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Safety and Efficacy of antiviral drugs against covid-19 infection: an updated systemic review

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Abstract:

SARS-CoV-2 infection is an acute pneumonia attack caused by a largely-infectious, recently elicited, and murdered virus with global public health issues and economic problems. Many antiviral agents were tried to eradicate COVID-19 infections, and some showed significant benefits with minimal toxicity. Although other agents showed some acceptable efficacy, these agents were associated with serious adverse effects. In this regard, we conducted a systematic review of the literature to evaluate antiviral therapies that could help patients eliminate COVID-19.

To conduct this review, we used many search engines, including the electronic databases Science Direct, Google Scholar, PubMed, Scopus, and Web of Science, from Nov. 2020 to Apr. 2022.

This research aims to evaluate the Efficacy and safety of antiviral agents that have been clinically tested against COVID-19 infection, with an emphasis on FDA-approved antiviral agents such as remdesivir, Paxlovid, and molnupiravir to reduce the severity of COVID-19 infection and lower the mortality rate.

Keywords: SARS-CoV-2, antiviral potency, safety, Efficacy.

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Introduction

SARS-CoV-2, a virus infection that caused one of the most dangerous and spread epidemics associated with severe acute respiratory syndrome, first appeared in China in some patients from Wuhan city in late 2019. This virus rapidly spread to different areas of the world in July 2020 and infected more than 10 million patients with a high mortality rate. The main problems in managing these cases were that no specific antiviral agents were available, and different drugs were tested to overcome this infectious pandemic [1]. Although most cases have been mild, patients with more aggressive types may rapidly develop acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), and even death. Therefore, it is important to find potent antiviral drugs against COVID-19 that are essential to delay or halt disease progression [2].

Genomic Structure and Replication of Covid-19

The genomic structure of Covid 19 virus is a spherical envelope containing a single-stranded RNA. This RNA can directly access transcript to protein (positive sense) and connect to nucleoproteins enclosed with a protein capsid, as shown in (Figure 1).

The cover consists of assembly glycoprotein projections; moreover, several coronaviruses have a hem agglutinin-esterase protein (HE). This type of virus is one of the genus called Beta-coronavirus, one of the Coronaviridae family. The coronal virus membrane is made up of three or four viral proteins, such as envelope (E) and membrane (M) glycoprotein, which triples the size of the membrane bilayer by forming a short NH2-terminal domain outside the capsid with a long COOH-terminal domain (cytosolic site) within the viral genome, and spike protein (S), which is the primary inducer of neutralizing antibodies [3].

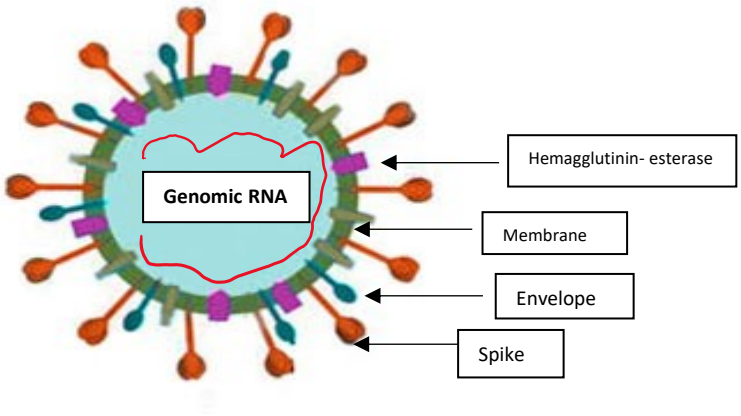

Figure (1): Structure of the coronavirus

SARS-CoV-2 spreads from one person to another through respiratory droplets and aerosols. This virus uses its protein S with its core protease termed TMPRSS2 to attach the angiotensin II receptor (AT) to pulmonary alveolar epithelial cells and allows virus particles to attack and infect these cells. Inside host cells, viruses are uncoated. The genome is transcribed on the cytoplasmic membranes using unique RNA helicase and then translated with the help of RNA-dependent RNA polymerase and cyclic phosphodiesterase activities [4]. The newly generated nucleocapsids are trapped in the endoplasmic reticulum membrane and translocated to the lumen, then to the cell membrane through exocytosis through Golgi vesicles. These new particles are beginning to readily attack

neighboring epithelial cells with viral attacks and make new viral genetic material on them, as illustrated in (figure 2) [5].

