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REVIEW ARTICLE

COVID-19: PHARMACOLOGICAL AND THERAPEUTIC APPROACHES

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ABSTRACT
In the end of 2019, SARS-CoV-2, a new virus from Corona viruses family, has been detected in China and was responsible for COVID-19 disease. This disease has been suddenly and vigorously disseminated among individuals all over the world. Based on genetic vicinity, this novel virus is similar to SARS-CoV and MERS-CoV and it can spread from an unknown animal host to individuals. Many published clinical data and *in vitro* studies may offer treatment strategies of some effective antiviral and repurposed drugs, including remdesivir, favipiravir, lopinavir/ritonavir, corticosteroids, etc. This narrative review describes current pharmacological proposed treatments for COVID-19 patients and available experimental and clinical studies for these drugs. Eventually, these data may help to explain the most preferable way to treat COVID-19 and lessen the accompanied symptoms and complications.
Keywords: Favipiravir, Monoclonal antibodies, Pathophysiology, Remdesivir, SARS-COV-2.

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INTRODUCTION

The COVID-19 pandemic is the most destructive pandemic evolved in the last 10 decades after Spanish flu which occurred between1918-1920.*Yang et al.*,[1]. COVID-19, a viral respiratory disease, caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in Wuhan in 2019[2]. It is known that coronaviruses are composed of single-stranded RNA viruses which are described by a spherical structure. These viruses are classified into α, β, γ, and δ-coronaviruses[3]. In the past two decades, severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), type of β-coronaviruses, were found in China in 2002 and Saudi Arabia in 2012, respectively. However, COVID-19, a novel type of β-coronaviruses, is a highly contagious virus and has spread throughout the world[4]. The WHO has declared that COVID-19 is a global pandemic disease as its deaths surpass 500,000 with 10 million infected patients. The transmission of this epidemic disease began from animal to human[5] and then transmitted among individuals *via* respiratory droplets[6]. The clinical features of COVID-19 patients involve flu-like symptoms including, fever, dry cough, fatigue, and developed in severe cases into pneumonia and kidney failure. Noteworthy, patients with COVID-19 had a profound lymphopenia, and a storm of proinflammatory cytokines and chemokine[7]. Accordingly, this storm of cytokines may lead to acute respiratory distress syndrome (ARDS), sepsis, and death[8]. In case of severe cases, pharmacological therapies and antivirals drugs should be provided to decrease the severity of symptoms. This review aims to summarize the available treatments administered in COVID-19 patients focusing on the pharmacological mechanisms, safety, and experimental and clinical trials.

METHOD

This review work was performed using PubMed to identify relevant articles published.

SARS-CoV-2

Pathophysiology of SARS-CoV-2

SARS-CoV-2, a single-stranded viral RNA, has four structural proteins, which are "S" for a spike, "E" for an envelope, "M" for membrane, and "N" for nucleocapsid

and its sequence is similar to bat SARS-like coronavirus[5]. The viral spike (S) protein can bind to angiotensin-converting enzyme-2 receptor (ACE2) and transmembrane serine protease (TMPRSS2) facilitates cell entry. The S protein is divided into S1 and S2 by proteases. While, S1 binds to ACE2, S2 is divided by TMPRSS2, with a consequent fusion of the membrane. After binding, and fusion, the virus enters the host cells and then replication and transcription commence[9]. The nonstructural proteins produced from autoproteolytic cleavage are responsible for anchoring the coronavirus replication/transcription complex through recruitment of intracellular endoplasmic reticulum to form double-membrane vesicles (DMV). RNA-dependent RNA polymerase (RdRp) and helicase localize to DMV and drive the production of sub genomic RNAs from which the structural and accessory proteins are produced in the next phase of translation[10].

Available pharmacological treatments for COVID-19

Antiviral agents

Many antiviral drugs are used to treat some of human virus diseases including, hepatitis C, influenza virus, human immunodeficiency virus (HIV), etc. Note worthily, certain antiviral agents are administered off-label for the treatment of COVID-19 patients. This section discusses the antiviral drugs which are currently available for the treatment of infected patients with COVID-19.

Remdesivir is shown to be the most promising antiviral drug against wide spectrum of RNA viruses including MERS and SARS-Cov *in vitro* and *in vivo* models[11]. It is a monophosphate prodrug that metabolized to an active C-adenosine nucleoside triphosphate analog which inhibits RNA-dependent RNA polymerase (RdRp) proteins resulting in premature termination of viral RNA transcription[12]. Due to many positive case reports and clinical trials of remidisiver in highly affected countries[13]; Food and Drug Administration (FDA) finally approved remdesivir for the treatment of COVID-19 in hospitalized adult and pediatric patients. It shows great success to control the clinical situation of COVID-19 patients[14]**.** However, the follow up for the possible side effects is mandatory in the following months after this approval.

