Review Article

Review of COVID-19 Treatment

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Received: 05-06-2020.
Accepted: 29-08-2020.
Published: 11-01-2021.

ABSTRACT

Many contagious diseases, such as plague or cholera, played a role in changing the pathway of history. In this respect, although coronavirus was not as dangerous as novel diseases such as swine flu and Ebola, the spread and the power of coronavirus infiltration caused public fear across the world. Three viruses among coronaviruses have been epidemic during the recent years, including severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 or new coronavirus. Respiratory droplets transmit the coronavirus through direct and indirect contact, and it can be transmitted through the contact in the case of remaining, the infected person's secretion on the surface. Based on the conducted studies on the treatment of COVID-19 disease, there is virtually no cure or vaccine for coronavirus infections yet. Those infected with Covid 19 are quarantined to prevent the outbreak of this disease. However, the researchers carried out different studies to investigate the impact of the various drugs on this virus, which in this study, we will examine the outline of this disease and the other conducted studies.

KEYWORDS: *COVID-19, drug, treatment, virus*

INTRODUCTION

Coronaviruses, first recognized in 2017, has infected a wide range of domestic and wild animals. This virus is one of the major RNA viruses. In late December 2019, a series of inexplicable cases of acute and chronic pulmonary pneumonia was reported in Wuhan, China. On January 12, 2020, the World Health Organization (WHO) temporarily titles this new virus

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_20_72

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How to cite this article: Sadeghi S, Momenzadeh M, Nasri P, Nickpour M. Review of COVID-19 treatment. J Res Pharm Pract 2020;9:169-74.

Table 1: Antiviral drugs

Anti viral drugs	Indications
Favipiravir	Chen et al. in 2020 chosen 240 normal patients (patients who were not diagnosed with acute stage of illness) from Hubei Province with the purpose of investigating the effect of favipiravir on the treatment of coronavirus. The results revealed that the symptoms of fever[19] and cough eliminated more rapidly in the favipiravir group, favipiravir constrained the activity of the virus by impeding the copying of the genetic content of the virus.[19] But now low evidence are available in favor of using this for treating COVID-19
Lopinavir and Ritonavir (Kaletra)	Based on the conducted studies,[20] an anti-HIV drug known as Kaletra, composed of two protease inhibitors, ritonavir and lopinavir that had therapeutic effects on SARS and MERS, was recently suggested by the National Health Commission of the People's Republic of China for the treatment of COVID-19 pneumonia[20]
Interferon	Consumed for SARS and MERS patients, were also proposed for COVID-19 patients, the effectiveness of these drugs can be discussed[21,22] for COVID-19 accept benefits of this drugs[21,22]
Remdesivir	Remdesivir were effective in controlling the Coronavirus-2019 infection in laboratory conditions and could be assessed in COVID-19 disease. In addition to one case of COVID-19 pneumonia with hopeful clinical responses to Remdesivir and two clinical trials[23] in China.[23,24] It was encouraging that these compounds had the potential to treat Coronavirus-2019 infections
Ribavirin	This antiviral drug, that was used during MERS and SARS outbreaks, was applied in some study that results are controversy[24]

SARS=Severe acute respiratory syndrome, MERS=Middle East respiratory syndrome

as a novel Coronavirus-2019 and then introduced as pandemic.[1,2] Coronaviruses are enveloped, nonsegmented viruses and viruses with single-stranded RNA, positive-sense viruses with the origin of the animal. These viruses have two different types of surface proteins and are called based on their apparent feature. The coronavirus family is divided into alpha, beta, gamma, and delta in terms of genotype and serological features. Human coronaviruses are created by alpha and beta material.[3] Epidemiological review of primary cases of pneumonia of novel coronavirus-2019 revealed that most cases were at risk of the Huanan seafood market in Wuhan.[4,5] Some of them are live animals, such as hedgehogs, badgers, snakes, turtles, birds, and possibly anteaters.[6] Researches support the theory that the transfer chain began from bats to humans.[7] Furthermore, Zhou *et al*. deduced that the similarity of the sequence between coronavirus-2019 and severe acute respiratory syndrome (SARS) coronavirus was 75/9%. The findings of numerous studies were different concerning the mortality rate and disease transmission in patients with coronavirus-2019 from 2/87% to 14%.[8-11] The production of safe and stable vaccines is a major challenge, and there will be a wide range of vaccines. However, there were many studies conducted on the issue of investigating the effect of the use of various drugs on this disease in which this study will review some of them.

