Avicenna Journal of Pharmaceutical Research
2020 December;1(2):87-90 http://ajpr.umsha.ac.ir

Mini Review

doi:10.34172/ajpr.2020.16

Potential Antiviral Drug Intervention for Treatment of COVID-19: A Minireview

Davoud Ahmadimoghaddam[1], **Zohreh Izadidastenaei**[2*]

[1]Department of Pharmacology and Toxicology, School of Pharmacy, Hamadan University of Medical Sciences, Hamadan, Iran
[2]Department of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Corresponding author:**
Zohreh Izadidastenaei, Department of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Tel: 0098-2188202508,
Email: zohreizadi@sbmu.ac.ir

Abstract

In this minireview, we evaluated the studies that underlie the usage and suggestion of antivirals for the treatment of coronavirus disease 2019 (COVID-19). Until now, there has been no known curative treatment for COVID-19. However, many clinical trials have used antiviral medicines including remdesivir, lopinavir (LPV), ritonavir (RTV), ribavirin, favipiravir (FPV), oseltamivir, umifenovir, and nitazoxanide. Using remdesivir in patients with severe COVID-19 has improved respiratory symptoms, making the remdesivir one of the specific drugs suggested for the treatment of severe COVID-19. It has been shown that triple antiviral therapy (LPV, RTV, and ribavirin) can improve symptoms and consequently shorten the duration of viral shedding and hospital stay. However, the results of treatment with oseltamivir, umifenovir, and a combination of LPV and RTV were not different from the results of treatment with standard care in the time to clinical improvement. FPV showed better therapeutic responses to COVID-19 in terms of disease progression and viral clearance. Future clinical studies should evaluate the effect of antiviral agents for the treatment of COVID-19 outbreak. Therefore, it is suggested that highly active antiviral drugs should be used in combination with other therapeutic approaches for the treatment of COVID-19.

Keywords:COVID-19, Antiviral, Remdesivir, favipiravir, Oseltamivir

Received 24 September 2020, **Accepted**: 6 October 2020, **ePublished**: 30 December 2020

Introduction

In 2019, novel coronavirus rapidly spread from its origin in China to the rest of the world. The disease caused by this novel coronavirus was named coronavirus disease 2019 (COVID-19). Coronaviruses were appeared first in 2002 in China and have resulted in severe diseases since then. Severe acute respiratory syndrome (SARS) caused by beta coronavirus was transmitted from the bat to humans in China (1). The mortality rate for SARS was reported to be 11% (1). Almost a decade later in 2012, beta coronavirus caused the Middle East respiratory syndrome coronavirus (MERS-CoV) in Saudi Arabia. The origin of the coronavirus was the bat and emerged in Saudi Arabia via dromedary camels as the intermediate hosts with mortality rate of 34% (2). Nonetheless, the appearance of coronavirus was not finished by this time and it reappeared in December 2019. This time it emerged in China and spread to the world through human-to-human transmission (3,4). The case-fatality ratio, which estimates the proportion of deaths among identified confirmed cases, is widely different by country, from less than 0.1% to over 25% for COVID-19 (5). Until now, there has been no known curative treatment for COVID-19. The use of effective antiviral drugs, and new synthetic drugs (6), as well as drug combinations seems to be experimental in the treatment of COVID-19.

Pathogenesis

Today, it is believed that humans of all ages are susceptible to COVID-19 infection. COVID-19 infection is transmitted through large droplets generated during coughing and sneezing. It can be transmitted from symptomatic patients, as well as asymptomatic people (7). Infection is acquired either by inhalation of droplets or touching the nose, mouth, and eyes by contaminated hands. Patients during illness and even during recovery can be infectious. The virus can survive for several days in favorable atmospheric conditions; however, the use of sodium hypochlorite and hydrogen peroxide eliminates the virus. The incubation period is estimated to be from 4.5 to 5.8 days (median 5.1 days) (Figure 1). The symptoms will develop from 8.2 to 15.6 days (median 11.5 days) (8).