Possible targeting of COVID -19 for antiviral agents

The first attempt of antiviral agents is to target the disruption of the viral envelope and prevent viral attachment to host cells [6]. Antiviral agents could eradicate SARS-CoV-2 infection by targeting the Spike S glycoprotein, thus inhibiting viral fusion entry into host cells [7]. Another mechanism involved the inhibition of endosomal acidification; therefore, this action stopped pH-dependent activation of viral host endosomal membrane fusion and prevented uncoated viral and viral RNA release [8].

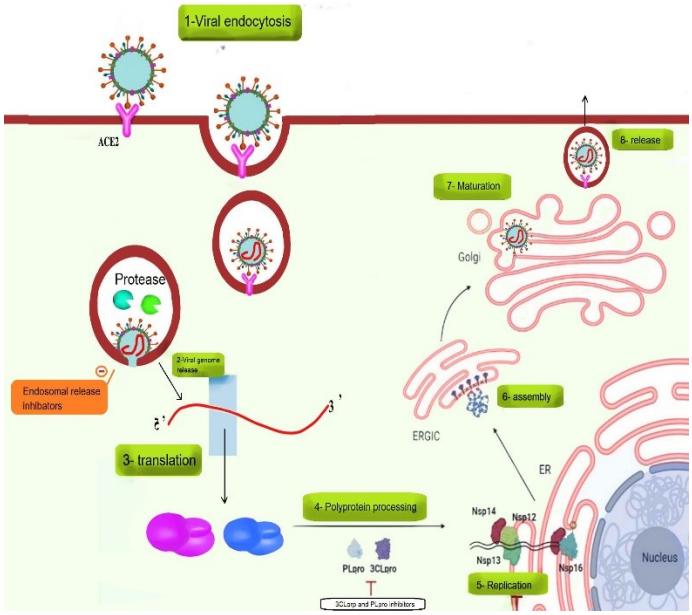

Figure (2): Possible targeting of COVID -19 for antiviral agents.

Antiviral agents tested for COVID-19 infection.

Azvudine

Azvudine is a structural analog of pyrimidine (2′-deoxy-2′-β-fluoro-4′-azidocytidine), which is a prodrug that requires intracellularly cytoplasmic deoxycytidine kinase for its phosphorylation in FNC triphosphate and inhibits viral RNA-dependent RNA polymerase (RdRp). It has a broad antiviral spectrum activity that includes Hepatitis C (HCV), Enterovirus 71 (EV71), and Human immunodeficiency virus (HIV) [10]. A clinical trial was conducted in a group of 20 COVID-19 patients who received Azvudine tablets that showed it reduces the nucleic acid negativity conversion time without recorded adverse effects [1]. Another clinical study revealed that 31 covid-19 patients received oral Azvudine 10 mg q.i.d for the first day and then 5 mg q.i.d for subsequent treatment, curing all treated patients by shortening the duration of the disease with minor adverse effects such as transient dizziness and nausea [11].

Darunavir/Cobicistat

Darunavir / Cobicistat is a fixed-dose combination antiretroviral agent for managing and preventing HIV infection. Darunavir is an active antiviral agent in this combination and acts by inhibiting the HIV protease enzyme. Darunavir is extensively metabolized by liver cytochrome P 450 (CYP3A), reducing its activity. Therefore, it is combined with cobicistat to block this liver enzyme and increase the effectiveness of darunavir [12]. Darunavir/Cobicistat reduced the mortality rate in 14 treated patients with critical SARS-CoV-2 infection [13]. This combination tested in 30

patients with a positive PCR test for COVID-19 resulted in a reduction in the onset of viral infectious symptoms to 3 days with some adverse effects including diarrhea, iron deficiency anemia, abnormal renal function test in approximately 13% of treated patients, and elevated level of transaminase enzyme [14].

Favipiravir

Favipiravir is a synthetic prodrug that needed intracellular phosphorylation to an active form, favipiravir-ribofuranosyl-5'-triphosphate (favipiravir-RTP). It could be administered orally or parenterally to treat viral infections from influenza and Ebola [15,16]. Its active form resembles a purine nucleotide which is competitively inhibited by RdRp, resulting in the termination of viral protein synthesis [17]. The Chinese clinical study revealed that favipiravir improved clinical COVID-19 within 7 days by relieving fever and cough and reducing the requirement for additional oxygen therapy or non-invasive mechanical ventilation [18]. Another Japanese observational study mentioned that favipiravir significantly reduced the time required for viral clearance of SARS-CoV-2 [19]. The most adverse effects of favipiravir appearing in patients are minor. They include reduced neutrophil count and transaminitis in 2% of patients, dose-dependent hyperuricemia and diarrhea in 5% of patients, psychiatric symptoms, and prolongation of the QTc interval [20].

