

The Efficacy and Safety of Antivirus Drugs for COVID-19: A Systematic Review

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ABSTRACT

Corona Virus Disease 2019 (COVID-9) is an acute respiratory infection caused by extreme acute coronavirus-2 (SARS-CoV-2) respiratory syndrome. WHO has designated COVID-19 as a pandemic with a very high mortality rate and increasing very rapidly, in only 3 months COVID-19 has infected 1.133046 people and in many cases only 14 days COVID-19 has caused death? With very high mortality and morbidity rates, no effective and safe of antivirus treatment has yet been found to cure COVID-19, so research is needed to find the most effective and safe of antivirus drugs to cure COVID-19. To know the best and safe of antivirus medication to cure COVID-19. This research uses a structured analysis focused on preferred reporting items for systematic reviews and meta-analyses (PRISMA) in order to classify all existing literature with appropriate keywords. The database using PRISMA (Preferred Reporting Items for Systematic Reviews & Meta Analyses) for instruments and used flowcharts based on the 2009 PRISMA checklist and based on inclusion and exclusion criteria, we found 6 anti-virus drugs used to treat SARS-CoV-1 or MERS-CoV and very potential to treat COVID-19, that is Favipiravir (Avigan, Favilavir), Lopinavir and Ritonavir (LPV / RTV; Kaletra), Neuraminidase inhibitors (eg, oseltamivir), Umifenovir (Arbidol) Remdesivir, and Baloxavir. The most efficacy and safe of anti-virus is Favipiravir because this drug can improve significantly time-to-relief for fever and cough and is associated with manageable adverse effects.

Keywords: SARS-CoV-2; COVID-19; Anti-Viral; Anti-Virus

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INTRODUCTION

Corona Virus Disease 2019 (COVID-19) is an acute respiratory disease caused by the Corona Novel virus (nCoV-2019) which then On February 11, 2020, the World Health Organization (WHO) changed the name of the new virus to Severe acute respiratory syndrome coronavirus - 2 (SARS-CoV-2). SARS-CoV-2 first appeared in Wuhan, China and then spread throughout the world and on 11 March 2020 the WHO officially declared COVID-19 is a pandemic with a rapidly increasing and sharp incidence which from the latest WHO data showed in 3 months COVID-19 has infected 209 countries and every day there are approximately 5,798 people infected with COVID-19 and a fairly high mortality rate of 62,773 people who have died with high morbidity as well as 1.133046 people who have been diagnosed with COVID-19[1]-[4].

Based on the latest data from John Hopkins University, shows the first place is USA with an incidence of 398,785 people, second place in Spain with an incidence of 141,942 people, third place in Italy with an incidence of 135,586 people. Indonesia ranks 38th with a total of 2,491 cases [5] Based on the latest data from the Republic of Indonesia Ministry of Health, the highest number of COVID-19 cases in Indonesia is in DKI Jakarta with a total of 1,232 cases, the second place in West Java with a total of 263 cases, the third is East Java with a total of 189 cases. While on the island of Sulawesi the first ranks is South Sulawesi with a total of 113 cases[6].

After transmission, the virus enters the upper airway system and then replicates in the upper airway epithelial cells (carrying out its life cycle) after that spread to the lower airway system. In several studies found SARS-CoV-2 can infect gastrointestinal cells and brain cells. The incubation period of the virus until the disease appears around 3-7 days.[7]-[9]. In several studies of SARS-CoV-2

show that the virus replicates in the upper and lower airway system followed by a specific and innate immune system response. Viral and immune system factors play an important role in pathogenesis of SARS-CoV-2. In the first stage diffuse damage to alveolar, macrophages, and T cell infiltration and proliferation of type 2 pneumocytes. At the chest X-ray at the beginning of the infectious stage, pulmonary infiltrate looks like patches. In the second stage, organization occurs so that changes in infiltrates or extensive consolidation in the lungs. Infection is not limited to the respiratory system, but the virus also replicates in enterocytes, causing diarrhea and feces in the stool, as well as urine and other body fluids. Several study showed SARS-CoV-2 was not detected in the nasopharyngeal swab but was detected from in cerebrospinal fluid[7], [9].

