently at ClinicalTrials.gov (NCT04261270, NCT04255017, and NCT04303299).

Lopinavir/ritonavir

Lopinavir/ritonavir is protease inhibitors coformulation approved for the treatment of human immunodeficiency virus (HIV) infection since 2000. Protease has an essential role in the HIV lifecycle in cleaving both structural and functional proteins from precursor viral polypeptide strands.[21]

- **Mechanism of actions**

The SARS-CoV-2 virus is a single-stranded RNA Betacoronavirus. The 3-chymotrypsin-like protease (3CL^pro) enzyme plays an important role in processing the viral RNA. Lopinavir, as a protease inhibitor, restrains the action of 3CL^pro and disrupts viral replication process and their release from host cells.[22]

- **Pharmacokinetics**

Lopinavir is three to four times more active than ritonavir as a potent inhibitor of HIV-1 protease, but its bioavailability is poor. An additional low dose of ritonavir, a strong CYP3A4 inhibitor intended as a pharmacokinetic enhancer, dramatically increases lopinavir blood concentrations.[22] The drug maximum concentration can be achieved within 4 hours after drug administration. Most of the molecule (98–99%) is bound to plasma protein. The elimination half-life ranges from 2–3 hours after single-dose and from 4–6 hours after multiple-dose administration. Lopinavir is metabolized by hepatic CYP3A4 and CYP3A5 to its inactive metabolite. The drug is eliminated through fecal route and urinary excretion.[22]

- **Adverse effects**

The lopinavir/ritonavir combination is well tolerated, with mild to moderate degrees of diarrhea, nausea, and vomiting as the most common adverse effects.[21] Lopinavir/ritonavir is a substrate which also acts as an inhibitor or inducer of CYP3A4 and CYP3A5 that may cause interactions with other drugs metabolized by those enzymes.[21]

- **Clinical study of lopinavir/ritonavir in COVID-19**

Studies of antiviral activity of lopinavir/ritonavir against coronavirus families had been performed in an experimental animals infected with MERS-CoV.[23,24] Lopinavir *in vitro* activity against SARS associated coronavirus was demonstrated at the concentrations of 4 mg/ml.[24] In mice, prophylactic combination of lopinavir, ritonavir, and interferon beta (LPV/RTV-IFNb) slightly reduced viral loads but did not affect other disease parameters. Therapeutic LPV/RTV-IFNb improved pulmonary function without reducing virus replication or severe lung pathology.[23]

In one clinical study, 41 SARS-CoV patients were treated with lopinavir/ritonavir and ribavirin and were followed up for 3 weeks to document the clinical progress and virologic outcomes. Compared to historical controls of 111 patients treated with ribavirin only, the adverse clinical outcome (acute respiratory distress syndrome or death) was significantly lower in the treatment group than in the historical controls (2.4% *versus* 28.8%, *p* = 0.001) at day 21 after the onset of symptoms.[25] However, considering its open-label with historical control nature, the results of the study should be interpreted carefully.

In the pandemic outbreak of SARS-CoV-2 infection, lopinavir/ritonavir has been used in small number of cases, and few clinical trials have been carried out.[26–28] An RCT comparing lopinavir/ritonavir (99 patients) with standard care only (100 patients) in hospitalized adult patients with severe COVID-19 in China showed similar clinical improvement (hazard ratio [HR] = 1.31; 95% confidence interval [CI] = 0.95–1.80), and mortality within 28 days (19.2% *versus* 25.0%; 95% CI = −17.3–5.7) between the lopinavir/ritonavir and the standard care groups, respectively. The treatment group in this trial received 400 mg/100 mg lopinavir/ritonavir for 14 days in addition to standard care.[27]

