

New Challenge Antiviral Treatment of Corona Virus Disease 2019 (COVID-19) Include Renal Impairment

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ABSTRACT

In almost every country around the world, the current pandemic of coronavirus disease 2019 (COVID-19) caused by extreme acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has provided unparalleled challenges to healthcare systems. There are currently no effective vaccines or therapeutic agents against the virus that have been developed. Infection prevention and control procedures and supportive treatment, including supplemental oxygen and mechanical ventilator assistance, are part of existing clinical management. The creation of SARS-CoV-2 virology research and clinical evidence indicates a possible list of repurposed medicines with sufficient pharmacological effects and therapeutic effectiveness in the treatment of patients with COVID-19.

Researchers are striving to find a virus-specific antiviral. Several medications have been used in China, such as chloroquine, hydroxychloroquine, lopinavir / ritonavir and favipiravir and the use of the investigational drug remdesivir for the treatment of COVID-19, with some positive findings to date. This paper summarizes agents that are potentially effective against SARS-CoV-2.

Keywords: corona virus disease 2019, COVID-19, Antiviral treatment, renal impairment

INTRODUCTION

Coronavirus 2 (SARS-CoV-2) is a new strain of coronavirus that causes acute respiratory infections known as 2019 coronavirus disease (COVID-19). (1) SARS-CoV-2 is a positive sense, with ~79 percent similarity to SARS-CoV and ~50 percent similarity to Middle East respiratory syndrome corona virus, the single-stranded RNA virus belongs to the genus Betacoronavirus.

The virus first originated in Wuhan, China in December 2019, and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. (2) The clinical manifestations of COVID-19 vary; most have mild and self-limiting airway disorders (81%), although a limited percentage of patients (5%), typically those

with a reduced immune system, are elderly or have some comorbidities, c⁽³⁾,

There has been a major challenge to global public health in the last two decades. Serious acute respiratory syndrome (SARS, 2002-2004⁽⁴⁾⁽⁵⁾ and Middle East respiratory syndrome (MERS, 2012-current⁽³⁾ SARS and MERS are a new class of public health concern that can continue to arise in human populations: coronavirus-induced respiratory syndromes (CoVs) that are transmitted by close contact from person to person, resulting in high morbidity and infectious mortality. While SARS and MERS are initially present in fever, dyspnea, and cough as mild, influenza-like diseases, progression to more serious symptoms is characterized by atypical interstitial pneumonia and diffuse alveolar harm. Both SARS-CoV and MERS-CoV are

capable of triggering the most serious type of acute lung injury, acute respiratory distress syndrome (ARDS), in which alveolar inflammation, pneumonia, and hypoxic lung conditions contribute to respiratory failure, multiple organ disease, and death in 50% of ARDS patient⁽⁶⁾ The total number of patients reported to be infected with highly pathogenic CoVs is relatively low (approximately 10,000 cases of both SARS and MERS since 2002), but CoVs are of particular concern because of high case fatality rates, lack of proven therapeutics, and the demonstrated capacity of these pathogens to seed outbreaks that rapidly cross geographical and geopolitical boundaries to other countries.

General Mechanism of COVID-19 involvement renal impairment:

The SARS-CoV-2 pathogenesis mechanism helps researchers to identify targets for novel therapeutic agents for the prevention or treatment of a disease. A single stranded, RNA-enveloped virus⁽⁸⁾ is SARS-CoV-2. Mechanisms based on spike-s-protein contact with host cell equation s-protein priming interacts with host cell receptor in the basic target of host cell proteases accessible is human lung epithelial cells⁽⁹⁾.

SARS-CoV-2 binds through its S-protein to angiotensin converting enzyme 2 (ACE2) receptors on the surface of human cells and, following this initial binding, 2 transmembrane serine protease (TMPRSS2) primes the S-protein, facilitating viral entry into the cell via endosomes⁽⁸⁾⁽⁹⁾ Once the virus has reached the human cell, it is able to hijack the machinery of the host cell to undergo viral rupture via endosomes⁽⁸⁾⁽⁹⁾ The binding to ACE2 of S-proteins

Receptors are a critical step needed for viral entry and are a possible target for pharmacotherapy with COVID-19⁽¹⁰⁾.

Acute kidney injury (AKI) occurred in 5 % to 15% of cases in previous studies of SARS and MERS-CoV infections and had a high mortality rate (60 percent-90 percent).

