Drug Designing: Open Access

OPEN ACCESS Freely available online

Research Article

Potential Drug Candidates for the Treatment of Coronavirus Disease 2019 (COVID 19): Current Clinical Trials and their Interpretations

Jafer Siraja*

Department of Pharmacy, Mizan-Tepi University, Mizan-Aman, Ethiopia

ABSTRACT

The occurrence of the coronavirus disease 2019 (COVID-19) is formally recognized as a severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) and characterized as a universal public health problem. Coronavirus disease 2019 (COVID-19) infects the lower respiratory system to cause viral pneumonia, and also leads to multiple organ damage including kidney, liver and etc. The coronavirus disease 2019 is spread and transmits through human-to-human by means of droplets, feco-oral, and direct contact. Applying the protective mechanism is the only option to control COVID-19 infection due to the absence of approved antiviral treatment or vaccine for the prevention and treatment of COVID-19. Therefore, developing a safe and effective therapeutic agent is necessary to overcome the overcoming potential impact of coronavirus disease in 2019 in the world. This review focus on the current clinical trials under investigation on the potential drug candidates for the treatment of coronavirus disease 2019 to support the scientific community for further research and development efforts to discover safe and effective therapeutic and preventive agents for COVID-19. Drug under investigation especially remdesivir had benefits to reduce duration of symptom onset from clinical manifestation and reduce duration of hospitalization in some patients. Based on clinical trial, the known and potential benefits of remdesivir outweigh the known and potential risks of the drug for the treatment of severe COVID-19 in hospitalized patients depends on data obtained from clinical trial.

Keywords: COVID-19; Antiviral; Antimalarial; Clinical data

INTRODUCTION

Coronaviruses are comparatively big viruses comprising a single-stranded positive-sense RNA genome encapsulated within a membrane envelope. The crown like appearance coronaviruses are obtained when the virus membrane is strewed with glycoprotein spikes. Although coronaviruses is the disease of both humans and animals, some animals like bats are resistant to coronavirus disease [1]. Generally, coronaviruses classified as alpha, beta, gamma, and delta the first two coronaviruses (alpha- and beta) originated from mammals and gamma-and delta-CoVs are from avian origin. All class coronaviruses that affect respiratory system and observed in the two decades including COVID-19 are categorized under betacoronavirus. Even though COVID-19 damage the lower respiratory system to cause viral pneumonia like SARS-CoV and MERS-CoV, it also causes multiple organ damage including kidney, liver and etc. [2,3].

The occurrence of the coronavirus disease 2019 (COVID-19) is formally recognized as severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) and characterized as universal public health problem [4,5]. The mechanism by which severe acute respiratory syndrome-related coronavirus affect respiratory system is that it contaminates ciliated bronchial epithelial cells and type-II pneumocytes by using angiotensin-converting enzyme 2 (ACE2) as receptor [6,7]. Middle East respiratory syndrome-CoV contaminates unciliated bronchial epithelial cells and type-II pneumocytes through CD26 as a receptor [6,8]. In COVID-19 the main problem on designing the right preventive and therapeutic agent is that there is no clear mechanism by which the virus infects human beings but, authors suggests it may contaminates human cells by using angiotensin-converting enzyme 2 (ACE2) as receptor [9].

The coronavirus disease 2019 is spread and transmits through human-to-human by means of droplets, feco-oral, and direct contact. Applying the protective mechanism is the only option to control COVID-19 infection due to absence approved antiviral treatment or vaccine for prevention and treatment of COVID-19. Therefore, developing safe and effective therapeutic agent is necessary to overcome the overcoming potential impact of coronavirus disease 2019 in the world. This review focus on the current clinical trial under investigation on the potential drug candidates for the treatment of coronavirus disease 2019 to support

Correspondence to: Jafer Siraja, Department of Pharmacy, College of Health Science, Mizan-TepiUniversity, Mizan-Aman, Ethiopia, Tel: +251 912 841073; E-mail:sirajjafer@gmail.com

Received: July 15, 2020; **Accepted:** July 30, 2020; **Published:** August 06, 2020

Citation: Siraja J (2020) Potential Drug Candidates for the Treatment of Coronavirus Disease 2019 (COVID 19): Current Clinical Trials and their Interpretations. Drug Des 9: 167. doi: 10.35248/2169-0138.20.9.167

the scientific community for further research and development efforts to discover safe and effective therapeutic and preventive agents for COVID-19 [10].