The Pathogenic Mechanism and Side Effects of Coronavirus

SARS-CoV and Middle East respiratory syndrome (MERS)-CoV infections in early stages can be without any sign, but they can create pneumonia, renal failure, and even death in the following stages. The immune response is essential for controlling and destroying the coronavirus, and immune system dysfunction can lead to immunopathology and death of the patient. The defect or deviation of the immune system can increase virus replication. On the other hand, excessive immune system activity can cause histological damages. Angiotensin convertase enzyme 2 (ACE2) was introduced as a receptor for coronavirus, which was essential for its entry. Comprehensive expression of ACE2 in various cells, including lung AT2 cells, the upper esophagus, epithelial cells, and absorptive enterocytes of the ileum and colon, may be effective in coronavirus multifactorial infection.[12] Therefore, along with the respiratory and body contact, the stool and oral transmission is a potential path for infection.[13] After binding to the receptor, the viral spike protein is broken down by acid-dependent proteolysis by Cathepsin, compared to other coronavirus proteins, spike protein has the most variable sequence of amino acids, which is the strongest choice among all coronavirus genes for compatibility with its hosts. It can be explained that human ACE2 has high similarity with the Chinese horseshoe bats, cats, and pigs.[12,13]

Innate Immunity Response

Like other viruses, the immune system is able to detect coronavirus through innate immune receptors, including NOD-like receptor, retinoic acid-inducible gene-I-like receptor, and toll-like receptor. Interferon (IFN) Type 1 is in the first line of defense against viruses. Studies revealed that although SARS-CoV and other coronaviruses are sensitive to alpha and beta IFNs, they remain pathogenic. These viruses escape the host immune system using different methods such as Janus kinase signal transducer and activator of transcription

pathway signaling inhibition, which is created by IFN Type 1.[14]

Acquired Immune Response

+8 test-key critical dimension cells are about 80% of all inflammatory cells entered into the lungs, which entered into the lung of patients with SARS-CoV and played a constructive role in eradicating the virus from infected cells. This matter infers the important role of T-cells relative to B-cells in controlling the pathogenesis of MERS-CoV infection. On the other hand, the T-helper cells can be contributory to controlling the infections by means of producing inflammatory cytokines. The cytokines of the family interleukin (IL)-17 are effective in controlling the infections by simulating monocytes and neutrophils to the infection site and activating the production of other inflammatory cytokines such as IL 1, 6, 8, and tumor necrosis factor-alpha.[15]

Humoral Immunity

It is cleared that humoral immunity is essential to control the resistant phase of the coronavirus. The virus uses its surface proteins as an adhesive factor to enter into host cells through a special receptor called dipeptidyl peptidase-4. This receptor is raised as a key factor in activating the immune system in infected people. Therefore, it appears that the production of monoclonal antibodies against this protein can prepare useful immunity in the vaccine design. For instance, a human monoclonal antibody called 336 m, which was prepared by the phage display method, was reacted with one part of the surface protein of MERS-CoV, which connected the virus to cell receptors, in laboratory conditions and neutralized it. The extended production period of immunoglobulin (Ig) G can declare the importance of IgG in the humoral immune response to the acute phase of SARS-CoV, on the one hand, and the role of this antibody in treating the remnants of viral infection during the recovery period on the other hand.[16]

Treatment of COVID-19

There is no definite treatment yet. With the outbreak of a new acute respiratory disease in January, first in China, and then the other countries such as Iran, Italy, Spain, France, Germany, and the United States, the doctors rapidly began testing available drugs. In the following, the results of researches on some main options will be reviewed.

Chloroquine and Hydroxychloroquine

Singh *et al*. in 2020 conducted the research with the aim of investigating the comparison of the effect of chloroquine and hydroxychloroquine on the treatment of COVID-19 in diabetic or nondiabetic patients with a systematic search and a story review with specific referral to India and other developing countries. Unfortunately, they mentioned that no confirmed drug was introduced for coronavirus. Hence, with regard to the successful backgrounds of the two drugs raised in this study, called chloroquine and hydroxychloroquine, this old malaria drug heartened many people. Chloroquine was well characterized by the effects of *in vitro* in uncoating inhibition and posttranslational modification in newly synthesized proteins, especially inhibition of glycosylation in many viruses such as immunodeficiency virus. The scientists believed that there was not enough evidence for effectiveness of these drugs. Hydroxychloroquine also led to negative results. The side effects of this drug are completely serious and affect the heart rhythm and prolonged QT.[17] The last multinational registry study that was done in 761 hospitals on 96,032 patients, identified the mortality increased with using chloroquine and hydroxylchloroquine.[18]

AntiViral drugs

In this study, we review some of the antiviral drugs that were used for the treatment of other diseases in coronavirus groups [Table 1].

Intravenous immunoglobulin

In March 2020, the Cao and his team of researchers were able to isolate and purify the antibodies from the first blood sample and then use ultrafiltration techniques to remove the remaining undesirable material from the final product and concentrate the antibodies. The team used donated blood from improved COVID-19 patients to clear antibodies that could neutralize the coronavirus. This treatment is safe, low-risk, and very effective against coronavirus. With this method, Ig is prepared after the separation of antibodies in the patient's blood from corona. This method is very different from plasma therapy, and it should be noted that treatment with hyper intravenous immunoglobulin (H-IVIG) is normally approved by the US Food and Drug Administration (FDA). On the other hand, plasma treatment is allowed only in emergencies due to side effects. Dow University research team led by Dr. Shaukat Ali has developed this H-IVIG after days of hard work, given the current crisis situation. They isolated and purified the antibodies from the first blood sample and then removed the remaining unwanted material from the final product by ultrafiltration and concentrated the antibodies. The team used donated blood from improved COVID-19 patients to clear antibodies that could neutralize the coronavirus.[25]