Recently, 44 percent of 710 sequential COVID-19 hospitalized patients had proteinuria and hematuria, and 26.7 percent had hematuria on admission. The prevalence was 15.5 percent and 14.1 percent respectively of elevated serum creatinine and blood urea nitrogen. AKI has been an independent risk factor for in-hospital mortality of patients.⁽¹¹⁾⁽¹²⁾

The exact mechanism of kidney involvement is uncertain: sepsis leading to cytokine storm syndrome or direct cellular damage due to the virus are suspected mechanisms.

Elevated serum levels of interleukin-1 β (IL-1 β), IL-2, IL-7, IL-8, IL-9, IL-5, interferon- γ , tumor necrosis factor alpha (TNF-a), G-CSF (granulocyte colony stimulating factor) and GM-CSF (granulocyte macrophage colony stimulating factor) have been associated with cytokine storm associated with COVID-19 pneumonia, resulting in inflammatory response and subsequently tissue damage such as pulmonary pneumonia⁽¹³⁾. AKI may therefore be the product of body inflammation, increased vascular permeability, volume loss, and cardiomyopathy in this state, which can lead to a cardio-renal reaction⁽¹⁴⁾. In addition, by inducing shock, rhabdomyolysis following tissue hypoxia, and elevated CPK level in patients admitted to ICU, these mediators can exert deleterious effects on renal tissue⁽¹⁵⁾⁽¹⁶⁾⁽¹⁷⁾. This condition involves systemic endothelial damage causing pleural effusion, edema, intra-abdominal hypertension, loss of third space fluid, reduction of intravascular fluid and hypo-abdominal hypertension.

Clinical description of COVID-19

The clinical features of COVID-19 vary, ranging from asymptomatic to acute respiratory distress syndrome and multi-organ dysfunction. Typical clinical features are fever (not all), cough, sore throat, headache, exhaustion, headache, myalgia, and breathlessness. Conjunctivitis has been reported as well. Thus, they are

indistinguishable from other respiratory disorders. The disease will lead to pneumonia, respiratory failure and death by the end of the first week in a subset of patients. This development is associated with severe increases in inflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF alpha⁽¹⁸⁾.

In addition, in serious cases of COVID-19, complications such as pneumonia, acute respiratory distress syndrome (ARDS), acute lung injury, and secondary infections are also normal⁽¹⁸⁾. In coronavirus infected patients, other complications are also common, such as neurological damage⁽¹⁹⁾,

Infection of the ocular surface, cardiac arrhythmia, renal injury, and tests of abnormal liver function⁽²⁰⁾. Fever and cough were the primary symptoms, while upper respiratory and gastrointestinal symptoms were uncommon, suggesting variations between viral tropism and SARS-CoV⁽²¹⁾, MERSCoV⁽²²⁾ and influenza⁽²³⁾. In the laboratory test results, most patients had normal or reduced white blood cell counts and lymphocytopenia⁽²⁴⁾, but the levels of neutrophils, D-dimers, blood urea and creatinine were substantially higher in extreme patients, and the counts of lymphocytes appeared to decrease. In addition, inflammatory factors (interleukin (IL)-6, IL-10, tumor necrosis factor alpha (TNF-alpha)⁽²⁵⁾⁽¹³⁾) have been identified

Antiviral treatments of COVID-19

Remdesivir

Remdesivir is a novel antiviral drug developed by Gilead Sciences, originally for the treatment of Ebola virus disease and Marburg virus infections. Remdesivir is a prodrug of a nucleotide analog that is intracellularly metabolized to analog of adenosine triphosphate that inhibits viral RNA polymerases. Remdesivir has broad spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses [e.g., SARSCoV and Middle East respiratory syndrome coronavirus (MERSCoV)] and

has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses.

In vitro testing has also shown that remdesivir has activity against SARS-CoV-2 with an EC50 value of 1.76 μ M in Vero E6 cells suggesting its working concentration is likely to be achieved in nonhuman primate models⁽²⁶⁾

Recently, the results of a trial of remdesivir in the treatment of patients with severe COVID-19 under sympathetic medication were published. The data have shown that 68 % of severe patients have relieved symptoms after using remdesivir and the mortality of those patients is 13 %, which is noteworthy though these findings need to be confirmed in the ongoing randomized, placebo-controlled trials of remdesivir therapy for COVID-19⁽²⁷⁾ However, randomized and controlled trials are still needed to determine the safety and efficacy of remdesivir.

