



Effectiveness of Antiviral Drugs as Covid-19 Therapy

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Abstract

SARS-CoV 2 firstly emerged in China on December 2019 and it was spreading rapidly across the world until now. At this time, there is no vaccine or medication approved by the FDA. However, there are some FDA approved medicines for treating other diseases that can be used for Covid-19 based on tests. This review focuses on therapy efficacy, work mechanism, pharmacokinetic profile, safety, and future perspective. Article review related to therapy on Covid-19 patients, particularly antiviral therapy which was the combination of lopinavir and ritonavir, chloroquine, hydroxychloroquine, remdesivir, and favipiravir. The reviewed relevant articles were observational study, in vitro test, case report, and clinical test. A total of 13 articles met the requirement, 9 articles discussed the result of therapy during the medication of COVID-19 patients, 2 reports of in vitro test, and 2 results of clinical trials. From several studies that had been conducted, remdesivir, combination of lopinavir and ritonavir, as well as favipiravir showed benefits in various clinical studies on Covid-19 patients. Meanwhile, chloroquine and hydroxychloroquine showed limited effects and did not affect the decrease of mortality.

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1. Introduction

Coronavirus (Covid-19) caused by acute respiratory syndrome (SARS-CoV-2) is a single chain RNA virus whose genome encodes

structural proteins, non-structural proteins, and accessory proteins [1]. It becomes a global concern and health problem since December 2019. Until October 2020, the World Health Organization (WHO) reported that coronavirus

had been spreading to 216 countries and infecting 36.9 million people with 1.06 million deaths confirmed around the world. Meanwhile, 27.7 million patients had recovered from the total affected population [2].

Even though the number of patients keeps increasing, there are no approved-FDA drugs for COVID-19. The treatment for each individual is only based on the occurring symptoms and when it worsens, organ supporting tools are used [3]. Some medications based on previous experience with other viruses such as malaria, ebola, cholera are suggested and implemented for controlling COVID-19. After SARS outbreak in 2003, screening and identification were conducted on approved drugs i.e. lopinavir (inhibitor protease type 1 HIV) which has SARS-CoV inhibitor properties in vitro and combined with Ritonavir to increase the half-life of plasma through cytochrome P450 inhibition [4].

Until now, effective vaccines or antiviral agents specified for SARS-CoV-2 has not been approved yet. Therefore, the management of Covid-19 patients is focusing mainly on supportive treatment and symptomatic medication. The collaborative solution suggests clinical trials for treating Covid-19 and developing Covid-19 vaccines by researchers from some countries. There is no effective medication confirmed for Covid-19, however, the researchers attempt to develop antiviral strategies for COVID-19. This review describes the recent evidence on therapies that are significantly proposed or had been experimentally tested for COVID-19.

2. Experimental section

Searching for literature was carried out by collecting the data from January 2020-October 2020 using PubMed, Google Scholar, and Science Direct. The keywords were "Treatment for COVID-19", "Anti-viral drugs, Antimalarial drugs for COVID-19", or "COVID-19" along with the name of each drug under study, that were the combination of lopinavir and ritonavir, chloroquine, hydroxychloroquine, remdesivir, and favipiravir. The reviewed relevant articles were observational study, in vitro test, case

report, and clinical trial. Moreover, the studies that were not found could be identified by checking the references from the selected articles. The inclusion criteria in choosing the literature were COVID-19 patients who received therapy with one of the drugs under study (combination of lopinavir and ritonavir, chloroquine, hydroxychloroquine, remdesivir, and favipiravir) with or without combination with other drugs, the number of research sample >100 and in vitro test or related laboratory tests. The exclusion criteria were article duplication, incomplete article, literature review, the number of sample <100, and therapy with other than the specified drugs.

3. Results and Discussion

Overall, a total of 13 articles met the requirements. 9 articles discussed the results of therapy given during the treatment of COVID-19 patients, 2 reports on in vitro test, and 2 results of clinical trial. The results of literature study are listed in Table 3.