Clinical Characteristics and Diagnosis

The ordinary clinical characteristics of the COVID-19 include headache, cough, sore throat, fever, breathlessness, fatigue, myalgia, and conjunctivitis (Figure 1). One of the most important facts concerning COVID-19 is that it is not distinguishable from other respiratory infections. COVID-19 is a progressive disease which starts with

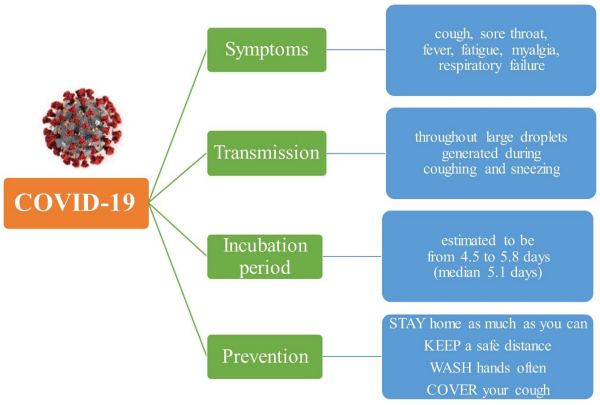

Figure 1. Schematic depiction of symptoms, transmission, incubation period, and prevention of COVID-19.

pneumonia at the end of the first week and is followed by respiratory failure and sometimes death in the other days. The progression of COVID-19 is linked with an increase in inflammatory cytokines such as IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNF-α (9). The symptoms in 25%–30% of patients are acute respiratory distress syndrome, acute lung injury, shock, and acute kidney injury that end in hospitalization and need for intensive care. People with underlying co-morbidity and the elderly are at high risk with adverse outcomes and death.

However, the prevention of person-to-person transmission can be reduced by stay home as much as you can, keep a safe distance, wash hands often, cover your cough as recommended by WHO (Figure 1).

Nowadays, molecular tests such as reverse transcription polymerase chain reaction (RT-PCR) tests and antigen tests are useful for the diagnosis of suspected cases. Moreover, the chest X-ray (CXR) is usually used to define the involvement of the lung. However, in the early stage of the disease, the CXR usually shows normal lung morphology. Along with the progress of the disease, CXR usually shows lung bilateral infiltration.

Antiviral Treatment Strategies

Since the first case in 2019, no particular method has been confirmed to be effective for the treatment of COVID-19 However, many clinical trials have used antiviral medicines including remdesivir, lopinavir (LPV)), ritonavir (RTV), ribavirin, favipiravir (FPV), oseltamivir, umifenovir, and nitazoxanide.

Remdesivir is a broad-spectrum nucleoside antiviral medication analog that has been used for the treatment of lethal Ebola and Nipah virus infections in nonhuman primates and tested for the treatment of COVID-19 (10). It has been authorized for emergency use and resulted in shortening the time it takes to recover from the infection (11). In the healthy volunteers, the most common side effect includes liver inflammation and increased aspartate aminotransferase, hypotension, nausea (related to the intravenous infusion), and sweating. However, the most common adverse effect for patients with positive COVID-19 infection includes respiratory failure, constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin (12). Hence, a high percentage of patients stopped receiving remdesivir because of adverse events such as gastrointestinal symptoms (anorexia, nausea, and vomiting), aminotransferase or bilirubin increases, and worsened cardiopulmonary status (12). Remdesivir can inhibit the replication of multiple coronaviruses in a respiratory epithelial cell by RNA-dependent RNA polymerase (RdRp) inhibitor action (13). The first patient in Korea received chartered medication to remdesivir on the evening of the 6th day of admission and received it intravenously on the evening of the seventh day of admission without adverse reactions. Vancomycin and cefepime were discontinued the following day. On the eighth day of admission (the twelfth day of onset), the patient's clinical symptoms were improved, and the oxygen saturation increased to 94%. Although the patient was still hospitalized till January 30, 2020, all symptoms had resolved except for cough and occasional runny nose (14). Using remdesivir in patients with severe COVID-19 has improved respiratory symptoms, making remdesivir one of the specific drugs for the treatment of severe COVID-19. Nevertheless, reducing the number of viral copies in the patient's body is an important factor for acute infectious diseases. Furthermore, the pharmacokinetic data of the ongoing phase-III clinical trials should be considered in evaluating the efficacy of remdesivir (13). At the beginning of the COVID-19 pandemic, the World Health Organization indicated that remdesivir has a great potential to be the best candidate for the treatment of COVID-19.

A multicenter, prospective, open-label, randomized, phase II trial in adults with COVID-19 was done in Hong Kong. The patients were divided into two groups. The first group received a 14-day combination of LPV 400 mg and RTV 100 mg every 12 hours, ribavirin 400 mg every 12 hours, and three doses of 8 million IU of interferon beta-1b on alternate days (the combination group). While the second group received a 14-day combination of LPV 400 mg and RTV 100 mg every 12 hours (the control group). The results of this clinical trial showed that in patients with mild to moderate COVID-19, early triple antiviral therapy was safe and superior to the combination of LPV and RTV alone. It was also shown that triple antiviral therapy can improve symptoms and consequently shorten the duration of viral shedding and hospital stay (15).

