



Anti COVID-19 Drugs: Need for More Clinical Evidence and Global Action

Zakir Khan · Yusuf Karataş · Hazir Rahman

Received: March 27, 2020
© The Author(s) 2020

ABSTRACT

The World Health Organization (WHO) called the outbreak of coronavirus infectious disease-2019 (COVID-19) a “Public Health Emergency of International Concern” (PHEIC). According to the WHO, Centers for Disease Control and Prevention (CDC), and the US Food and Drug Administration (FDA), currently there are no medicines or vaccines that have been claimed to be useful in the prevention or treatment of COVID-19. Several existing antiviral drugs, previously developed or used as treatments for severe acute respiratory syndrome (SARS),

Middle East respiratory syndrome (MERS), human immunodeficiency virus (HIV), and malaria, are being investigated as COVID-19 treatments and some of them are being used in clinical trials. According to the CDC and Chinese treatment guidelines for COVID-19, chloroquine, hydroxychloroquine, lopinavir/ritonavir, and one of the investigational agents (remdesivir) are recommended in critically ill older patients. The use of other potential drugs reported in different studies may be considered if treatment with first-line drugs is ineffective. There are currently no complete data available from large randomized clinical trials (RCTs) to provide clinical guidance on the use, dosing, or duration to validate the effective role, safety profile, and adverse effects of all of the trial drugs for prophylaxis or treatment of COVID-19. Until now, it is still unclear which drug can successfully fight against the disease. Therefore, for the better safety of patients with COVID-19, further clinical trials and large randomized controlled studies are needed to validate the effective role, safety profile, and adverse effects of all the potential drugs. Such a measure requires action at the global level.

Digital Features To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.12136476>.

Z. Khan (✉) · Y. Karataş
Tıbbi Farmakoloji Anabilim Dalı, Tıp Fakültesi,
Çukurova Üniversitesi, Sarıçam, Adana, Turkey
e-mail: zakirkhan300@gmail.com

Z. Khan
Department of Pharmacy, Quaid-i-Azam University,
Islamabad, Pakistan

Y. Karataş
Pharmacovigilance specialist, Balcalı Hospital,
Cukurova University, Adana, Turkey

H. Rahman
Department of Microbiology, Faculty of Chemical
and Life Sciences, Abdul Wali Khan University
Mardan (AWKUM), Mardan, KPK, Pakistan

Keywords: Adverse effects; China; Chloroquine; Coronavirus infectious disease-2019 (COVID-19); Drugs; MERS; SARS; Therapy

Key Summary Points

Coronavirus infectious disease-2019 (COVID-19) is an emerging global health threat. The World Health Organization (WHO) called the outbreak of COVID-19 a “Public Health Emergency of International Concern” (PHEIC).

According to the WHO, Centers for Disease Control and Prevention (CDC), and the US Food and Drug Administration (FDA), there is currently no proven effective drug or vaccine for the treatment or prevention of COVID-19. However, several existing drugs are being investigated as COVID-19 treatments and some of them are being used in clinical trials.

According to the CDC, two licensed drugs (chloroquine and hydroxychloroquine) and investigational agent (remdesivir) are currently in use in the USA. On the other hand, the China International Exchange and Promotive Association for Medical and Health Care (CPAM) has released COVID-19 guidelines and recommended the use of lopinavir/ritonavir tablets or chloroquine in critically ill older patients. Hydroxychloroquine is also recommended when chloroquine is unavailable. The use of other potential drugs reported in different studies may be considered if treatment with first-line drugs is ineffective.

Currently no complete data are available from large randomized clinical trials (RCTs) to provide clinical guidance on the use, dosing, or duration to validate the effective role, safety profile, and adverse effects of all of the trial drugs for prophylaxis or treatment of COVID-19. Until now, it is still unclear which drug can successfully fight against the disease.

Further clinical trials, large randomized controlled studies, and global action are needed for effective and safe Anti COVID-19 therapy.

The city of Wuhan, China became the center of an outbreak of an unknown cause of pneumonia in December 2019 and raised intense global attention. Chinese scientists isolated a novel coronavirus from infected patients in Wuhan by January 7, 2020. This strain of coronavirus became formally known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and also referred to as 2019-nCoV. The infection caused by this virus is known as coronavirus infectious disease-2019 (COVID-19) [1]. Cases of COVID-19 are no longer restricted to Wuhan, with the growing number of cases and expanding geographic distribution raising serious questions about the outbreak's future trajectory [2, 3]. The World Health Organization (WHO) called the outbreak of COVID-19 a “Public Health Emergency of International Concern” (PHEIC) on January 30, 2020 [4]. COVID-19 cases had been recorded around the world, including Western Pacific, European, Southeast Asia, Eastern Mediterranean, Americas, and African regions. More than 220 countries registered cases of COVID-19 with 1,773,084 confirmed cases and 111,652 deaths worldwide, according to the WHO report on April 13, 2020 [5].