This analysis was conducted based on controlled randomized studies published for Covid-19 medication, clinical trials that had been successfully conducted, as well as several agents based on in vitro tests or observational study. At this moment, there are about 3500 researches recorded as Covid-19 clinical trials that can be accessed in the database of Clinical Trials.gov and through WHO international clinical trial registration platform [5]. The urgent need in finding Covid-19 medications resulted in two proposed approaches: administration of approved drugs (initially introduced for other diseases) with high safety profile and shows promising in vitro results to SARS-CoV, MERS-CoV, and SARS-CoV-2 combined with convalescent plasma, and the second one is developing new antiviral agents and vaccines to protect against SARS-Cov-2 [6]. Some drugs that are frequently used and discussed in this review are chloroquine, hydroxychloroquine, lopinavir/ritonavir, remdesivir, and favipiravir. Rapid mechanism of action and pharmacokinetic profiles are presented in Table 1 and Table 2.

Table 1 Mechanism of Action [7]

Group	Drug	Mechanism of Action
Working when virus enter	Lopinavir/Ritonavir	3-chymotrypsin-like protease inhibitor
	Chloroquine	Increasing pH endosome, and disrupting glycosylation of ACE-2 receptor
	Hydroxychloroquine	
Working during virus replication	Remdesivir	Analog adenosine nucleotide, prodrug, inhibiting RdRp activities
	Favipiravir	Analog guanosine nucleotide, prodrug, inhibiting RdRp activities

Table 2 Pharmacokinetic Profile [7],[8]

Pharmacokinetics	Chloroquine	Hydroxychloroquine	Lopinavir/ Ritonavir	Remdesivir	Favipiravir
Absorption	Fast absorption and almost perfect	Incomplete and varied (~70%)	Tmax : 4-6 hours	100% after IV administration	Approaching 100%
Distribution	Vd : 200 L/kg Protein binding: ~55%	Vd : 153-1650 L Protein binding: ~40%	Protein binding : 98%-99%	Distributed in free fraction 12.1%	Protein binding: 54%
Metabolism	Desethylchloroquine 39%	Desethylchloroquine 18% Desethylhydroxychloroquine 16%	Ritonavir inhibits lopinavir metabolism	Remdesivir triphosphate	Hepatic metabolism especially by aldehyde oxidase (AO) and partly by xanthin oxidase (XO)
Excretion	Urine : ~70%, ~35% shape did not change	Urine : 15-25%	Feces : 20% did not change Urine : 2.2% did not change	Feces : 18% Urine : 74% shape changed and did not change	Urine
Half Life	6-60 days (average 20 days)	Blood : 172.3 hours-50 days Plasma : 32 -123.5 days	5-6 hours	1 hour	2-5.5 hours

Table 3 Literature Studies on Therapy to Covid-19 Patients

No.	Research Design	Research Sample	Inclusion Criteria	Intervention	Result	Reference
1.	In Vitro	Using infected Vero cells	Isolation of SARS-CoV-2 virus strain spread in Vero cells	Hydroxychloroquine (400 mg/12 hours followed by 200 mg/12 hours for 4 days)	Vero cell test showed that in vitro hydroxychloroquine was more potent than chloroquine and 3x more potent when given at a dose of 500mg/12 hours.	[9]
2.	In Vitro	Using infected Vero E6 cells	Vero E6 cells infected into SARS-CoV-2	Remdesivir and Chloroquine	Remdesivir and chloroquine were effective to control Covid-19 infection in vitro	[10]
3.	Randomized control open-label trial	99 people received LPV/r, 100 people received standard therapy	Patient with confirmed SARS-CoV-2 infection, oxygen saturation 94% or less	Lopinavir (400 mg/12 hours) and Ritonavir (100 mg/12 hours)	The average time required to improve patients' clinical condition was 15 days compared to 16 days for the standard therapy group. There was no significant difference in the time required for clinical improvement between the two groups (lopinavir, ritonavir, and standard therapy)	[11]
4.	Randomized control trial	116 people received Favipiravir, 120 people received Arbidol	Patient age ≥ 18 years-old, early symptom in 12 days, diagnosed pneumonia Covid-19	Favipiravir (1600 mg/12 hours followed by 600 mg/12 hours) and Arbidol (200 mg/ 8 hours)	Improvement in clinical conditions on day 7 was not significantly different between the two groups. Favipiravir significantly increased latency to recover from fever and cough.	[12]
5.	double-blind, randomized, placebo-controlled trial	538 patients received Remdesivir, and 521 patients received placebo	Adult patients with Covid-19 with involvement of lower respiratory tract	Remdesivir IV 200 mg loading dose on the first day, followed by 100 mg a day to 9 days	Remdesivir had recovery time at an average of 11 days, mortality at day 14 was 7.1%, and severe adverse events in 114 of 541 patients (21.1%). Compared to placebo, the average recovery was 15 days, 11.9% mortality, and severe adverse events occurred in 141 of 522 patients. (27.0%).	[13]