Lopinavir-ritonavir

Lopinavir-ritonavir is used as antiretroviral combination therapy to manage HIV positive patients. Lopinavir inhibits the HIV protease, an enzyme required for new viral assembly. Due to its poor oral bioavailability and extensive biotransformation, lopinavir is coadministered with ritonavir in order to prolong levels in the human body and enhance its exposure⁽²⁸⁾⁽²⁹⁾. Protease is a key enzyme in coronavirus polyprotein processing and lopinavir and/or ritonavir has anti coronavirus activity in vitro. Most in vitro studies have shown that SARS-CoV could be inhibited by lopinavir and that the EC50 of lopinavir is acceptable. Lopinavir showed an antiviral effect against SARS-CoV-2 virus in Vero E6 cells with the estimated EC50 at 26.63 μ M⁽³⁰⁾. Lopinavir-ritonavir was investigated in an open-label, individually randomized, controlled trial, where patients with COVID-19 received either lopinavir-ritonavir 400 mg/ 100 mg, orally twice daily plus standard of care, or standard of care alone. No benefit was

observed with lopinavir-ritonavir treatment beyond standard care.

The most common adverse effect of lopinavir-ritonavir includes gastrointestinal disturbance (up to 28%), Hepatotoxicity (2–10%) Diarrhea, nausea, and asthenia were the most frequently reported adverse effects in patients receiving lopinavir-ritonavir-based regimen⁽³¹⁾.

Favipiravir

Favipiravir was developed by Toyama Chemical in Japan in 2014. antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. Favipiravir undergoes an intracellular phosphoribosylation to be an active form, favipiravir ribofuranosyl-5B-triphosphate (favipiravirRTP), which is recognized as a substrate by RdRp, and inhibits the RNA polymerase activity in the catalytic domain of RdRp is conserved among various types of RNA viruses, this mechanism of action may underpins a broader spectrum of antiviral activities of favipiravir⁽³²⁾. The dysregulation in viral RNA replication results in increased number and frequency of transition mutations including replacement of guanine (G) by adenine (A) and cytosine (C) by thymine (T) or C by Uracil (U) which induces destructive mutagenesis in RNA viruses⁽³³⁾. Genome sequencing of the 2019-nCoV identified the virus as a single-stranded RNA beta-coronavirus with the RdRp gene similar to those of SARS-CoV and MERS-CoV. Therefore, favipiravir is considered as one of the potential candidates for COVID-19, though confirmed in vitro and preclinical animal studies are not available yet. In an in-vitro study, SARS-CoV-2 was inhibited by favipiravir in Vero E6 cells with an EC50 of 61.88 μ Mol⁽³⁴⁾. Favipiravir has been used in the treatment of infectious diseases caused by RNA viruses such as influenza, Ebola, and norovirus⁽³⁵⁾.

Ribavirin

Ribavirin, a nucleoside analog, that inhibits viral RNA-dependent and RNA polymerase may through multiple mechanisms of action, including lethal mutagenesis, specific or nonspecific chain termination, and inhibition of nucleotide biosynthesis to eliminate RNA viruses⁽³⁶⁾. Its limited ability to establish a definitive therapeutic benefit during the 2003 SARS-CoV and 2012 MERS-CoV outbreaks have led to its lower levels of clinical testing during COVID-19⁽³⁷⁾. It has been approved for the treatment of respiratory syncytial virus (RSV) by FDA⁽³⁸⁾ through the occurrence of SARS, as mentioned before, ribavirin was used extensively for most cases with or without concomitant use of steroids in Hong Kong⁽³⁹⁾. However, there was considerable doubt from overseas and local experts on the efficacy of ribavirin.⁽⁴⁰⁾ Because there was a report mentioned that ribavirin had no significant activity against SARS-CoV in vitro⁽⁴¹⁾.

And the use of ribavirin was found to be associated with significant toxicity, including hemolysis (in 76%) and decrease in hemoglobin (in 49%).⁽⁴²⁾ However, Morgenstern et al⁽⁴³⁾ had reported that ribavirin and interferon- β synergistically inhibited the replication of SARS - associated coronavirus in animal and human cell lines. In view of adverse reactions and the lack of in vitro efficacy, the use of ribavirin should be seriously considered for the treatment of COVID -19, even in combination with other antiviral drugs.

CONCLUSIONS

There is no evidence to recommend any specific antiCOVID-19 treatment. There are no antiviral drugs proven to be effective now. The use of chloroquine, hydroxychloroquine and lopinavir/ritonavir are based on small-scale clinical studies.

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