Recent studies shown that increases of proinflammatory cytokines in serum such as IL1B, IL6, IL12, IFN γ , IP10, and MCP1 are associated with inflammation in the lungs and extensive damage in lung tissue in patients with SARS-CoV-2[2]. In a study of first 41 patients COVID-19 pneumonia in Wuhan was found to be of high level of IL1 β , IFN γ , IP10, and MCP1, and possible activating T-helper-1 (Th1) cell responses. In addition, based on this latest study, patients who require treatment in the ICU found higher concentrations of GCSF, IP10, MCP1, MIP1A, and TNF α compared patients who did not require treatment in the ICU. This underlies the possibility of Cytokine Storm related to the severity of the disease. In addition, SARS-CoV-2 infection also initiates an increase in the secretion of T-helper-2 cytokines (such as IL4 and IL10) that play a role in suppressing inflammation, which is different from SARS-CoV infection[2].

In comparison to viruses, bacteria and protozoans do not rely on host cell machinery to reproduce them so that

processes unique to these species are able to produce antibacterial and antiprotozoal drugs. Since viruses are essential intracellular parasites, antiviral agents have to be able to suppress viral functions without affecting the host, making it very difficult to produce these medicines. Another drawback is that several rounds of replication of the virus take place during incubation and before symptoms arise, it spreads and renders the medication fairly ineffective. Active or not highly effective antiviral medications against viruses without vaccinations are required[10].

Antivirals are a class of medicines used for the prevention of viral infections. Most viral infections resolve spontaneously in immunocompetent individuals. Antiviral treatment is intended to decrease symptoms and infectivity and reduce the duration of the disease. These medicines work by stopping the viral replication process at various stages. Antiviral treatment for a small range of infections is currently only available [10]. Because viruses are intracellular pests, targets for medicines that interfere with viral replication are difficult to identify without harming host cells as well. Antiviral medicines, unlike other antimicrobials, do not kill or destroy the microbe (in this case the virus) but work through inhibitors of replication. It stops the viral load from being pathogenesis and allows the body to neutralize the virus through its innate process of immune function [10].

In fact, antivirals that can differentiate between virals and host replicates have been very difficult to produce [10]. With very high mortality and morbidity rates, no effective and safe of antivirus treatment has yet been found to cure COVID-19, so research is needed to find the most effective and safe of antivirus drugs to cure COVID-19.

METHOD

Several search strategies are used to identify relevant studies. Search for data and information using electronic sites as data sources. The article search results are used PRISMA (Preferred Reporting Items for Systematic Reviews & Meta Analyses) for instruments and using the flowchart based on the 2009 PRISMA checklist, eliminating articles that are not relevant to the criteria of identification, screening, eligibility, and finally downloading the article which is relevant. The first step is to open a Scopus, Proquest, Sciencedirect / Elsevier database, NCBI, NEJM, Nature, Wiley, Oxford academy, then use advanced search. Document selection using the keywords "Anti-Viral For Covid-19" OR "Anti-virus For Covid-19" AND "Anti-Viral for SARS-CoV-2" OR "Anti-Viral for SARS-CoV-2" in the journal Scopus, Proquest, Sciencedirect / Elsevier database, NCBI, NEJM, Nature, Wiley, Oxford academy. The researcher found 613 documents based on full text access for free or paid documents, documents based on publication year (3 years) and based on English. Then reselection the journal by title and abstract into 237 documents, then we find 39 documents that meet the research criteria and then we analyze the document.

The document inclusion criteria that we deem appropriate

for conducting a systematic review are journals of research, reported in English, published last 3 years (2018 - 2020), relevant and reliable discussing COVID-19 or SARS-CoV-2, specific studies discussing antivirus for COVID-19 or SARS-CoV-2. Studies are excluded if they cannot be accessed, do not have reliable references, are expensive.

RESULTS

The researcher identified the database using PRISMA (Preferred Reporting Items for Systematic Reviews & Meta Analyses) for instruments and used flowcharts based on the 2009 PRISMA checklist and based on several criteria such as documents that can be accessed for free or paid full text, in English and published in the last 3 years and following inclusion and exclusion criteria. We obtained 613 documents, then based on titles and abstracts we obtained 237 relevant studies and 376 irrelevant studies. Then based on the inclusion and exclusion criteria obtained 39 journals that match the criteria, the study discusses the overall COVID-19 or SARS-CoV-2 disease such as epidemiology, characteristics, pathogenesis, cytokine storm, and anti-viral drugs for COVID-19 or SARS-CoV-2, as well as some mortality and morbidity data from COVID-19. Then 39 studies that were relevant and had eligibility were analyzed systematically.

Based on the results of a systematic analysis, there are 6 anti-viral drugs used to treat SARS-CoV-1 or MERS-CoV and very potential to treat COVID-19, Favipiravir (Avigan, Favilavir), Lopinavir and Ritonavir (LPV / RTV; Kaletra), inhibitors of neuraminidase (e.g. oseltamivir), Remdesivir (Arbidol) and Baloxavir (Table 1).