In a non-randomized, open-label clinical trial comparing lopinavir/ritonavir (45 patients) and favipiravir (35 patients) in mild to moderate COVID-19, lopinavir/ritonavir was inferior than favipiravir in viral clearance and improvement of computed tomography scan images. Viral clearance time was shorter in the favipiravir arm compared to the lopinavir/ritonavir arm (median [interquartile range], 4 [2.5–9] days *versus* 11 [8–13] days, $p<0.001$). The improvement of chest imaging in the favipiravir arm was more significant compared to the control arm, with an improvement rate of 91.43% *versus* 62.22% (p = 0.004).[28] In this study, both groups also received IFN-α inhalation.[28] More data obtained from good quality of RCTs are needed to enable us to draw robust conclusions regarding the efficacy of lopinavir/ritonavir on COVID-19 patients. Most clinical trials comparing the use of lopinavir/ritonavir with other antivirals in patients with COVID-19 will be completed in 2021.

Favipiravir

Favipiravir (chemical name: 6-fluoro-3-hydroxypyrazine-2-carboxamide) was first developed by Toyama Chemicals Japan (Avigan®). In 2014, it obtained a marketing authorization in Japan for influenza therapy, for cases that did not respond to conventional treatment.[29]

• **Mechanism of actions**

Favipiravir is a prodrug. It undergoes intracellular ribosylation and phosphorylation into the active form of favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP).[29–31] Favipiravir-RTP binds to and inhibits the viral RdRp, resulting in inhibition of transcription and replication of the viral genome.[29–31] The catalytic domain of RdRp is similar among RNA viruses, which contributes to favipiravir's broad-spectrum activity as anti-RNA virus.[29]

• **Pharmacokinetics**

Favipiravir is available in oral form. Food delays its peak plasma levels for 1.5 hours. About 54% of favipiravir is bound to plasma protein, and it is widely distributed within the body, including to the trachea and lungs.[32] Favipiravir is metabolized in the liver into the main metabolite (M1) by the aldehyde oxidase, while the active metabolite (favipiravir-RTP) is formed intracellularly. The half-life is approximately 6 hours, and prolongs at high doses (≥800 mg).[32] Favipiravir metabolites are excreted through the kidney.

• **Adverse effects**

In phase three clinical trials for the treatment of influenza, the adverse effects of favipiravir were the increase of uric acid levels, gastrointestinal disturbances, diarrhea, and aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Based on the study in experimental animals, favipiravir is teratogenic and embryotoxic.[32] The use of favipiravir is contraindicated in women who are pregnant or may possibly be pregnant. For females of childbearing potential, the use of appropriate contraception is advised up to 7 days after the end of treatment. Men who have taken favipiravir and have partners of childbearing potential are advised to use condoms up to 7 days after the end of the treatment. The use of favipiravir in pediatrics is not recommended based on the findings in juvenile animal toxicity studies (degeneration and necrosis of hepatocytes, papillary muscle in the heart, degeneration of skeletal muscle fiber, and gait disturbance).[32]

In an *in vitro* study, favipiravir inhibits *hERG* current at a concentration of 157 µg/ml, which is three times higher than maximum concentration achieved in humans at a therapeutic dose. The risk of QT interval prolongation of favipiravir is considered to be not high. In healthy people, the effects of single-dose 1,200 mg and 2,400 mg of favipiravir on QT intervals did not differ from subjects receiving placebo.[32]

• **Clinical study of favipiravir in COVID-19**

Currently, evidence of the efficacy and safety of using favipiravir in COVID-19 is very limited. Clinical studies of favipiravir that involved a total of 320

COVID-19 patients in China claimed to prove the efficacy and safety of favipiravir. One of those studies, an open-label non-randomized controlled study, was conducted in Shenzen, China in 80 COVID-19 patients (35 favipiravir and 45 lopinavir/ritonavir).[28] However, the published study results was temporarily retracted, therefore, the efficacy and safety data cannot be reviewed.

