Communication

DOI: 10.5582/ddt.2020.01012

Discovering drugs to treat coronavirus disease 2019 (COVID-19)

Liying Dong[1], Shasha Hu[2], Jianjun Gao[1,*]

[1] Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, Shandong, China;
[2] Department of Pathology, the Affiliated Hospital of Qingdao University, Qingdao, Shandong, China.

SUMMARY The SARS-CoV-2 virus emerged in December 2019 and then spread rapidly worldwide, particularly to China, Japan, and South Korea. Scientists are endeavoring to find antivirals specific to the virus. Several drugs such as chloroquine, arbidol, remdesivir, and favipiravir are currently undergoing clinical studies to test their efficacy and safety in the treatment of coronavirus disease 2019 (COVID-19) in China; some promising results have been achieved thus far. This article summarizes agents with potential efficacy against SARS-CoV-2.

Keywords novel coronavirus, pneumonia, COVID-19, 2019-nCoV, SARS-CoV-2

The virus SARS-CoV-2 (formerly designated 2019-nCoV) emerged in December 2019 and then spread rapidly worldwide, particularly to China, Japan, and South Korea. As of February 21, 2020, a total of 76,288 confirmed cases of coronavirus disease 2019 (COVID-19) and 2,345 deaths have been reported in mainland China (*1*). Scientists are endeavoring to find drugs to treat this disease. Research thus far has revealed more than 30 agents including Western medicines, natural products, and traditional Chinese medicines that may have potential efficacy against COVID-19. Some of these agents have been quickly tested in clinical studies and demonstrated preliminary efficacy against COVID-19. Antivirals including interferon α (IFN-α), lopinavir/ritonavir, chloroquine phosphate, ribavirin, and arbidol have been included in the latest version of the Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia issued by the National Health Commission (NHC) of the People's Republic of China for tentative treatment of COVID-19 (Table 1) (*2*).

The Guidelines have been revised 5 times since first being issued on January 15, 2020; the latest edition (the 6th edition) was issued on February 18, 2020. The fifth edition of the Guidelines recommends antivirals including IFN-α, lopinavir/ritonavir, and ribavirin for treatment of COVID-19 (*3*). Chloroquine phosphate and arbidol are included in the sixth edition of the Guidelines based on the preliminary outcomes of clinical studies (*2*). The specific method for administration of IFN-α is vapor inhalation at a dose of 5 million U (and 2 mL of sterile water for injection) for adults, 2 times/day. The dosage of lopinavir/ritonavir is 400 mg/100 mg for adults, 2 times/day. Ribavirin should be administered *via* intravenous infusion at a dose of 500 mg for adults, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir. Chloroquine phosphate is orally administered at a dose of 500 mg (300 mg for chloroquine) for adults, 2 times/day. Arbidol is orally administered at a dose of 200 mg for adults, 3 times/day. The duration of treatment is no more than 10 days.

IFN-α is a broad-spectrum antiviral that is usually used to treat hepatitis, though it is reported to inhibit SARS-CoV reproduction *in vitro* (*4*). Lopinavir/ritonavir is a medication for the human immunodeficiency virus (HIV) used in combination with other medications to treat adults and children over 14 days of age who are infected with HIV-1 (*5*). Chu *et al*. found that lopinavir/ritonavir has anti-SARS-CoV activity *in vitro* and in clinical studies (*6*). Ribavirin is a nucleoside analogue with a broad-spectrum of antiviral effects. A study compared 111 patients with severe acute respiratory syndrome (SARS) treated with ribavirin monotherapy and 41 patients with SARS treated with lopinavir/ritonavir and ribavirin; patients treated with the combined therapy had a lower risk of acute respiratory distress syndrome (ARDS) and death (*6*). Chloroquine is a widely used antimalarial that was found to be a potential broad-spectrum antiviral in 2006 (*7*). Chloroquine was found to block SARS-CoV-2 infection at low-micromolar concentration, with a half-maximal effective concentration (EC_{50}) of 1.13 μM and a half-cytotoxic concentration (CC_{50}) greater than 100 μM (*8*). Arbidol is an antiviral that can be used to treat influenza virus. A study has revealed that arbidol can effectively inhibit SARS-CoV-2 infection at a concentration of 10-30 μM

Table 1. Antivirals included in the Guidelines (version 6) for treatment of COVID-19

Drug	Dosage	Method of administration	Duration of treatment
IFN-α	5 million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	No more than 10 days
Ribavirin	500 mg each time, 2 to 3 times/day in combination with IFN-α or lopinavir/ritonavir	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500 mg (300 mg for chloroquine) each time, 2 times/day	Oral	No more than 10 days
Arbidol	200 mg each time, 3 times/day	Oral	No more than 10 days

in vitro (*9*).