Favipiravir has been approved as treatment for influenza viruses' subtypes and Ebola viruses. It is a guanine analog prodrug and selectively inhibits RdRp, halting viral replication. A clinical trial of hospitalized COVID-19 patients in Wuhan has indicated that the patients who received favipiravir tested negatively in 4 days only compared with the control group (11 days) and the symptoms of pneumonia were markedly diminished[15]. Lately, several clinical trials have supported the use of favipiravir in the treatment of COVID-19 patients.

Lopinavir/Ritonavir is a combination of antiretroviral protease inhibitors used with high specificity for the treatment of HIV. Ritonavir increases lopinavir half-life *via* the inhibition of cytochrome P450. This combination has promising outcomes in treatment patients with SARS infection and MERS-CoV infection and its efficacy have also been evaluated in combination with interferon-β[16]. A contemporary study has noticed that the efficacy of Remdesivir was superior to that of Lopinavir/Ritonavir[11].

Umifenovir (Arbidol) is a non-nucleoside antiviral and immunomodulating agent that was commonly used for influenza treatment in Russia and China. *In vitro* data based on the activity of arbidol against SARS has suggested a great effect of it in treating COVID-19 patients[17]. Thus, for SARS-CoV-2, Umifenovir is considered as a more promising antiviral agent through targeting S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope. Moreover, according to a retrospective cohort study, arbidol could enhance the process of viral clearance and improve chest radiologic images[18].

Camostat mesylate and Nafamostat, two synthetic protease inhibitors, are approved for the treatment of chronic pancreatitis in Japan. As previously mentioned, ACE2 and TMPRSS2 are essential for SARS-CoV-2 binding and cell entry. Therefore, both agents can prevent viral cell entry through inhibition of the host serine protease, TMPRSS2. This novel mechanism provides an additional drug target for future research[9].

Ivermectin is an antiparasitic agent and has antiviral activity against a wide range of viruses. The researchers recommended that its early administration may decrease the viral load and inhibit disease progression. Interestingly, a recent systemic review has highlighted the safety and efficacy of using a high dose of ivermectin compared to standard low one in treating COVID-19. More importantly, experts hypothesized that a combination of hydroxychloroquine and ivermectin may have a synergistic effect for the treatment of COVID-19 depending on the pharmacological action of both drugs. Consequently, ivermectin may be a promising agent against SARS-CoV-2 infection[19].

Anti-inflammatory and immune-modulatory agents:

As previously mentioned, COVID-19 disease is associated with cytokine storm and release of large number of proinflammatory cytokines and the development of cytokine storm, such as tumor necrosis factor-α (TNF-α) and interleukin-(IL)-1,-2,-6, particularly in severe cases. This augmented immune response and cytokine release may lead to sepsis, reduction in respiratory function, and significant organ damage, especially lung and kidney. Thus, several monoclonal antibodies, anti-inflammatory, and immune-modulatory agents are potential therapies for COVID-19 patients.

Tocilizumab is a monoclonal antibody that blocks the IL-6 receptor and has been approved for the treatment of rheumatoid arthritis[20]. There was no significant difference between tocilizumab and standard care patients after 28 days and patients experienced reduced fever and lower need for supplemental oxygen[21].

On the other hand, Corticosteroids, as anti-inflammatory agents**,** may be used against SARS-COV-2 to decrease acute lung injury and prevent ARDS. However, their use may lead to some adverse

events including, a higher risk of secondary infection and delayed clearance of the virus. Some observational and meta-analysis studies of using corticosteroids in patients with SARS and MERS confirmed an increased risk of mortality and secondary infection, and other complications[22]. Therefore, the use of corticosteroids should be with caution and under evaluation by physicians until confirmed clinical trials for its indication in COVID-19 patients.

Chloroquine and hydroxychloroquine, used in the treatment of malaria and other autoimmune diseases including systemic lupus erythematosus (SLE) and rheumatoid arthritis, can block viral entry and inhibit glycosylation of host receptors. Besides, they have immune-modulatory actions through the prevention of cytokine production, which makes them effective against SARS-COV-2[23]. These agents are off-label used for the treatment of COVID-19 patients in China and other countries[24]. A clinical study has shown that the combination of remdesivir/chloroquine or hydroxychloroquine is greatly effective against patients with SARS-Cov2 infection. Moreover, Gautret *et al.*,[25] have reported that the addition of azithromycin to hydroxychloroquine resulted in superior virus clearance (100%) compared with hydroxychloroquine alone (57%). It is worthy to note that both agents have impaired hepatic metabolism markedly in COVID-19 patients, resulting in a high risk of liver injury[26].