ANTIVIRAL DRUGS

Remdesivir

The RNA genome of SARS-CoV-2 needs insertion of nucleotides, adenosine, guaninosine, uridine and cytosine, and a range of analogues of these have been advanced as anti-viral treatments for different viral infections. Experimental nucleoside analogues (remdesivir and galidesivir) in the form of adenine or guanine derivatives target the RNA-dependent RNA polymerase and block viral RNA synthesis in a broad spectrum of RNA viruses, including human coronaviruses [11].

Remdesivir is an intravenous investigational nucleotide prodrug of an adenosine analog, which incorporates into nascent viral RNA chains and at last lands up in pre-mature termination. remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection *in vitro* [12].

Studies showed that a nucleotide prodrug remdesivir, can inhibit SARS-CoV and MERS-CoV replication in multiple *in vitro* and also had broad-spectrum anti-CoV activity against human CoV in primary human lung cells and bat-CoVs. Prophylactic and early therapeutic administration of remdesivir significantly reduced lung viral load, improved clinical signs and respiratory functions in a mouse infected with SARS-CoV [13].

Another *in vitro* prophylactic and therapeutic remdesivir administration in mice reported lung function improvement, reduction of respiratory viral loads and decreased severity of lung disease. In this study, superior antiviral activity of remdesivir over LPV and RTV was also detected [14]. In rhesus macaque, prophylactic remdesivir usage which started 24 hour earlier to inoculation showed that complete prevention of MERS-CoV associated clinical infection. Also, the treatment toughly repressed MERS-CoV replication in breathing tissues, and prevented the creation of lung abrasions. Additionally, therapeutic remdesivir in this rhesus macaque model which indicated after 12 hour of post inoculation showed reduction of clinical signs, reduced virus replication in the lungs, and decreased formation of lung lesions [15].

Non clinical study conducted in two groups of six rhesus macaques infected with SARS-CoV-2 and treated with remdesivir and vehicle solution reported that signs of respiratory disease did not detected in rhesus macaque treated with remdesivir. Also, rhesus macaque treated with remdesivir had reduced pulmonary intrudes on radiographs and virus titers in bronchoalveolar lavages were significantly reduced after the first treatment was administered within 12hrs. At necropsy on day 7 after inoculation, lung viral loads of remdesivir-treated animals were significantly lower and there was a transparent reduction in damage to the lung tissue. Accordingly, therapeutic remdesivir treatment initiated early during infection encompasses transparent clinical advantage in SARS-CoV-2-infected rhesus macaques [16].

FDA issued an emergency use authorization for the antiviral drug under investigation (i.e. remdesivir) for the treatment of COVID-19 in hospitalized patients especially critically ill adults and children. In a clinical trial, remdesivir reduced recovery time to shorten the time to in certain patients but little is known about the safety and efficacy of using this investigational drug for the treatment of COVID-19 in hospitalized patients. The emergency use authorization allows for remdesivir be distributing within the U.S.A and administering intravenously by health care providers due to the reason that the known and potential benefits of remdesivir outweigh the known and potential risks of the drug for the treatment of severe COVID-19 in hospitalized patients the depends on data obtained from clinical trial [17].

Clinical trial results and supporting data for EUA are: A randomized, double-blind, placebo-control clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalized adult patients with COVID-19. The trial enrolled 1063 hospitalized patients in a 1:1 manner to receive remdesivir or placebo. The primary clinical endpoint was time to recovery within 28 days after randomization. In a preliminary analysis of the primary endpoint performed after 606 recoveries were attained, the median time to recovery was 11 days in the remdesivir group compared to 15 days in the placebo group (hazard ratio 1.31; 95% CI 1.12-1.54, P<0.001). The preliminary results also showed a mortality rate of 8.0% and 11.6% for the remdesivir and placebo groups, respectively (P=0.059) [17].