Besides the drugs above that have been included in the Guidelines, favipiravir is a drug that warrants attention. Favipiravir was approved for treatment of novel influenza on February 15, 2020 in China. This drug is currently undergoing clinic trials in treating COVID-19. Favipiravir is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor. In addition to its anti-influenza virus activity, favipiravir is capable of blocking the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses (*10*). Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, thus inhibiting RNA polymerase activity (*11*). Therefore, favipiravir may have potential antiviral action on SARS-CoV-2, which is a RNA virus. On February 14, a clinical trial on favipiravir for the treatment of COVID-19 initiated by the Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen achieved promising results. The preliminary results from a total of 80 patients (including the experimental group and the control group) indicated that favipiravir had more potent antiviral action than that of lopinavir/ritonavir (*12*). No significant adverse reactions were noted in the favipiravir treatment group, and it had significantly fewer adverse effects than the lopinavir/ritonavir group (*12*).

Remdesivir is another potential drug for treatment of COVID-19. Remdesivir is a nucleoside analogue and a broad-spectrum antiviral. Animal experiments (*13*) indicated that remdesivir can effectively reduce the viral load in lung tissue of mice infected with MERS-CoV, improve lung function, and alleviate pathological damage to lung tissue. Wang *et al*. found that remdesivir potently blocks SARS-CoV-2 infection at low-micromolar concentrations and has a high selectivity index (half-maximal effective concentration (EC_{50}), 0.77 μM; half-cytotoxic concentration (CC_{50}) > 100 μM; SI > 129.87) (*8*). Holshue *et al*. reported that remdesivir yielded promising results in the treatment of a patient with COVID-19 in the United States (*14*). In order to evaluate the efficacy and safety of the drug in patients with COVID-19, a randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial was launched on February 5, 2020 in China (*15,16*). Patients in the experimental group received a initial dose of 200 mg of remdesivir and a subsequent dose of 100 mg for 9 consecutive days *via* intravenous infusion in addition to routine treatment. Patients in the control group received routine treatment and the same dose of a placebo. The trial is expected to conclude by the end of April 2020.

Studies have also revealed some other drugs may have potential efficacy in treating COVID-19. One is darunavir, which is a second-generation of HIV-1 protease inhibitor. On February 4, 2020, researchers in China announced that darunavir inhibited SARS-CoV-2 infection *in vitro* (*9*). Cell experiments indicated that darunavir significantly inhibited viral replication at a concentration of 300 μM *in vitro* and that its inhibition efficiency was 280-fold that in the untreated group (*9*). Other potential drugs include type II transmembrane serine protease (TMSPSS2) inhibitors and BCR-ABL kinase inhibitor imatinib. Hoffmann *et al*. indicated that SARS-CoV-2 uses the SARS-CoV receptor, ACE2, and the cellular protease TMPRSS2 to enter target cells. A TMPRSS2 inhibitor would block entry and thus constitute a treatment option (*17*). Imatinib has anti-coronal activity primarily because it inhibits the fusion of virions with the endosomal membrane (*18*).

A joint research team of the Shanghai Institute of Materia Medica and Shanghai Tech University performed drug screening in silicon and an enzyme activity test, and they reported 30 agents with potential antiviral activity against SARS-CoV-2 on January 25, 2020 (*19*). These agents are indinavir, saquinavir, lopinavir, carfilzomib, ritonavir, remdesivir, atazanavir, darunavir, tipranavir, fosamprenavir, enzaplatovir, presatovir, abacavir, bortezomib, elvitegravir, maribavir, raltegravir, montelukast, deoxyrhapontin, polydatin, chalcone, disulfiram, carmofur, shikonin, ebselen, tideglusib, PX-12, TDZD-8, cyclosporin A, and cinanserin. The same study also found that Chinese herbal medicines such as Rhizoma Polygoni Cuspidati and Radix Sophorae Tonkinensis may contain active ingredients against SARS-COV-2 (*19*).