Table 3

No.	Research Design	Research Sample	Inclusion Criteria	Intervention	Result	Reference
6.	<i>randomized, double-blind, placebo-controlled, multicenter trial</i>	158 patients received Remdesivir IV, and 79 patients received placebo infusion	Patients ≥ 18 years-old with symptom onset of 12 days or less, oxygen saturation of 94% or less, and radiologically confirmed pneumonia. Conducted at 10 hospitals in Hubei, China.	Remdesivir 200 mg IV D1, followed by 100 mg D2-D10 in a daily single infusion	Remdesivir group had a shorter time to clinical improvement although it was not statistically significant. For adult patients with severe Covid-19, Remdesivir was not associated with statistically significant clinical benefits.	[14]
7.	<i>Randomized, open-label clinical trial</i>	197 patients received remdesivir for 10 days, 199 patients received remdesivir for 5 days, 200 patients received standard therapy	Patients with confirmed severe acute SARS-CoV-2 infection, and moderate pneumonia Covid-19 (<i>pulmonary infiltrate</i> & oxygen saturation $>94\%$)	Remdesivir 200mg IV D1 continued with 100mg	Remdesivir treatment for 10 days did not have a statistically significant difference in clinical status compared to standard therapy. Remdesivir treatment for 5 days had statistically significant differences with standard therapy but was not clinically important.	[15]
8.	<i>Randomized, open label, phase 3 trial</i>	197 patients received remdesivir for 10 days, 200 patients received remdesivir for 5 days	Patients confirmed of SARS-CoV-2 infection, oxygen saturation $\leq 94\%$, radiological evidence of pneumonia	Remdesivir 200mg IV D1 continued with 100mg/day	Did not show significant differences in remdesivir administration for 5 days or 10 days.	[16]
9.	Observational study	811 patients	Patients with confirmed SARS-CoV-2 treated in hospital	HCQ 600mg 2x a day D1, and 400mg for 5 days	HCQ did not affect intubation or mortality in patients with COVID-19	[17]
10.	<i>Randomized, double-blind, placebo-controlled trial</i>	201 patients received HCQ, 194 patients received placebo	Adults with symptoms, not hospitalized, laboratory-confirmed Covid-19 or at high risk of exposure to Covid-19 within 4 days of symptom onset	HCQ 800mg/day followed by 600mg within 6-8 hours, then 600mg/day for 4 days	HCQ did not reduce the severity of symptoms in minor COVID-19 outpatient	[18]
11.	<i>multicenter, open-label, randomized controlled trial</i>	136 patients received HCQ, 157 control	Adult confirmed with SARS-CoV-2 infection without hospitalization with symptoms <5 days	HCQ 800mg/day and 400mg/day for 6 days	HCQ did not show benefits in patients with mild Covid-19	[19]
12.	<i>Multi-center retrospective observational study.</i>	1202 patients received HCQ, 783 patients received HCQ+Azitromisin, 147 patients received Azitromisin, 409 patients received other drugs	Age ≥ 18 years-old, treated in Hospital for minimum 48 hours	HCQ 400mg 2x a day D1, 200mg 2x a day D2-D5 Azitromisin 500mg 1x a day, 250mg/day for 4 days.	HCQ only or with azithromycin in patients with COVID-19 was associated with mortality decreases related to COVID-19.	[20]
13.	<i>Retrospective multicenter cohort study</i>	271 patients received HCQ, 735 patients received HCQ+Azitromisin, 211 patients received Azitromisin, 221 patients received other drugs	Laboratory confirmed Covid-19 and had been hospitalized for 24 hours	Not specified	HCQ with or without azithromycin was not significantly different related to mortality rate at hospital	[21]