Favipiravir is a new type of inhibitor of RNA-dependent RNA (RdRp) polymerase. [11] and Approved nucleoside analogues[12]. Favipiravir has been transformed into the active phosphoribosylated form (Favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, which inhibits the RNA polymerase activity. A total of 80 patients (including the study group and control group) have been shown to have a more potent antiviral activity on favipiravir than lopinavir and ritonavir[11]. In the research conducted by Wang, favipiravir has been shown to be 100% effective in protecting mice against Ebola virus challenge and reported its activity against COVID-19 (EC50 = 61.88 μ M in Vero E6 cells)[13].

Guanine analog approved for the treatment of influenza, favipiravir (T-705) can effectively inhibit RNA-dependent polymerase of RNA viruses such as influenza, Ebola, yellow fever, chikungunya, norovirus, and enterovirus [12]. RNA-dependent RNA polymerase inhibitor with wide spectrum antiviral activities; however, SARS-CoV-2 was shown to have a high EC50 but was successful, given similarly high EC50 values, in protecting mice from Ebola. Patients with COVID-19 are currently being evaluated in Clinical Trial NCT04273763. This agent is not approved by the FDA or available in the US [14]. Favipiravir treatment significantly improved time-to-relief for fever and cough, and is associated with manageable adverse effects[15].

Table 1. Anti-Virus Drugs For COVID-19

Drugs	Rationale	Trial and Clinical Experience	Dosage	Comments
Favipiravir (Avigan, Favilavir)	<p>Wide-in vitro spectrum antiviral against many viruses, including coronaviruses [12]–[17].</p> <p>In-vitro evidence of activity against SARS-CoV-2 reported high concentrations of the drug in infected Vero E6 cells [13], [14].</p> <p>Licensed for influenza diagnosis in Japan and China [12], [15], [16].</p>	<p>Just very small clinical evidence to date available to test Favipiravir's use in COVID-19 care.</p> <p>Open-label, Prospective randomized, The study was associated with a higher 7-day clinical recovery rate compared to umifenovir-treated control group in 236 adults with COVID-19 in China Favipiravir (1600 mg orally two times daily on day one, followed by 600 mg orally two times daily 7 to 10 days later) than in Umifenovir-treated control group (Arbidol®; 200 mg 3 times daily 7–10 days).</p> <p>The clinical remediation rate at day 7 for pts with mild COVID-19 pneumonia was stratified as severe, 71% for favipiravir vs. 56% for umifenovir; for those with extreme COVID-19 pneumonia, the clinical recuperation rates were 6% versus 0%, respectively.</p> <p>Compared to the group receiving umifenovir, the favipiravir group had serious illness twice as many pts.[15]</p>	Oral favipiravir : 600 mg on day 1, twice a day, followed by 600 mg twice a day 7-10 days [15].	<p>Not available commercially in USA</p> <p>Not established Efficacy and Safety of favipiravir for COVID-19 treatment</p> <p>More evidence required to support initial efficacy findings for COVID-19 care and determine the optimum dosage and length</p>
Neuraminidase inhibitors (e.g., oseltamivir)	Antivirals active against influenza viruses	<p>76% of patients received antiviral therapy (75 mg orally per 12 hours) in the retrospective sequence of 99 COVID-19 patients at one center in Wuhan from 1/20 to 1/20/20. During the time of this review, 58% of patients were hospitalized, 31% were released and 11% died [18]</p> <p>While oseltamivir has been used extensively in confirmed or suspected cases of COVID-19 in Chinese hospitals, no detailed evidence of its impact on COVID-19 has been given to date [19]</p>	oseltamivir was 75 mg orally every 12 hours in 99 patients [18]	Use for COVID-19 treatment is supported by very limited data available to date
Remdesivir	<p>Broad-spectrum antiviral with coronavirus activity.</p> <p>SARS, MERS, and Ebola have previously been tested.</p> <p>In vitro proof of SARS behavior-CoV-2 [13].</p> <p>In vitro activities against SARS-CoV and MERS-coV; successful in SARS and MERS animal models; prevented MERS from being administered before infection in rhesus macaques and given</p>	In vitro studies have shown that remdesivir and chloroquine control in vitro COVID-19 infection is highly successful. [13]	Warren et coll. showed that 10 mg / kg of intravenous remdesivir in the NHP model resulted in concomitant constant blood levels (10 µM) and 100% Ebola virus safety[13].	<p>Not available on the market; most promising antiviral currently under investigation for COVID-19.</p> <p>Security and effectiveness not established; additional information needed.</p>

Drugs	Rationale	Trial and Clinical Experience	Dosage	Comments
	benefits after already contagious animals [13], [20]–[25].			
Baloxavir	Antiviral active against influenza viruses	The efficacy of favipiravir + interferon- α (ChiCTR200001029600) and favipiravir + baloxavir marboxil (an authorised inhibitor of influenza targeting cap-dependent endonuclease) is being recruited in randomized trials (ChiCTR2000029544)[17].	No data to date support the use of COVID-19 in treatment	No evidence to date support the use of COVID-19 care.