As a result of the serious global health threat, international health authorities' efforts have concentrated on rapid detection and isolation of patients with COVID-19, as well as the search for treatments capable of mitigating the disease's most serious consequences. In the absence of a known effective treatment and because of the public health emergency, the world is endangered by the risk of a SARS-CoV-2 pandemic. According to the WHO [6], Centers for Disease Control and Prevention (CDC) [7], and the US Food and Drug Administration (FDA) [8], there is currently no proven effective drug or vaccine for the treatment or prevention of SARS-CoV-2 infection. Now the world is desperately searching for ways to stop the spread of the novel coronavirus and find effective therapies. Drug repositioning (drug repurposing) is the investigation of existing drugs for new therapeutic purposes. It is a line of scientific research aimed at developing safe and effective treatments for COVID-19 [9]. Therefore, different clinical trials have been

conducted to identify possible treatment options for COVID-19. Several existing antiviral drugs, previously developed or used as treatments for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), human immunodeficiency virus (HIV), and malaria, are being investigated as treatments for COVID-19 and some have moved into clinical trials conducted around the globe [10]. According to the CDC, two licensed drugs (chloroquine and hydroxychloroquine) and one investigational agent (remdesivir) are currently in use in the USA [11]. However, remdesivir is not approved by the FDA for a COVID-19 indication [12]. On the other hand, the China International Exchange and Promotive Association for Medical and Health Care (CPAM) has released COVID-19 guidelines and recommended the use of lopinavir/ritonavir tablets (400 mg/100 mg orally twice daily) or chloroquine (500 mg orally two times daily) in critically ill older patients. Hydroxychloroquine (orally 400 mg once daily) is also recommended when chloroquine is unavailable [13].

The use of other drugs such as hydroxychloroquine plus azithromycin [14, 15], ribavirin [16, 17], interferon [18, 19], oseltamivir [20], favipiravir [21], sofosbuvir [22], ivermectin [23], ozone therapy [24], and tocilizumab [25] has not been recommended as first-line therapies; however, use of such drugs may be considered if treatment with first-line drugs (chloroquine, hydroxychloroquine, and lopinavir/ritonavir) is ineffective [13]. These products have shown some effectiveness in laboratory and animal experiments but it is not possible to make an evidence-based recommendation on their use in COVID-19 treatment unless a large human trial is conducted. The name “SOLIDARITY trial” was given to such an effort by the WHO [26].

Currently, limited data from randomized clinical trials (RCTs) are available to inform clinical guidance on the use, dosing, or duration of the aforementioned drugs for prophylaxis or treatment of SARS-CoV-2 infection [8, 14]. Moreover, the recommended anti COVID-19 medications are likely to have adverse effects, such as the risk of macular retinopathy [27] and cardiomyopathy due to chloroquine [28], and

cardiotoxicity (prolonged QT syndrome) due to extended use of hydroxychloroquine alone or in combination with azithromycin in hepatic, renal, and immunocompromised patients [11, 29]. Additionally, hydroxychloroquine in combination with azithromycin has been reported to reduce the detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared to a non-randomized control group but did not assess clinical benefit [15], and in a recent randomized, controlled, open-clinical trial in China, lopinavir/ritonavir did not show promise for the treatment of hospitalized patients with COVID-19 and pneumonia [30].

Therefore, for the better safety of patients with COVID-19, further clinical trials and large randomized controlled studies are needed to validate the effective role, safety profile, and adverse effects of all the test drugs [26, 31]. However, any approvals for the use of a new drug, of course, require further clinical testing, followed by the approval of widespread use by the relevant regulatory body for medical treatment in each country. To accomplish this, there is an urgent need for global collaboration, access conditions for public funds, and upfront agreements and affordability arrangements with those involved in the development of new medical technologies. Products for the prevention and treatment of COVID-19 should be global public goods. Such a measure requires action at the global level.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosures. Zakir Khan, Yusuf Karataş, and Hazir Rahman declare no conflict of interest.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc/4.0/>.