As the epidemic spreads, scientists around the world are actively exploring drugs that would be potentially effective in combating COVID-19. Generally, there are

no finally verified antivirals specific to COVID-19 at present. The efficacy and safety of these candidate drugs in the treatment of COVID-19 need to be confirmed in further preclinical and clinical trials.

References

1. Update on the prevalence and control of novel coronavirus-induced pneumonia as of 24:00 on February 21. *http://www.nhc.gov.cn/xcs/yqtb/202002/543cc508978a48d2b9322bdc83daa6fd.shtml* (accessed February 23, 2020). (in Chinese).
2. Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia, The 6th ed. *http:// www.nhc.gov.cn/yzygj/s7653p/202002/8334a8326dd94d329df351d7da8aefc2/files/b218cfeb1bc54639af227f922bf6b817.pdf* (accessed February 23, 2020). (in Chinese).
3. Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia, The 5th ed. *http://www.nhc.gov.cn/yzygj/s7653p/202002/d4b895337e19445f8d728fcaf1e3e13a/files/ab6bec7f93e64e7f998d802991203cd6.pdf* (accessed February 18, 2020). (in Chinese).
4. Stockman LJ, Bellamy R, Garner P. SARS: Systematic review of treatment effects. PLoS Med. 2006; 3:e343.
5. Su B, Wang Y, Zhou R, Jiang T, Zhang H, Li Z, Liu A, Shao Y, Hua W, Zhang T, Wu H, He S, Dai L, Sun L. Efficacy and tolerability of lopinavir/ritonavir- and efavirenz-based initial antiretroviral therapy in HIV-1-infected patients in a tertiary care hospital in Beijing, China. Front Pharmacol. 2019; 10:1472.
6. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, Kao RYT, Poon LLM, Wong CLP, Guan Y, Peiris JSM, Yuen KY. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. Thorax. 2004; 59:252-256.
7. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. Lancet Infect Dis. 2006; 6:67-69.
8. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res. 2020.
9. News: Abidol and darunavir can effectively inhibit coronavirus *http://www.sd.chinanews.com/2/2020/0205/70145.html* (accessed February 21, 2020). (in Chinese).
10. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Res. 2018; 153:85-94.
11. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad, Ser B, Phys Biol Sci. 2017; 93:449-463.
12. News. *http://www.szdsyy.com/News/0a6c1e58-e3d0-4cd1-867a-d5524bc59cd6.html* (accessed February 22, 2020). (in Chinese).
13. Sheahan TP, Sims AC, Leist SR, *et al*. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020; 11:222.
14. Holshue ML, DeBolt C, Lindquist S, *et al*. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020.
15. Mild/Moderate 2019-nCoV Remdesivir RCT. *https://clinicaltrials.gov/ct2/show/NCT04252664* (accessed February 22, 2020). (in Chinese).
16. Severe 2019-nCoV Remdesivir RCT. *https://clinicaltrials.gov/ct2/show/NCT04257656* (accessed February 22, 2020). (in Chinese).
17. Hoffmann M, Kleine-Weber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. bioRxiv. 2020. 2020.2001.2031.929042.
18. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM, Frieman MB. Abelson kinase inhibitors are potent inhibitors of severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus fusion. J Virol. 2016; 90:8924-8933.
19. Shanghai Institute of Materia Medica website, Chinese Academy of Sciences. A joint research team of the Shanghai Institute of Materia Medica and Shanghai Tech University discover a group of old and traditional Chinese medicines that may be efficacious in treating the novel form of pneumonia. *http://www.simm.ac.cn/xwzx/kydt/202001/t20200125_5494417.html* (accessed February 22, 2020). (in Chinese).

Received February 23, 2020; Revised February 27, 2020; Accepted February 28, 2020.

**Address correspondence to:*
Jianjun Gao, Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, China.
E-mail: gaojj@qdu.edu.cn