A randomized, open-label multi-center clinical trial of patients with severe COVID-19 compared 197 adult patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg once daily for 9 days (for a total of 10 days of intravenously administered therapy) with 200 adult patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg for 4 days (for a total of 5 days of intravenously administered therapy), plus standard of care. The primary clinical endpoint was clinical status assessed by a 7-point ordinal scale at Day 14 after randomization. The study suggested that patients receiving a 10-day treatment course of remdesivir had similar improvement in clinical status compared with those receiving a 5-day treatment course (10-5day odds ratio:0.76; 95% confidence interval [CI] 0.51-1.13] on Day 14) [17].

A randomized controlled trial of remdesivir versus placebo for severe COVID-19 in China showed that remdesivir was not associated with statistically significant clinical benefits for adult patients admitted to hospital for severe COVID-19. 237 patients were enrolled and randomly assigned to a treatment group (158 to intravenous remdesivir and 79 to normal saline placebo). For patients who started study drug within 10 days of symptom onset, faster time to clinical improvement was seen in the remdesivir arm than in the placebo arm, even though not statistically significant (median 18.0 days vs. 23.0 days, respectively; HR 1.52, 95% CI, 0.95-2.43). Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early because of adverse events in 18 (12%) patients versus four (5%) patients who stopped placebo early. Generally, this study showed that there was no difference in time to clinical improvement, 28day mortality, or rate of viral clearance between the remdesivir-treated patients and placebo-treated patients [18].

LOPINAVIR/RITONAVIR

Lopinavir/ritonavir is an inhibitor of severe acute respiratory syndrome-related coronavirus (SARS-CoV) known as 3-chymotrypsin-like protease (3CLpro) *in vitro* [19]. This enzyme (i.e. 3-chymotrypsin-like protease (3CLpro)) seems highly preserved in SARS-CoV-2 and together with papain-like protease (PLpro), they're responsible enzymes for cleavage of polyproteins into an RNA-dependent RNA polymerase and a helicase within which the replication of SARS-CoV-2 depends on [20,21].

In clinical study done in hospitalized adult patients with critically ill Covid-19, lopinavir–ritonavir treatment did not showed clinical advantage over standard care. During this clinical test, 199 patients randomized to lopinavir 400 mg/ritonavir 100 mg orally twice daily for 14 days, but these patients failed to have a shorter time to clinical improvement over standard of care (SOC). In lopinavir/ritonavir treated group, a lower death rate and shorter ICU stay was observed in this group than within the SOC group (6 days vs. 11 days; difference=-5 days; 95% CI,-9 to 0). But this difference is not statistically significant. The duration of hospital stays and time to clearance of viral RNA from respiratory tract samples did not differ between the lopinavir/ritonavir and SOC arms [22].

An exploratory randomized controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol reported that LPV/r or arbidol monotherapy showed little benefit for improving the clinical outcome of patients hospitalized with mild/moderate COVID-19 over supportive care. This clinical trial efficaciously enrolled 86 patients with mild/moderate COVID-19 with 34 randomly allotted to receive LPV/r, 35 to arbidol and 17 with no antiviral medication as control [23]. The time to a negative severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) nucleic acid pharyngeal swab was analogous for patients receiving lopinavir/ritonavir (mean of 9 days [SD 5.0]) and for those receiving SOC (mean of 9.3 days [SD 5.2]). Progression to severe situation happened among eight patients receiving lopinavir/ritonavir and two patients on SOC (12%).

ANTIMALARIAL DRUGS

Chloroquine

In vitro, chloroquine has antiviral action against different RNA viruses as well as several DNA viruses. The antiviral activity of chloroquine is obtained though blocking virus infection by increasing endosomal pH essential for virus/cell fusion. Additionally, chloroquine blocks the infection interfering with the glycosylation of cellular receptors of SARS-CoV. Chloroquine worked at both entry, and at post-entry stages of SARS-CoV-2 infection in Vero E6 cells especially in a time-of-addition assay. Chloroquine has an immune-modulating action which may augment its antiviral activity of this drug *in vivo* [24].