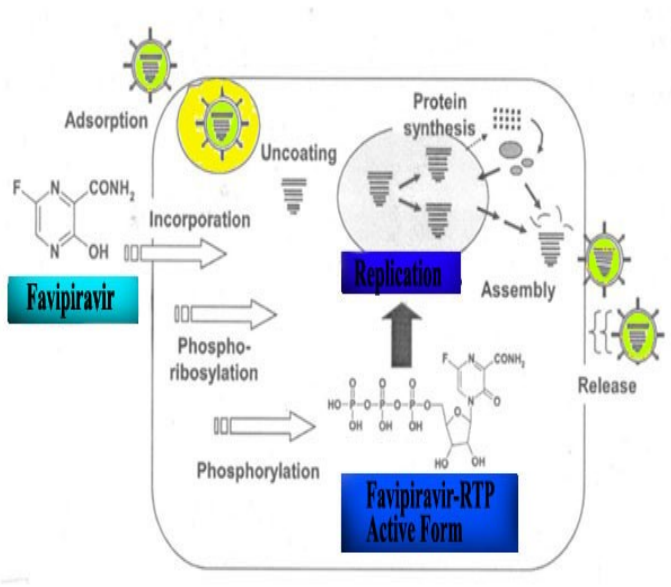

Figure (3): Favipiravir's intracellular activation and mechanism of action.

Remdesivir

Remdesivir is a prodrug analog of an adenosine nucleotide with a broad antiviral spectrum covering filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses. An intracellular esterase, phophoamidase, and nucleoside phosphate kinase are required to convert it to the active form, which interacts with the action of RdRp, causing a decrease in viral RNA replication [21]. Early prescribing of remdesivir is necessary to improve clinical symptoms in COVID-19 patients [22]. Remdesivir is administered to patients with severe COVID-19 infection who receive an O2 supplement in the hospital with a dose of 200 mg IV on the first day, then 100 mg daily for up to 9 days, resulting in a reduced time to clinical recovery. But no benefits were observed in those taking high-flow O2 supplements [23]. The serious adverse effects associated with the use of remdesivir are elevation in

alanine aminotransferase, anemia, and renal failure [24].

Umifenovir

Umifenovir is a heterocyclic complex composed of a functional indole core and different substituents with broad antiviral activity, including influenza and hepatitis C. It prevented viral envelopes from the fusion cell membrane of human cells and had more activity against RNA virus than DNA virus. It also had an immunomodulation effect, such as excitation of humoral immune response, promoting interferon production, and enhancing macrophage phagocytic function. It induced a negative PCR result on day 14 in adult COVID-19 patients [25]. Umifenovir in 200 mg t.i.d with standard care for seven days is the most effective for managing COVID-19 infections compared to Favipiravir. Umifenovir shortened latency to relieve pyrexia and cough with a minor adverse effect that appeared in 3 patients, elevated serum uric acid [18].

Sofosbuvir and Daclatasvir

Sofosbuvir is a prodrug of the protide type and is one of the common antiviral classes that inhibit nucleotide polymerase. It is considered second-line therapy for hepatitis C infection. Its action requires intracellular activation for the nucleotide analog termed 2'-deoxy-2'-α-fluoro-β-C-methyluridine-5'-triphosphate. Thus, it is competitively competing with the natural one for viral RNA polymerase. This mechanism terminated viral RNA elongation with a lower chance of resistance development [26]. Daclatasvir is an inhibitor of HCV phosphoprotein 5A (NS5A) that prevents viral RNA replication and virion assembly. It is also used with other antiviral agents as chronic therapy for hepatitis C infection [27]. A clinical trial was conducted in 96 Egyptian patients with COVID-19, who received 400 mg of sofosbuvir and 60 mg of daclatasvir for two weeks in combination with conventional therapy resulting in a short hospital stay, reduced mortality rate, and rapid negative PCR performance [28]. Sofosbuvir/daclatasvir reduced mortality and improved clinical recovery in patients with moderate to severe COVID-19 without any reported serious adverse effects [29,30].