3.1 Lopinavir/Ritonavir

Protease is an essential enzyme for the production and maturation of the viral genome. The main antiviral effect of protease inhibitors is the prevention of viral replication, thus limiting spread into host cells. The therapeutic reason for using LPV/r arises from an in vitro study showing inhibition of the 3-chymotrypsin protease found in the coronavirus. [22]. Lopinavir is formulated with ritonavir (LPV/r) to increase pharmacokinetic activities and LPV half-life through CYP450 inhibition. Structurally, the two compounds are the derivative 1,6-diphenyl-4-hydroxy-2,5-diaminohexane whose aminohexane group contains side chains with various substituted cyclic groups such as phenoxy/ 3,5-diazinan (Lopinavir) or 1,3-thiazole [6].

Lopinavir/ritonavir is available in single tablets with a dose of 400/100 mg or 200/100 mg. For COVID-19, the dosage is 400 mg/100 mg orally twice daily for 14 days. Lower doses of 200/100 mg twice a day can be considered if the side effects are within the threshold of tolerability, given that lower doses may not substantially reduce toxicity. Ritonavir is a strong CYP3A4 inhibitor which is the main enzyme for metabolism and elimination of many drugs, so special attention needs to be paid if it is used in elderly patients with COVID-19 who have comorbidities and are receiving polypharmacy therapy because interactions can occur between drugs. [22].

Treatment with LPV/r can cause intolerable gastrointestinal toxicity, although administration with food may improve the severity of these symptoms. 24% of patients had diarrhea and improved within 2 weeks. In studies for usage in SARS found an elevation in serum amylase and liver enzymes; therefore, routine monitoring of liver function tests is necessary as well as supportive care with antiemetics and antimotility should be considered [22]. According to the Infectious Diseases Society of America (IDSA), the clinical data published on LPV/r regarding its efficacy against COVID-19 is insufficient to recommend

this drug as a therapy, only in the context of clinical trials. [23].

3.2 Chloroquine Phosphate and Hydroxychloroquine

Regarding the activities of SARS CoV-2, the mechanism of action of these two drugs is categorized into: first, inhibition of enzymes/processes in viruses (DNA virus and/or RNA polymerase), glycosylation of viral proteins, transport of new virus particles, and release of viruses. The second is inhibiting ACE2 cellular receptor, acidifying the cell membrane surface so it inhibits viral fusion, and immunomodulating the release of cytokines. Structurally, these two compounds are 7-chloro-quinoline derivatives with the novaldiamine substituent in the fourth position, where HCQ has an additional hydroxyl group at the end of the structure. The addition of hydroxyl group increases hydrosolubility, flexibility, and polarity as well as decreases in polarity compared to CQ [6].

Chloroquine is formulated as a tablet in the form of phosphate salt for oral administration. In treating COVID-19, experts recommend chloroquine phosphate tablets at a dose of 500 mg orally twice/day for 10 days [22]. The recommended therapeutic dose of HCQ from several Covid-19 treatment guidelines is 800mg/day on day 1, followed by 400mg/day for 4 days [24], [22]. The most common side effects are gastrointestinal intolerance such as nausea, vomiting and stomach cramps, prolonged QT interval (after short-term treatment), and acute toxicity in the form of cardiomyopathy, neuropathy, or myopathy. Retinopathy occurs when using hydroxychloroquine and chloroquine especially in high doses and over a long period. [25].

There have been reports of hypoglycemia progressing to loss of consciousness when used in patients with diabetes history and in concomitant use with antidiabetic agents [6], [22]. A retrospective study conducted on 95 hospitalized COVID-19 patients treated with CQ

showed that 23% of the patients showed prolonged QT interval [26].