Lopinavir-Ritonavir is an anti-virus that works in the translation process. Lopinavir- Ritonavir works as a Protease inhibitor in the translation process in infected host cells. Lopinavir-Ritonavir is often used in HIV / AIDS patients [26]. Lopinavir-ritonavir treatment was not associated with a difference in time from standard care to clinical improvement (hazard ratio for clinical improvement, 1.31; confidence interval of 95 per cent [CI], 0.95 to 1.80). In the lopinavir-ritonavir group and the standard-care group, 28-day mortality was similar (19.2 per cent vs. 25.0 per cent; difference, -5.8 percentage points; 95 per cent CI, -17.3 to 5.7). In the lopinavir-ritonavir group, gastrointestinal adverse events were more common but in the standard care group, serious adverse events were more common. No substantial improvements in viral RNA load reduction, viral RNA detection period, oxygen therapy period, hospitalization time or duration from randomization to death. In 13 patients (13.8 percent) treatment with lopinavir – ritonavir was stopped early due to adverse events[27].

In vitro studies on tianan yao animals, Lopinavir (LPV) is an effective agent that inhibits coronaviral protease activity [28]. Neuraminidase inhibitors are anti- viruses that work in the process of inhibiting the process of virus attachment and penetration. Specifically works to inhibit the activation of interferon-alpha. Neuraminidase inhibitors (NAIs) such as oral oseltamivir, are recommended as antiviral treatment in influenza [19]. In Hongzhou Lu 's work there is no clear proof that oseltamivir is effective in treating COVID-19 [19]. Routine use of antibiotics and antivirals such as oseltamivir in reported cases should be avoided and the COVID-19 has no major effect [29].

Remdesivir is an anti-virus nucleoside analogue that works on the process of RNA- dependent RNA polymerase (RdRp) inhibitor. Remdesivir recommended as antiviral treatment in MERS-CoV or SARS-CoV-1[21], [23]. In-vitro research conducted by Maria L. Agostini, showed that Remdesivir can inhibit the development of SARS-CoV-2 [21]. Significant reduction of pulmonary virus in a murine SARS-CoV, good SARS-CoV-2 antiviral activity, a suitable parenteral remdesivir therapeutic risk profile, and a randomized trial of Ebola virus disease, highly expected clinical application of remdesivir in COVID-19 cases [25]. Baloxavir is anti-virus nucleoside An approved influenza inhibitor targeting the cap-dependent endonuclease[17]. No data to date supports the use of COVID-19 in treatment.

CONCLUSION

Based on a systematic review it can be concluded that the best drug to cure SARS- CoV-2 or COVID-19 which is the most effective and safe first place is Favipiravir, although there are no data to show that patients treated with Favipiravir can recover 100%, but Favipiravir treatment has significantly improved time to relieve it. Fever and cough and are associated with manageable side effects.

The second is Remdesivir, because in vitro studies show that Remdesivir and chloroquine are highly effective in controlling in vitro infection in SARS-CoV-2. Remdesivir effective reduction of pulmonary viral load in a murine model of infection with SARS-CoV, and very potential to be antiviral activity against SARS-CoV-2.

The third grade is Umifenovir with substantial high negative coronaviral conversion and may be beneficial for preventing the development of lung lesions and reducing the possibility of respiratory and gastrointestinal transmission in order to decrease COVID-19 viral load.

The fourth range is lopinavir-ritonavir, but in hospitalized patients with extreme Covid-19 no effects were found with non-standard lopinavir-ritonavir therapy. Lopinavir-ritonavir treatment was stopped early because of adverse effect is to much. No major variations in viral RNA load reduction, viral RNA detection time, oxygen therapy period, hospitalization durations and death randomization rate. But in-vitro studies in animals have shown that Lopinavir-ritonavir can suppress COVID-19. Neuraminidase inhibitors (oseltamivir).

To date, no credible evidence was found for the efficacy of oseltamivir in COVID-19 therapy.

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