Hemoperfusion

Seraph 100 is the only "hemoperfusion device" approved for the reduction of pathogens in blood. In recent EU clinical cases, improved lung function and rapid reduction of drug-resistant *bacterial* pathogens occurred with Seraph 100 treatment. Stabilization of blood pressure has also been observed, including during COVID-19 treatment. Another potential benefit of Seraph 100 treatment of COVID-19 is reduction in blood-borne virus/RNA, and the simultaneous treatment of bacterial and fungal "secondary infections." Clinical results and virus-binding studies suggested that Seraph 100 treatment should help in the treatment of COVID-19, and in future epidemics, before vaccines are available. The measured binding capacity of a single Seraph 100 filter (about the size of a 12-ounce soda can) is huge in comparison to the amount of virus present in the bloodstream of critically-ill patients. Reducing the viral levels of COVID-19 may allow the body's immune system to combat the deadly pathogen. Since Seraph 100 treatments have also consistently produced improved oxygenation/lung function, we believe that this feature together with virus reduction may be a useful combination for treating COVID-19, while simultaneously treating the dangerous secondary infections that can occur in COVID-19 patients Seraph 100 has CE Mark approval in the European Union but is not currently approved by the FDA for the use in the United States.[26]

Convalescent plasma

The use of convalescent plasma collected from previously infected individuals to passively-transfer antibodies to protect or treat humans dates back almost 100 years, with some evidence for benefit against rabies, hepatitis B, polio, measles, influenza, Ebola, and other pathogens.[27] Two publications from China reported the use of convalescent plasma to treat fifteen critically ill patients without adverse events.[28] All eventually improved clinically and cleared virus.

Convalescent plasma could provide short-medium term humoral immunity against the SARS-CoV-2 coronavirus. The vast majority of patients who recover from COVID-19 illness develop circulating neutralizing antibodies to various SARS-CoV-2 proteins 2–3 weeks following infection, detectable by ELISA or other quantitative assays. Transfer of plasma from these patients should neutralize virus, preventing further replication and halting ongoing tissue damage. This approach would be predicted to work best in patients with less severe infection, earlier in the disease course, or prophylactically in highly susceptible individuals such as exposed health-care workers or family caregivers of COVID-19 patients.

Known risks of plasma transfusion include inadvertent infection with another infectious pathogen, as with any blood product, general reactions such as transfusion-associated circulatory overload, and transfusion-associated acute lung injury in patients with already severe lung damage. Additional concerns include potential worsening of immune-mediated tissue damage through the poorly understood phenomenon of antibody-dependent enhancement and blunting of endogenous immunity to the virus.

In the US, on March 24, 2020, the FDA allow individual physicians to treat patients with serious COVID-19 disease with convalescent plasma.[29]

Glucocorticoids

Many different researches were done a bout of efficacy of using glucocorticoids in COVID-19 pandemic. Glucocorticoid therapy may increase the risk of death in patients with COVID-19 who have mild symptoms.[30] For adults with COVID-19 and refractory shock, guidelines suggest using low-dose corticosteroid therapy.[31,32]

Conclusion

Similar to MERS-CoV and SARS-CoV, there is still no specific antiviral treatment for COVID-19.[33] Isolation and supportive care, including oxygen therapy, fluid management, and antibiotics treatment for secondary bacterial infections, is recommended.[34] Some COVID-19 patients progressed rapidly to ARDS and septic shock, which was eventually followed by multiple organ failure.[16,35] Therefore, the effort on the initial management of COVID-19 must be addressed to the early recognition of the suspect and contain the disease spread.

Understanding and comprehending of COVID-19 are ongoing. Temporary guidance is provided by the WHO and the US Centers for the Disease Control and Prevention. Coronaviruses are considered as a large group of viruses that can infect animals and humans and cause respiratory discomfort. These discomforts may be progressed to be as mild as a cold or as severe as pneumonia. In rare cases, animal coronavirus infects humans and then spreads between them. The SARS virus (acute respiratory syndrome) was known as a sample of the Coronavirus that was transmitted from animals to humans. The other noticeable and most recent outbreak of Coronavirus was MERS, which was originated in the Middle East in 2012, and scientists mentioned that the virus was first transmitted from camels to humans. In general, it can be declared that the outbreak of COVID-19 became a clinical threat to the general population and health-care personnel

worldwide. The remarkable antiviral treatment and vaccination options are currently being under assessment and promotion. At home-treatment may be possible for people who have mild illness and can be properly isolated as an outpatient. Regular use of a mask for disease prevention is not recommended for individuals without symptoms. It is advised to observe the distance in the community in places that have a social carrier. Hopefully, COVID-19 can be overcome in the near future with the help of vaccination discovery, drug effective therapeutic actions over the virus.

Authors' Contribution

Somayeh Sadeghi: Design and concept of the manscript. Mahnaz Momenzadeh: Writing of the manuscript. Mina Nickpour: Design, and concept and revising the manuscript. Peiman Nasri: Revising and reviewing the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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