LPV and RTV are two protease inhibitors used against HIV infection as a fixed-dose combination. Recently, this combination was used for patients with COVID-19. A randomized, controlled, open-label trial was done on 199 patients with laboratory-confirmed COVID-19 in Wuhan, Hubei Province, China. The patients were assigned to the LPV–RTV group (400 mg and 100 mg, orally twice

a day) and standard care group (supplemental oxygen, noninvasive and invasive ventilation, antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation) for 14 days. The results of this study showed that treatment with LPV–RTV was not different from the treatment with standard care in the time to clinical improvement (16). Mortality at 28 days and percentages of patients with detectable viral RNA at various time points were similar in the LPV–RTV group and the standard care group. It was observed that patients treated with LPV–RTV led to a median time to clinical improvement that was shorter by one day than that observed for the standard care patients. In patients who received LPV–RTV medication, gastrointestinal adverse events and lymphopenia were more common, but serious adverse events (respiratory failure and acute kidney injury) were more common in the standard care group (16).

Oseltamivir, an inhibitor of the viral neuraminidase, is an antiviral medication that is approved for the treatment of influenza A and B. Oseltamivir blocks the release of viral particles from the host cells, consequently reducing the spread to the respiratory tract (17). Moreover, it has been used in some clinical trials for the treatment of COVID-19 during the epidemic in China. It was used in combination with other medications such as antibiotics, corticosteroids, chloroquine, and FPV (18,19). In one of these clinical trials, 124 patients received different doses of oseltamivir and methylprednisolone depending on disease severity; however, no effective outcomes were observed (18).

FPV, an RNA polymerase inhibitor, is an antiviral medication that is approved for the treatment of influenza A virus. It has been used to treat COVID-19 infection in China. In an open-label control study, the effect of FPV versus LPV/RTV for the treatment of COVID-19 was evaluated. The first group of patients (the FPV group) received oral FPV (day 1: 1600 mg twice a day; days 2–14: 600 mg twice a day) plus interferon (IFN)-α by aerosol inhalation (5 million IU twice a day). The second group of patients (the control group) received LPV/RTV (days 1–14: 400 mg/100 mg twice a day) plus IFN-α by aerosol inhalation (5 million IU twice a day). Their results indicated that the FPV group showed better therapeutic responses to COVID-19 in terms of disease progression and viral clearance (20). Additionally, a case of successful treatment of severe COVID-19 pneumonia with FPV in a post kidney-transplant-recipient has been reported. The patient was treated with FVP together with decreased immunosuppression and anti-IL-6 receptor antibody. This combination therapy provided favorable outcomes (21). These preliminary clinical results provide useful information concerning the usage of FPV for the treatment of COVID-19 infection.

Umifenovir, which prevents contact between the virus and target host cells, is an antiviral medication for the treatment of influenza infection (22). It was used for the treatment of COVID-19 infection in some clinical trials (23-25). However, a systematic review and meta-analysis showed that there is no evidence to support the use of umifenovir for improving patient-important outcomes in patients with COVID-19 (26).

Nitazoxanide, the FDA-approved antiparasitic drug, possesses antiviral activity against different viral infections such as coronaviruses, influenza, hepatitis C virus, and hepatitis B virus. It was demonstrated to exhibit an *in vitro* activity against MERS-CoV and other coronaviruses (27). Due to its good safety profile, it has been suggested that nitazoxanide could be incorporated in a new protocol for the management of COVID-19 infection. It has been proposed that nitazoxanide could be useful when it combines with other drugs such as azithromycin and hydroxychloroquine (28,29).

Conclusion

To conclude, it seems that some antiviral medications such as remdesivir, FPV, and triple antiviral therapy (LPV, RTV, and ribavirin) can improve respiratory symptoms and consequently shorten the duration of viral shedding and hospital stay. However, using antivirals such as oseltamivir, umifenovir, LPV, and RTV either in combination or alone has shown no effective outcomes. Future clinical studies should evaluate the effect of antiviral agents for the treatment of COVID-19 outbreak. Therefore, it is suggested that highly active antiviral drugs be used in combination with other therapeutic approaches for the treatment of COVID-19.

Conflict of Interests

The authors declare that they have no conflict of interests.

Acknowledgements

The authors would like to thank Amir Nili-Ahmadabadi for his contribution in preparing the figure.