In a clinical test conducted to investigate the safety and efficacy of two chloroquine dosages in patients with severe coronavirus disease 19, high-dose chloroquine (600 mg twice daily) increased mortality rate in patients received azithromycin and oseltamivir simultaneously. This randomized, double-blind, Phase 2b study compared two different chloroquine regimens for the treatment of COVID 19: high-dose chloroquine (600 mg twice daily for 10 days) versus low-dose chloroquine (450 mg twice daily for one day followed by 450 mg for four days). The study participants were hospitalized adults with suspected severe coronavirus disease 19 and all participants received ceftriaxone plus azithromycin; 89.6% of the patients also taken oseltamivir. The entire death rate was 27.2%. In day 13, death toll was higher within the high-dose division than within the low-dose division (death in 16 of 41 participants [39%] vs. in 6 of 40 participants [15%]; P=0.03). But, this difference wasn't statistically significant when controlled by age (or 2.8; 95% confidence interval [CI], 0.9-8.5) [25].

In a small randomized, controlled trial in China, the effectiveness of chloroquine was compared to the lopinavir/ritonavir and at last, there was no significant clinical advantage observed with chloroquine in the treatment of coronavirus disease 19 [26]. During this study, 22 hospitalized patients with coronavirus disease 19 (none critically ill) were randomized and ten patients taken oral chloroquine 500 mg twice daily and 12 patients taken lopinavir 400 mg/ritonavir 100 mg twice daily for 10 days. The chloroquine-treated group had improved from the clinical symptom early to beginning of treatment (2.5 days vs. 6.5 days, **P**<0.001) compared to the lopinavir/ritonavir-treated patients. At day 10, 90% of the chloroquine-treated group and 75% of the lopinavir/ritonavir-treated patients had a negative SARS-CoV-2 PCR test result. At day 14, the odds for the chloroquine-treated patients and also the lopinavir/ritonavir-treated patients were 100% and 91.2%, respectively. At day 10, 20% of the chloroquine-treated patients and 8.3% of the lopinavir/ritonavir-treated patients had CT scan improvement. At day 14, the odds for the chloroquine-treated patients and also the lopinavir/ritonavir-treated patients were 100% and 75%, respectively. At day 14, 100% of the chloroquine-treated patients and 50% of the lopinavir/ritonavir-treated patients were discharged from the hospital.

Hydroxychloroquine

Controlled trial of hydroxychloroquine versus standard of care revealed that administration of hydroxychloroquine failed to lead to significantly higher negative conversion probability than standard of care alone in patients mainly hospitalized with persistent mild to moderate COVID–19 [27]. This multicenter, randomized, open-label trial compared hydroxychloroquine 1,200 mg once daily for 3 days followed by hydroxychloroquine 800 mg once daily for the rest of the treatment duration (two weeks for patients with mild/moderate coronavirus disease 19 [99% of the patients] and three weeks for one patient with severe disease) versus standard of care (SOC). 75 patients were enrolled in each study group. No difference was found between the hydroxychloroquine group and also the standard of care group in negative PCR conversion rate within 28 days (85.4% of participants vs. 81.3% of participants, respectively) or in time to negative PCR conversion (median of 8 days vs.7 days, respectively). There was no difference within the rate of symptom improvement between the groups in the intention-to-treat analysis. There was more quick normalization of CRP and lymphocytopenia in the hydroxychloroquine group.

In a randomized controlled trial in China on hydroxychloroquine plus standard treatment versus standard treatment alone, reported that the use of hydroxychloroquine could significantly shorten TTCR and promote the absorption of pneumonia among patients with coronavirus disease 19. Compared to the control patients, the hydroxychloroquine-treated patients had a 1 day-shorter mean duration of fever (2.2 days vs.. 3.2 days), cough (2.0 days vs.3.1 days) and none of them experienced progression of coronavirus disease 19. 80.6% of the hydroxychloroquine-treated patients and 54.8% of the control patients experienced either moderate or significant improvement in chest CT scan [28].

CONCLUSION

Even though different reports have published and presented on the medical journals and press claiming the potential of different agents for the effective treatment of patients with COVID-19, there are no Food and Drug Administration (FDA)-approved drugs for the treatment of this disease. More or less absolute clinical trial data are needed to recognize safe and effective treatments for coronavirus disease 2019. Infection prevention and control methods and supportive care, including supplemental oxygen and mechanical ventilatory support when needed are the suggested management decision for patients infected with coronavirus disease 2019.