Favipiravir received a marketing authorization in China for the indication of COVID-19 treatment based on the results of the above studies. Other studies related to favipiravir are still ongoing in China and Thailand (NCT04310228, NCT04303299). The usual adult dosage for treatment of influenza is 1,200 mg of favipiravir administered orally as the initial dose and 400 mg as the second dose on day 1, followed by 400 mg orally BID from day 2 to day 5.[32] As a trial drug for COVID-19, favipiravir was given orally for 7–10 days, a maximum of 14 days with a first day dose of 1,600 mg BID, followed by 600 mg BID (day 2 to day 7 or 10).[28]

Remdesivir

Remdesivir is a broad-spectrum antiviral originally developed for Ebola virus infection. It is a prodrug of adenosine analogue which is metabolized into nucleoside triphosphate, its active form, by the host. Remdesivir is an investigational drug that has not been approved yet by any national drug regulatory agency.[33] It is one of the drugs to be evaluated in an international clinical trial (Solidarity Trial) launched by WHO.[34]

- **Mechanism of action**

Remdesivir acts by inhibiting viral RdRp, a protein complex used for RNA-based genome replication. The active form (RTP) competes with adenosine triphosphate and incorporates with the RNA strand, causing premature termination of RNA synthesis and halting the RNA replication.[33,35]

- **Pharmacokinetics**

Remdesivir intravenous infusion exhibited a dose-linear pharmacokinetic at 3 to 225 mg dose range. Repeated once-daily 1-hour infusions of 150 mg remdesivir solution formulation for 14 days demonstrated time-linear pharmacokinetic. The intracellular half-life was more than 35 hours. Reversible increase of AST and ALT occurred during remdesivir administration. The administration of remdesivir is not recommended in patients with glomerular filtration rate less than 30 ml/min.[36]

- **Clinical study of remdesivir in COVID-19**

The *in vitro* study of remdesivir showed antiviral activity against RNA viruses, including Coronaviridae (e.g., SARS-CoV, MERS-CoV, and SARS-CoV-2), Paramyxoviridae (e.g. respiratory syncytial virus), and Filoviridae (e.g. Ebola virus).[33,37] Remdesivir showed potent *in vitro* activity against several Coronaviridae including SARS-CoV-2 (EC_{50} = 0.77 μM and EC_{90} = 1.76 μM).[7,23] In macaque, the administration of remdesivir within 24 hours before MERS-CoV inoculation could prevent clinical symptoms, inhibit viral replication in the respiratory tissue, and prevent the formation of pulmonary lesions. Moreover, the use of the drug within 12 hours after virus inoculation could decrease the clinical symptoms, suppress viral replication in the pulmonary tissue, and reduce the severity of pulmonary lesions.[38]

An interim report of a cohort study which evaluated remdesivir use in COVID-19 patients found clinical improvement in 36 of 53 (68%) patients with COVID-19 infection given intravenous remdesivir for 10 days.[39] The patients included in this study were COVID-19 patients with oxygen saturation 94% or less at room temperature or who received oxygen support. The dose given was 200 mg on the first day, and 100 mg on day 2 to 9. Mortality was found in 7 out of 53 (13%) patients; 6 out of 34 (18%) patients who received invasive ventilation and 1 out of 19 (5%) patients who received additional non-invasive oxygen. The death risk increases especially in patients over 70 years and in patients with higher serum creatinine levels on the baseline. The most common adverse effects were the increase of hepatic enzymes, diarrhea, rash, impaired kidney function, and hypotension. Severe adverse effects occurred in 12 (23%) patients, in the form of multiple organ dysfunction syndrome, septic shock, acute kidney injury and hypotension, and in those who were mechanically ventilated from the beginning. This study was open-label and did not use a control group, so conclusions regarding the results should be drawn carefully.[39] At present, there are at least five clinical trials regarding the use of remdesivir which is registered at ClinicalTrials.gov (NCT04292899, NCT04292730, NCT04252664, NCT04323761, and NCT04257656).