References

1. Chan-Yeung M, Xu RH. SARS: epidemiology. Respirology. 2003;8(Suppl 1):S9-14. doi: 10.1046/j.1440-1843.2003.00518.x.
2. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. Lancet. 2020;395(10229):1063-77. doi: 10.1016/s0140-6736(19)33221-0.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506. doi: 10.1016/s0140-6736(20)30183-5.
4. Bastola A, Sah R, Rodriguez-Morales AJ, Lal BK, Jha R, Ojha HC, et al. The first 2019 novel coronavirus case in Nepal. Lancet Infect Dis. 2020;20(3):279-80. doi: 10.1016/s1473-3099(20)30067-0.
5. World Health Organization (WHO). Estimating Mortality from COVID-19. WHO; 2020.
6. Chehardoli G, Bahmani A. A quick overview of recent approaches to the synthesis and design of new drugs. Avicenna J Pharm Res. 2020;1(1):46. doi: 10.34172/ajpr.2020.08.
7. Rothe C, Schunk M, Sothmann P, Bretzel G, Froeschl G, Wallrauch C, et al. Transmission of 2019-nCoV infection

from an asymptomatic contact in Germany. N Engl J Med. 2020;382(10):970-1. doi: 10.1056/NEJMc2001468.
8. Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med. 2020;172(9):577-82. doi: 10.7326/m20-0504.
9. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507-13. doi: 10.1016/s0140-6736(20)30211-7.
10. Lo MK, Feldmann F, Gary JM, Jordan R, Bannister R, Cronin J, et al. Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. Sci Transl Med. 2019;11(494). doi: 10.1126/scitranslmed.aau9242.
11. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020;383(19):1813-1826. doi:10.1056/NEJMoa2007764.
12. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2020;395(10236):1569-78. doi: 10.1016/s0140-6736(20)31022-9.
13. Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Med Infect Dis. 2020;35:101647. doi: 10.1016/j.tmaid.2020.101647.
14. Kim JY, Choe PG, Oh Y, Oh KJ, Kim J, Park SJ, et al. The first case of 2019 novel coronavirus pneumonia imported into Korea from Wuhan, China: implication for infection prevention and control measures. J Korean Med Sci. 2020;35(5):e61. doi: 10.3346/jkms.2020.35.e61.
15. Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. 2020;395(10238):1695-704. doi: 10.1016/s0140-6736(20)31042-4.
16. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med. 2020;382(19):1787-99. doi: 10.1056/NEJMoa2001282.
17. Uyeki TM. Oseltamivir Treatment of Influenza in Children. Oxford University Press; 2018.
18. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9. doi: 10.1001/jama.2020.1585.
19. Kongsaengdao S, Sawanpanyalert N. Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine for Treatment of COVID19: A Randomized Control Trial (THDMS-COVID19). Bethesda, MD: National Library of Medicine; 2020.
20. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. Engineering (Beijing). 2020;6(10):1192-8. doi: 10.1016/j.eng.2020.03.007.
21. Thammathiwat T, Tungsanga S, Tiankanon K, Torvorapanit P, Chumpangern W, Udomkarnjananun S, et al. A case of successful treatment of severe COVID-19 pneumonia with favipiravir and tocilizumab in post-kidney transplant recipient. Transpl Infect Dis. 2020:e13388. doi: 10.1111/tid.13388.
22. Leneva IA, Russell RJ, Boriskin YS, Hay AJ. Characteristics of arbidol-resistant mutants of influenza virus: implications for the mechanism of anti-influenza action of arbidol. Antiviral Res. 2009;81(2):132-40. doi: 10.1016/j.antiviral.2008.10.009.
23. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. Clin Microbiol Infect. 2020;26(7):917-21. doi: 10.1016/j.cmi.2020.04.026.
24. Zhu Z, Lu Z, Xu T, Chen C, Yang G, Zha T, et al. Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19. J Infect. 2020;81(1):e21-e3. doi: 10.1016/j.jinf.2020.03.060.
25. Xu P, Huang J, Fan Z, Huang W, Qi M, Lin X, et al. Arbidol/IFN-α2b therapy for patients with corona virus disease 2019: a retrospective multicenter cohort study. Microbes Infect. 2020;22(4-5):200-5. doi: 10.1016/j.micinf.2020.05.012.
26. Huang D, Yu H, Wang T, Yang H, Yao R, Liang Z. Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. J Med Virol. 2020. doi: 10.1002/jmv.26256.
27. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health. 2016;9(3):227-30. doi: 10.1016/j.jiph.2016.04.001.
28. Kelleni MT. Nitazoxanide/Azithromycin combination for COVID-19: a suggested new protocol for early management. Pharmacol Res. 2020;157:104874. doi: 10.1016/j.phrs.2020.104874.
29. Calderón JM, Zerón HM, Padmanabhan S. Treatment with Hydroxychloroquine vs Hydroxychloroquine + Nitazoxanide in COVID-19 patients with risk factors for poor prognosis: a structured summary of a study protocol for a randomised controlled trial. Trials. 2020;21(1):504. doi: 10.1186/s13063-020-04448-2.