FDA issued an emergency use authorization for the antiviral drug under investigation (i.e. remdesivir) for the treatment of COVID-19 in hospitalized patients especially critically ill adults and children. In a clinical trial, remdesivir reduced recovery time to shorten the time to in certain patients but little is known about the safety and efficacy of using this investigational drug for the treatment of COVID-19 in hospitalized patients. The emergency use authorization allows for remdesivir be distributing within the U.S.A and administering intravenously by health care providers due to the reason that the known and potential benefits of remdesivir outweigh the known and potential risks of the drug for the treatment of severe COVID-19 in hospitalized patients the depends on data obtained from clinical trial.

The use of high-dose chloroquine (600 mg twice daily) for the treatment of COVID-19 was increased mortality especially when taken concurrently with azithromycin and oseltamivir. Also, the combination of hydroxychloroquine plus azithromycin and Lopinavir/ritonavir were restricted for the treatment of COVID-19 because of the potential for toxicities and unfavorable pharmacodynamics and negative clinical trial data, respectively. Full clinical studies will be necessary to know the safety and efficacy of antivirals and antimalarial agents on the patients with coronavirus disease 2019.

DECLARATION

The authors of this manuscript declare that there is no conflict of interest.

REFERENCES

1. Anthony SJ, Johnson CK, Greig DJ, Kramer S, Che X, Wells H, et al. Global patterns in coronavirus diversity. Virus Evol. 2017; 3(1):vex012.
2. Su S, Wong G, Shi W, Liu J, Lai ACK, Zhou J. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trends Microbiol. 2016; 24(6):490-502.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China. N. Engl. J. Med. 2020; 382(8):727-733.
4. Gorbalenya AE.The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol. 2020; 5(4):536-544
5. Kupferschmidt K, Cohen J. Will novel virus go pandemic or be contained?. Science. 2020; 367(6478):610-611.
6. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019; 17:181-192.
7. Qian Z, Travanty EA, Oko L, Edeen K, Berglund A, Wang J, et al. Innate immune response of human alveolar type II cells infected with severe acute respiratory syndrome-coronavirus. Am J Respir Cell Mol Biol. 2013; 48:742-748.
8. Raj VS, Mou H, Smits SL, Dekkers DHW, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013; 495:251-254.
9. Zhou P, Yang XL, Wang XG, Hu B, Zhang L. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020. 579(7798):270-273.
10. World Health Organization. Novel coronavirus (COVID-19) situation. 2020.
11. Li G, Le Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov. 2020; 19(3):149-150
12. Wang M, Cao R, Zhang L. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res. 2020;30(3):269-271.
13. Sheahan TP, Sims AC, Graham RL. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9(396).
14. Sheahan TP, Sims AC, Leist SR. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11(1):222.
15. De Wit E, Feldmann F, Cronin J. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A. 2020;117(12):6771-6776.
16. Williamson BN, Feldmann F, Benjamin Schwarz B. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. bioRxiv. 2020.
17. Food and Drug Administration. Fact sheet for health care providers emergency use authorization (EUA) of remdesivir (GS-5734™). 2020.
18. Wang Y, Zhang D, Du G. Remdesivir in adults with severe COVID-19: arandomised, double-blind, placebo-controlled, multicentre trial. The Lancet. 2020; 395(10236):1569-1578.
19. Liu X, Wang XJ. Potential inhibitors against 2019-nCoV coronavirus M protease from clinically approved medicines. J Genet Genomics. 2020;47(2):119-121.
20. Tahir ul Qamar M, Alqahtani SM, Alamri MA, Chen L. Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants. J Pharm Anal.2020.
21. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronavirusesdrug discovery and therapeutic options. Nat Rev Drug Discov. 2016;15(5):327-347.
22. Cao B, Wang Y, Wen D. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. 2020;382(19):1787-1799.
23. Li Y, Xie Z, Lin W. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI). medRxiv. 2020.
24. Devaux CA. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19. Int J Antimicrob Agents. 2020; 55(5):105938.
25. Borba MGS, Val FFA, Sampaio VS. Effect of high vs. low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. JAMA Netw Open. 2020;3(4):e208857.
26. Huang M, Tang T, Pang P. Treating COVID-19 with chloroquine. J Mol Cell Biol. 2020; 12(4):322-325
27. Tang W, Cao Z, Han M. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial. medRxiv. 2020.
28. Chen Z, Hu J, Zhang Z. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv. 2020.