Lopinavir/ritonavir

Lopinavir/ritonavir is a fixed-dose compound with an antiretroviral activity that is indicated for managing and preventing HIV infections. Lopinavir is a potent inhibitor of the HIV-1 protease enzyme. This enzyme is responsible for cleavage of the gap polyprotein, which is considered a critical point in producing mature infectious viral particles. Lopinavir acted as a peptidomimetic agent with a hydroxy ethylene scaffold that strongest the normal peptide bond; thus, it prevented the action of HIV-1 protease. Because lopinavir undergoes extensive liver oxidative metabolism through CYP3A isoenzymes, it is used in combination with Ritonavir, a potent inhibitor of CYP3A isoenzymes that results in better oral bioavailability of lopinavir [31]. Lopinavir (400 mg)/Ritonavir (100mg) was administered orally to 99 hospitalized COVID-19 patients, resulting in a nonsignificant shortening of clinical improvement time and improvement of the PCR negative test. However, this reduced mortality rate and shorter stay in the intensive care unit (ICU). Lopinavir/ritonavir could not be

used for a long time due to its induced adverse effects, including gastrointestinal effects (like nausea, vomiting, diarrhea, and change in liver function), anemia, rash, sleep disturbances, and prolonged QT intervals [32]. In a clinical trial involving 86 patients with mild/moderate COVID-19, randomly assigned with 34 to the Lopinavir/ritonavir group, 35 to the umifenovir group, and 17 without antiviral medication as the control group, there was no significant difference in the PCR negativity test, the rate of relief from fever, the resolution of cough, and the improvement in chest CT imaging [33].

Nirmatrelvir/Ritonavir

Nirmatrelvir/Ritonavir is an orally prescribed fixed combination antiviral drug under Paxlovid that blocks viral replication by inhibiting viral protease enzyme. Nirmatrelvir is combined with Ritonavir, a potent inhibitor of CYP3A enzymes, to overcome extensive liver oxidative metabolism and increase the bioavailability of nirmatrelvir [34]. Paxlovid is an FDA-approved antiviral therapy for mild-moderate COVID-19 infection in adults and pediatric patients (≥ 12 years of age)[35]. In a clinical trial, nirmatrelvir/ritonavir was administered multiple ascending doses twice daily for 10 days, resulting in a significant reduction in viral load in patients with COVID-19 and may reduce the chance of progression of severe hospitalization disease. The adverse effects associated with Paxlovid are mild and include nausea, vomiting, dysgeusia, and an increase in the level of thyroid-stimulating hormone [36].

Molnupiravir

Molnupiravir is a ribonucleoside prodrug of ribonucleoside termed β-D-N4-hydroxycytidine (NHC), which hinders certain RNA viruses' propagation. Intracellular metabolism to NHC triphosphate (NHC-TP) is required, which is incorporated into newly developed RNA with the help of viral RdRp resulting in viral mutations [34,35]. On Dec 23 2021, the food and drug administration (FDA) published that molnupiravir could be used for the management of adult patients with mild to moderate COVID-19 with early symptoms that begin within 5 days or tend to progress to severe disease and for whom alternative antiviral agents are not accessible [37]. In a clinical study, patients with mild to moderate COVID-19 infection who received 800 mg of molnupiravir improved signs and symptoms of COVID-19 pneumonia and reduced hospitalization and mortality rate. The adverse effects of molnupiravir are mild and include diarrhea, nausea, dizziness, and thrombocytopenia [38].

Interferons

Interferons (IFN) are a family of cytokines that have antiviral properties. It is produced and released by host cells in response to the presence of several viruses. Interferon α is used to treat hepatitis B and hepatitis C virus infections [39]. The two types of interferon were tested for patients who had severe conditions of COVID-19, randomly allocated into IFN-β1a (subcutaneous injections of 12,000 IU on days 1, 3, and 6 with hydroxychloroquine and lopinavir/Ritonavir) group, IFN-β1b (subcutaneous injections of 8,000,000 IU on days 1, 3, 6 with hydroxychloroquine and lopinavir/Ritonavir) group, or control group (hydroxychloroquine and lopinavir /

Ritonavir). IFN-β1a significantly reduced the time to clinical improvement within 5 days compared to the control group. But the mortality was significantly lower in both groups treated with interferons. The main adverse effect observed in treated patients is a change in the liver function test [40]. IFN-α exhibited a reduction in time to clinical improvement (11.5 days vs. 14 days for the control groups), time to radiological improvement on chest CT scans (8 days vs. 10 days for the control groups), and time to virus-negative conversion (7 days vs. 10 days for the control groups) with a decreased appetite as a mild adverse effect [41].

Conclusion:

All antiviral agents clinically tested for COVID-19 infection showed variation in Efficacy in decreasing the mortality rate, the PCR negativeness test, and relief of COVID-19 symptoms. The safety of these agents was also variable, ranging from negligible to moderate adverse effects. In addition to FDA-approved antiviral agents against COVID-19 infections, many other clinical studies are required to cover more possible effective antiviral agents.

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