REFERENCES

- World Health Organization (WHO). Coronavirus. 2020. <https://www.who.int/health-topics/coronavirus>. Accessed 23 Mar 2020.
- Centers for Disease Control and Prevention (CDC). Coronavirus symptoms and diagnosis. 2020. <https://www.cdc.gov/coronavirus/about/symptoms.html>. Accessed 23 Mar 2020.
- Khan Z, Muhammad K, Ahmed A, Rahman H. Coronavirus outbreaks: prevention and management recommendations. *Drugs Ther Perspect*. 2020. <https://doi.org/10.1007/s40267-020-00717-x>.
- World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation report—50. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200310-sitrep-50-covid-19.pdf?sfvrsn=55e904fb_2. Accessed 24 Mar 2020.
- World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) situation report—84. 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200413-sitrep-84-covid-19.pdf?sfvrsn=44f511ab_2. Accessed 14 Apr 2020.
- World Health Organization (WHO). Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. 2020. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected). Accessed 25 Mar 2020.
- Centers for Disease Control and Prevention (CDC). Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19). 2020. <https://www.cdc.gov/coronavirus/019-ncov/hcp/clinical-guidance-management-patients.html>. Accessed 25 Mar 2020.
- Food and Drug Administration (FDA). Coronavirus disease 2019 (COVID-19). 2020. <https://www.fda.gov/emergency-preparedness-and-response/coun-terterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19>. Accessed 25 Mar 2020.
- Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol*. 2020. <https://www.nature.com/articles/d41587-020-00003-1>. Accessed 25 Mar 2020.
- Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov*. 2020;19(3):149–50. <https://www.nature.com/articles/d41573-020-00016-0>.
- Centers for Disease Control and Prevention (CDC). Information for clinicians on therapeutic options for COVID-19 patients. 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html#r8>. Accessed 25 Mar 2020.
- Food and Drug Administration (FDA). Search Orphan Drug Designations and Approvals: remdesivir. 2020. <https://www.accessdata.fda.gov/scripts/opdlisting/opd/detailedIndex.cfm?cfgridkey=739020>. Accessed 25 Mar 2020.
- Smith T, Prosser T. COVID-19 drug therapy—potential options. 2020. https://www.elsevier.com/_data/assets/pdf_file/0007/988648/COVID-19-Drug-Therapy_Mar-2020.pdf. Accessed 25 Mar 2020.
- Centers for Disease Control and Prevention (CDC). Information for clinicians on therapeutic options for COVID-19 patients. 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html#r8>. Accessed 25 Mar 2020.

- [coronavirus/2019-ncov/hcp/therapeutic-options.html](#). Accessed 25 Mar 2020.
15. Gautret P, Lagier J, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020. <https://doi.org/10.1016/j.ijantimicag.2020.105949>.
 16. China Law Translate. Novel coronavirus pneumonia diagnosis and treatment plan (provisional 7th edition). 2020. <https://www.chinalawtranslate.com/en/coronavirus-treatment-plan-7/>. Accessed 25 Mar 2020.
 17. Korea Biomedical Review. 2020. <https://www.koreabiomed.com/news/articleView.html?idxno=7428>. Accessed 25 Mar 2020.
 18. Devlin H, Sample I. The Guardian. What are the prospects for a Covid-19 treatment? 2020. <https://www.theguardian.com/science/2020/mar/19/prospects-treatment-coronavirus-drugs-vaccines>. Accessed 25 Mar 2020.
 19. The Week News. All about Cuba's 'wonder drug' being pitched against coronavirus. 2020. <https://www.theweek.in/news/health/2020/03/24/all-about-Cubas-wonder-drug-being-pitched-against-coronavirus.html>. Accessed 25 Mar 2020.
 20. ClinicalTrials.gov. National Library of Medicine (US). 2020 Mar 11—identifier NCT04303299. Various combination of protease inhibitors, oseltamivir, favipiravir, and chloroquin for treatment of COVID-19: a randomized control trial (THDMS-COVID19). <https://clinicaltrials.gov/ct2/show/NCT04303299>. Accessed 26 Mar 2020.
 21. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering*. 2020. <https://doi.org/10.1016/j.eng.2020.03.007>.
 22. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci*. 2020;248:117477. <https://doi.org/10.1016/j.lfs.2020.117477>.
 23. Leon Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antivir Res*. 2020. <https://doi.org/10.1016/j.antiviral.2020.104787>.
 24. Zhou M. Ozone: a powerful weapon to combat COVID-19 outbreak. *China.org.cn*. 2020. http://www.china.org.cn/opinion/2020-02/26/content_75747237_4.htm. Accessed 26 Mar 2020.
 25. Slater H. Cancer Network News. FDA approves phase III clinical trial of tocilizumab for COVID-19 pneumonia. 2020. <https://www.cancernetwork.com/news/fda-approves-phase-iii-clinical-trial-tocilizumab-covid-19-pneumonia>. Accessed 26 Mar 2020.
 26. Kupferschmidt K, Cohen J. Science News. WHO launches global megatrial of the four most promising coronavirus treatments. 2020. <https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments>. Accessed 26 Mar 2020.
 27. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020. <https://doi.org/10.1016/j.ijantimicag.2020.105938>.
 28. Cubero GI, Reguero JJR, Ortega JMR. Restrictive cardiomyopathy caused by chloroquine. *Br Heart J*. 1993;69(5):451–2.
 29. Joyce E, Fabre A, Mahon N. Hydroxychloroquine cardiotoxicity presenting as a rapidly evolving biventricular cardiomyopathy: key diagnostic features and literature review. *Eur Heart J Acute Cardiovasc Care*. 2013;2(1):77–83. <https://doi.org/10.1177/2048872612471215>.
 30. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *NEJM*. 2020. <https://doi.org/10.1056/NEJMoa2001282>.
 31. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nat Biotechnol*. 2020. <https://doi.org/10.1038/d41587-020-00003-1>.