Until now there is no specific treatment for COVID-19. On the other hand, there is an urgent need for effective and safe drugs to treat the disease during the pandemic. Unfortunately, conducting the gold standard randomized controlled clinical trial to get specific effective and safe drugs requires a long time, which is not appropriate during a pandemic. This condition prompts the repurposing of "old drugs" such as chloroquine, hydroxychloroquine, oseltamivir, lopinavir/ritonavir, favipiravir, and the use of investigational drug known to have activity against coronaviruses such as remdesivir.

Chloroquine and hydroxychloroquine are drugs that have been used to treat malaria for a long time. Limited small-scale clinical studies, in which none of them had good quality RCTs, showed some efficacy of chloroquine and hydroxychloroquine for COVID-19 treatment, but the optimal dose and duration of treatment for COVID-19 was unknown.[9,10,14,19] For limited use in pandemic COVID-19, chloroquine phosphate is given to adult patients with a dose of 1,000 mg on day 1, then 500 mg QD for 4 to 9 days more, depending on the results of clinical evaluation. Based on experiences, chloroquine dose of 750–1,000 mg salt in single administration is relatively safe.[5] However, accumulation dose of chloroquine for 5 days of administration for COVID-19 patients (5,000 mg salt) reaches twice accumulation dose for standard malaria treatment given for 3 days (2,500 mg salt), which may lead to the occurrence of more adverse effects. Giving chloroquine more than 5 days in COVID-19 potentially increase the occurrence of its adverse effects. The accumulation dose of hydroxychloroquine in COVID-19 patients for 5-day treatment is similar to the accumulation dose for malaria treatment (2,000 mg salt).[5] Since the evidence of efficacy and safety of chloroquine and hydroxychloroquine use in COVID-19 are still limited, only based on small-scale clinical studies, they should be used cautiously for COVID-19 treatment.

In general, hydroxychloroquine is considered safer, causing less adverse effects than chloroquine. In Indonesia, before the COVID-19 pandemic, hydroxychloroquine availability was less than chloroquine, and the price was also more expensive. The potentially serious adverse effect of chloroquine and hydroxychloroquine during COVID-19 treatment is the prolongation of QT interval that may lead to cardiac arrhythmia. Care should be taken when patients also get other drugs with potential similar adverse effects such as azithromycin and levofloxacin.

Oseltamivir is a neuraminidase inhibitor used for influenza virus infections. The drug has no records of *in vitro* activity against SARS-CoV-2, which is understandable since the new coronavirus has no neuraminidase. Oseltamivir may not have a role, hence it is not recommended to use in the treatment of COVID-19. The use of oseltamivir might be acceptable if there is a strong suspicion that co-infection of influenza virus and COVID-19 occurs. Previously, the initial COVID-19 outbreak in China occurred during the peak influenza season, which urged the empirical use of oseltamivir, until SARS-CoV-2 was identified as the cause of the disease.[19]

Based on the available data, lopinavir/ritonavir seems to have only a limited efficacy against COVID-19.[27,28] Lopinavir/ritonavir is a substrate and inhibitor of CYP3A4 with a high potential to cause drug-drug interactions, and the drug is licensed for HIV treatment, so its availability for HIV patients must be maintained and the development of resistance should be prevented whenever possible. Taking into account all these facts, lopinavir/ritonavir is considered to be not a good option for COVID-19 therapy during the pandemic until further evidence proves otherwise.

Favipiravir is a second-line antivirus for influenza developed in Japan. Prior to COVID-19 pandemic, the use of this drug is also limited in Japan. Favipiravir mechanism of action in inhibiting virus replication by binding to RdRp contributes to its potential activity as anti-SARS-CoV-2.[29–31] The safety profile of this drug mostly has been documented from the results of clinical trials of an anti-influenza in Japan population, and are relatively mild, mainly in the form of gastrointestinal disorders. Considering its limited evidence of efficacy and safety, favipiravir can be used in COVID-19 treatment in context of clinilcal trial. Currently, favipiravir is not available in many countries.