Current preclinical and clinical data regarding the use of CQ and HCQ in SARS-CoV-2 infection are not considered robust [6], and the EMA does not endorse the use of chloroquine as a standard treatment in COVID-19 and is restricted to its use exclusively in clinical trials or through national emergency use programs [27]. In addition, WHO has discontinued clinical trials using hydroxychloroquine as a Covid-19 therapy because it does not provide effects on reducing the mortality of inpatients compared to standard care [28]. Among hospitalized COVID-19 patients, IDSA guidelines recommend against the use of hydroxychloroquine [29].

3.3 Remdesivir

Remdesivir is currently considered as the most promising therapy for SARS-CoV-2 infection based on the results obtained in phase III clinical trial by the National Institute of Allergy and Infectious Diseases (NIAID) in the Adaptive COVID-19 Treatment Trial (ACTT) [6]. RDV exhibits antiviral activity against other single-chain RNA viruses such as filovirus, pneumovirus, paramyxovirus, and MERS-CoV and SARS-CoV coronaviruses. Remdesivir is a monophosphate nucleotide analog product (GS-441524) which is metabolized rapidly in cells and tissues into its active form of adenosine triphosphate (GS-443902), which inhibits RNA-dependent RNA polymerase (RdRp) activities in the viral infection cycle. Another potential mechanism is causing lethal mutagenesis and chain breakdown [30],[31].

Structurally, RDV is a nucleoside analog which is very similar to AMP (adenosine monophosphate), an important structural difference occurs in both the nucleobase region, where the purine ring is replaced by pyrrolo [2,1-f] [1,2,4] triazine, and the ribose region where the cyanide group is in the fifth position. Moreover, the phosphate group is attached to the phenoxy group and α -Alanine-2-ethyl-butyl ester, which increases the lipofility of the molecule and the degree of structural flexibility. RDV acts as a competitive ATP (adenosine

triphosphate) inhibitor, targeting an enzyme involved in viral genome replication, which is RNA-dependent RNA polymerase (RdRp) [6].

It is formulated in two pharmaceutical forms (5mg/ml solution and 100mg lyophilized powder) and is recommended to be administered intravenously (30-120 minutes) after reconstitution in 0.9% saline solution or glucose 5% with a therapeutic dose 200mg on day-1 and 100mg/day for the next 9 days [31],[22].

3.4 Favipiravir

Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamide) is a pyrazine carboxamide oral and analog guanine derivative developed in Japan for treating influenza. These compounds work selectively and potently inhibit the RNA-dependent RNA polymerase (RdRp) of the RNA virus and cause deadly RNA transversion mutations resulting in a non-viable viral phenotype. Favipiravir is metabolized into its active form, favipiravir ribofuranosyl-50-triphosphate, which is metabolized in the liver and does not produce significant drug interactions, otherwise it does not affect human DNA polymerase subunit α , β , γ (up to 100 μ g/ml), so it does not cause toxic effects [22],[6].

In a clinical study conducted by National Clinical Research Center for contagious diseases in Shenzhen, two doses of 1.600mg favipiravir on the first day and two doses of 600mg for the following 13 days, in addition to the interferon- α aerosol inhalation (five million units twice a day), resulted in faster viral clearance than the lopinavir/ritonavir group, with an average of 4 days versus 11 days, as well as enhanced chest imaging. Randomized trials carried out for this drug in combination with other drugs are favipiravir + interferon- α , and favipiravir + baloxavir [7].

4. Conclusion

Nowadays, there is still no medication or vaccine approved for Covid-19 pandemic that is striking the world to date. However, there are several types of medicine approved by FDA that

are used to treat other diseases and can be used for Covid-19 based on in vitro and clinical tests on patients infected with SARS CoV-2. It is known that remdesivir, combination of lopinavir and ritonavir, as well as favipiravir showed benefits in various clinical studies on Covid-19 patients. Meanwhile, chloroquine and hydroxychloroquine had limited effects and did not affect the decrease of mortality.

Conflict of Interest

The authors declare there is no conflict of interest.

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