Baricitinib, another inhibitor of cytokine-release, is a Janus kinase reversible inhibitor approved for the treatment of rheumatoid arthritis. Furthermore, it seems to have antiviral impacts by blocking AP2-associated protein (AAK1), which may decrease SARS-CoV-2 endocytosis[27]. This seems to inhibit the cytokine storm associated with COVID-19 and reduce the progression of the disease. Richardson *et al.*, have suggested that baricitinib may be a potentially promising drug for COVID-19 patients[28].

Thalidomide, an immunomodulatory and anti-inflammatory drug, is considered to be used for the treatment of interstitial pulmonary fibrosis and effective against HIV through inhibition of nuclear factor-κB, pro-inflammatory cytokines secretion, and regulate immunity. Notably, Chen *et al.*,[29] have assumed, *via* randomized controlled clinical study, that using thalidomide in combination with glucocorticoids may be effective in the treatment of COVID-19 patients.

Interferon has shown mixed efficacy against SARS-CoV and MERS-CoV. Interferon, an anticancer and antiviral agent, is used in the treatment of hepatitis C, leukemia, and HIV. It inhibits SARS coronavirus in cell-based models so it may be examined against SARS-CoV-2. Interferon may be a safe treatment against COVID-19 patients in the early stages of infection[30].

Fluoxetine and Fluvoxamine:

Fluoxetine and fluvoxamine are interleukin- 6 (IL-6) blockers and thus participate in cytokine storms inhibition associated with COVID-19. This effect is a separate pathway than the selective serotonin reuptake inhibition pathway that makes fluoxetine and fluvoxamine to act as anti depressant agents. A clinical trial showed that taking fluvoxamine within week of first symptoms of COVID-19 can decrease the risk of respiratory distress[31].

Other Miscellaneous therapeutic options

IgG antibodies and convalescent plasma (CP)

Depending on the immune system of the patient to treat COVID-19 disease, scientists have suggested the use of immunoglobulin purified from IgG antibodies and convalescent plasma (CP) of COVID-19 patients who are recently recovered from this infection. The rationale for using this strategy is using antibodies from the recovered patients may help with immune cell clearance for the virus. It was shown that convalescent plasma from COVID-19 patients enhances the clinical symptoms and increases the survival rate[32].

Ascorbic acid (vitamin C) is a water-soluble vitamin used as an antioxidant. Recent reports have suggested that vitamin C inhibits cytokine production and lung fibrosis. Furthermore, Vitamin C has antiviral activity at higher concentrations and the ability to decrease the load of some viruses[33].

Azithromycin is a macrolide antibiotic and has both antibacterial and antiviral activities. It is mainly used in the treatment of skin infections, pneumonia, sinusitis, and has antiviral activity against Zika Virus[34]. As previously mentioned, experts have demonstrated that the combination of azithromycin and hydroxyl-chloroquine has a great efficacy against COVID-19 pneumonia patients and decrease viral load[25].

Coagulopathy is a significant abnormality in COVID-19 patients, with prominent elevation in D-dimers and fibrinogen. It is evidenced that pulmonary embolism and micro thrombosis found in severe COVID-19 patients have been documented from lung dissection[35]. Additionally, the hypoxia existed in COVID-19 patients can stimulate venous thromboembolism (VTE) and pulmonary embolism through increasing blood viscosity and hypoxia inducible transcription factor dependent signaling pathway as well[36]. For these reasons, experts have announced that confirmed or suspected COVID-19 patients should be treated with anticoagulants such as heparin or low molecular weight heparin (LMWH) to prevent the incidence of VTE[37].

Vaccination:

Currently, Pfizer-BioNTech and Moderna's COVID-19 vaccines are authorized both are of mRNA type of vaccines. Despite their high effectiveness and protection capability of both vaccines against the virus there are some obstacles that may face these vaccines such as: equal distribution of vaccines to all the affected areas are the safety and the vaccines in a large and diverse population will be still under spot. Our review is mainly concerning with the pharmacology of COVID-19 and we believe that the proper COVID-19 pharmacological treatment is the surviving ship in this strong storm for all areas in the world for both the developed and developing countries[38].

CONCLUSION

The repurposing drugs including, antiviral drugs, anti-inflammatory and immune-modulatory agents are

being used for treating COVID-19 patients and decrease the severity of this pandemic. A plethora of clinical trials have been conducted to investigate the validity of drugs used for COVID-19 patients and explore other new ones. Hopefully, all these efforts will corporate to produce treatment strategies that seem to be effective against COVID-19. Despite the development of vaccines; we have to continue exploring the pharmacological drugs used to control such pandemic especially after the evolution of new viral strains which keep this pandemic a possible danger in the future so we have to be ready.

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