In vitro studies of remdesivir, which is originally developed for the Ebola virus infection, showed a strong activity against SARS-CoV-2. The interim report of limited clinical studies showed some efficacy of remdesivir against COVID-19. Inclusion of this agent for treatment of COVID-19 may be considered during pandemic. However, remdesivir must be obtained via compassionate, expanded access, or enrollment in a clinical trial. This investigational antiviral is undergoing

clinical trials in several countries as a potential treatment for COVID-19.

Studies update

Indonesia contributes to the global search for effective COVID-19 drug treatment by participating in a multinational trial launched by WHO, the Solidarity Trial. The trial aimed to compare the effectiveness of four treatment options – hydroxychloroquine, remdesivir, lopinavir/ritonavir, and lopinavir/ritonavir plus interferon beta-1a.[34] More than 20 hospitals across Indonesia participate in this trial, which has been launched on April 23, 2020.[40]

On May 23, 2020, over safety concern, the Executive Group of the Solidarity Trial implemented a temporary pause of the hydroxychloroquine arm of the trial. The decision was based on the published results of a retrospective, non-randomized, multinational registry analysis of the safety and benefit of hydroxychloroquine or chloroquine use with or without macrolide for COVID-19 treatment. However, the publication was later retracted by three of its authors. They were unable to complete an independent audit of the data underpinning their analysis, therefore, can no longer confirm the accuracy of the primary data sources.[41] Following the retraction, and supported by the results of interim analysis by Data Safety Monitoring Committee of the Solidarity Trial that revealed no safety issue regarding the hydroxychloroquine use, WHO has reinstated the study without any trial protocol modification.[34]

Another ongoing clinical trial is the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial (NCT04381936), which tests a range of potential drugs for COVID-19, including hydroxychloroquine. The trial has been enrolling over 11,000 patients from 175 hospitals in the United Kingdom. Preliminary results of the study have shown no clinical benefits of hydroxychloroquine in patients admitted to hospital with COVID-19. A total of 1,542 patients randomised to hydroxychloroquine and 3,132 patients randomised to usual care alone showed no significant differences in the 28-day mortality (25.7% hydroxychloroquine *versus.* 23.5% usual care; HR = 1.11; 95% CI = 0.98–1.26; p = 0.10). The beneficial effects on hospital length of stay or other outcomes were also not proven. Based on the results, the trial will be no longer enrolling participants in the hydroxychloroquine arm, as announced by the chief investigators on June 5, 2020.[42] However, the preliminary result of RECOVERY Trial

has not been peer-reviewed yet. Since the specific treatment of COVID-19 is still not available, and the interim analysis by the Data Safety Monitoring Committee of the Solidarity Trial revealed no significant safety issue of hydroxychloroquine, in authors opinion, the hydroxychloroquine arm of the Solidarity Trial should not be discontinued in order to obtain data from various countries in the world, including Indonesia. Thus, a robust conclusion regarding the effectiveness and safety of hydroxychloroquine for the treatment of COVID-19 can be drawn. If it proves to be ineffective in the future, the focus of research can be directed to other therapeutic modalities.

This article is a narrative review, where certain degree of risk of selection and evaluation bias cannot be avoided due to the lack of systematic literature search. Only the most commonly used potential anti SARS-CoV-2 are reviewed, other potential antivirus such as ribavirin, darunavir, umifenovir, ivermectin, and many others are not included.

In conclusion, COVID-19 is a new disease caused by the new strain of coronavirus, SARS-CoV-2. Currently, there is no evidence to recommend any specific anti-COVID-19 treatment. Large-scale RCTs of COVID-19 drugs are still ongoing. The use of chloroquine, hydroxychloroquine, oseltamivir, lopinavir/ritonavir, favipiravir, and remdesivir in the management of COVID-19 at this moment are based on small-scale clinical studies, which are not sufficient to draw strong conclusions about their efficacy and safety. Based on this clinical pharmacology review, the decision to use these drugs during the COVID-19 pandemic must take into consideration the potential benefits and risks to the patient; the likelihood of the drug to be effective, available, affordable, with the lowest risk for the patients and the community.

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