

# Drug treatment options for the 2019-new coronavirus (2019-nCoV)

Hongzhou Lu<sup>1,2,3,\*</sup>

<sup>1</sup> Scientific Research Center, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China;

<sup>2</sup> Department of Infectious Diseases, Shanghai Public Health Clinical Center, Fudan University, Shanghai, China;

<sup>3</sup> Department of Infectious Disease, Huashan Hospital Affiliated to Fudan University, Shanghai, China.

**SUMMARY** As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (2019-nCoV) have been reported in 25 provinces (districts and cities) in China. At present, there is no vaccine or antiviral treatment for human and animal coronavirus, so that identifying the drug treatment options as soon as possible is critical for the response to the 2019-nCoV outbreak. Three general methods, which include existing broad-spectrum antiviral drugs using standard assays, screening of a chemical library containing many existing compounds or databases, and the redevelopment of new specific drugs based on the genome and biophysical understanding of individual coronaviruses, are used to discover the potential antiviral treatment of human pathogen coronavirus. Lopinavir /Ritonavir, Nucleoside analogues, Neuraminidase inhibitors, Remdesivir, peptide (EK1), arbidol, RNA synthesis inhibitors (such as TDF, 3TC), anti-inflammatory drugs (such as hormones and other molecules), Chinese traditional medicine, such ShuFengJieDu Capsules and Lianhuaqingwen Capsule, could be the drug treatment options for 2019-nCoV. However, the efficacy and safety of these drugs for 2019-nCoV still need to be further confirmed by clinical experiments.

**Keywords** 2019-nCoV, Coronaviruses, pneumonia

As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (2019-nCoV) have been reported in 25 provinces (districts and cities) in China (1). Among them, 95 cases were serious and 17 cases died (all from Hubei Province). WHO Collaborating Centre for Infectious Disease Modelling estimated a total of 4,000 cases of 2019-nCoV in Wuhan City (uncertainty range: 1,000-9,700) had onset of symptoms by 18th January 2020 (the last reported onset date of any case) (2). Identifying the drug treatment options as soon as possible is critical for the response to the 2019-nCoV outbreak (3).

At present, there is no vaccine or antiviral treatment for human and animal coronavirus (COV). Because of its key role in the virus cell receptor interaction, the surface structure of spike glycoprotein(s) is particularly important for the development of antivirals. Treatment of such severe influenza still presents multiple challenges. There are several general methods that could be used to discover a potential antiviral treatment for the human pathogen coronavirus.

The first one is to test the existing broad-spectrum antiviral drugs by using standard assays, which have been used to treat other viral infections (4). These methods can

measure the effects of these drugs on the cytopathy, viral production and plaque formation of living cells and/or pseudocoronaviruses. Examples of drugs identified using this method include interferon I (IFN- alpha, beta, kappa, lamda, epsilon, etc.) and interferon II (interferon gamma, etc.). These drugs have obvious advantages, known pharmacokinetic and pharmacodynamic properties, side effects and drug regimens. However, they have no specific anti coronavirus effect and may be related to serious adverse reactions.

The second method involves the screening of a chemical library containing many existing compounds or databases, including information about transcription characteristics in different cell lines (5). This method can quickly and high-throughput screen many easily obtained compounds, and then further evaluate them by antiviral assay. Various drugs have been identified in these drug reuse programs, including many drugs with important physiological and/or immunological effects, such as affecting neurotransmitter regulation, estrogen receptor, kinase signal transduction, lipid or sterol metabolism, protein processing and DNA synthesis or repair.

The third approach involves the redevelopment of

new specific drugs based on the genome and biophysical understanding of individual coronaviruses (6). Examples include siRNA molecules or inhibitors targeting specific viral enzymes involved in the viral replication cycle, mAb targeting host receptor, inhibitor of host cell protease, inhibitor of host cell endocytosis virus, human derived or humanized mAb targeting S1 RBD and antiviral peptide targeting S2. Although most of these drugs have anti coronavirus activity in vitro and/or in vivo, their pharmacokinetic and pharmacodynamic properties, as well as side effect characteristics, have yet to be evaluated in animal and human trials. In addition, development of these drugs can allow drugs to become clinically useful treatment options, but it usually takes several years to provide reliable treatment for patients. The main drawback of this approach is that although many of the identified drugs show anti-coronavirus activity in vitro, most of them are not clinically useful because they are associated with immunosuppression or have a value of half the EC50 of anti-coronavirus, which is significantly higher than the peak serum concentration (Cmax) that can be achieved at the treatment dose.

In general, these three drug discovery methods are usually used together during the emerging coronavirus outbreak, and can be roughly divided into virus based and host based treatment selection candidate drug compounds.

For the current new coronavirus, according to the guidelines (7), IFN- alpha (5 million U bid inh) and lopinavir/ritonavir(400 mg/100 mg *bid po*) are recommended as antiviral therapy. IFN- alpha is a broad spectrum antiviral drug, which can be used to treat HBV. Lopinavir is one kind of protease inhibitor used to treat HIV infection, with ritonavir as a booster. Lopinavir and/or lopinavir ritonavir have anti coronavirus activity in vitro. In Severe Acute Respiratory Syndrome (SARS) treatment, Hong Kong scholars found that compared with ribavirin alone, patients treated with lopinavir/ritonavir and ribavirin had lower risk of acute respiratory distress syndrome (ARDS) or death (8).

In addition, Nucleoside analogs may have multiple mechanisms of action, including lethal mutagenesis, specific or non specific chain termination, and inhibition of nucleotide biosynthesis (9). Fabiravir and ribavirin are representatives of nucleoside analogs, which combined with fabiravir and oseltamivir in the treatment of severe influenza is better than oseltamivir alone (10).

Besides, Remdesivir may be the best potential drug for the treatment of 2019-nCoV. Animal experiments showed that compared with the control group, Remdesivir can effectively reduce the virus titer of mice infected with Middle East Respiratory Syndrome (Mers)-CoV, improve the lung tissue damage, and its effect is better than that of the treatment group treated with Lopinavir/Ritonavir combined with interferon- $\beta$  (11). The drug has completed the phase III clinical trial for treatment of Ebola virus infection, and the

pharmacokinetics and safety for the human body have relatively complete data (12). However, the efficacy and safety of Remdesivir in patients with 2019-nCoV infection still need to be further confirmed by clinical research.

Neuraminidase inhibitors (NAIs) such as oral oseltamivir, inhaled zanamivir, and intravenous peramivir are recommended as antiviral treatment in influenza (13). Oral oseltamivir has been widely used for 2019-nCoV or suspected cases in China hospitals. The mainstay for patients is initiation of antiviral medication as soon as possible after illness onset. It has shown that neuraminidase inhibitors are effective as empirical treatment in MERS-CoV infection (14), however, there is no exact evidence that oseltamivir is effective in the treatment of 2019-nCoV.

At present, some other types of drugs have been found to be effective in vitro, such as fusion peptide (EK1) (15), arbidol (16), RNA synthesis inhibitors (such as TDF, 3TC) anti-inflammatory drugs (such as hormones and other molecules), *etc.* In addition, Chinese medicine, such as ShuFengJieDu Capsules and Lianhuaqingwen Capsules, has also played a role in the prevention and treatment of new respiratory infectious diseases such as influenza A (H1N1) (17,18). However, the efficacy and safety of these drugs in 2019-nCoV need to be further confirmed by clinical experiments.

In general, there are no specific antiviral drugs or vaccines for 2019-nCoV. All of the drug options come from experience treating SARS, MERS or some other new influenza virus previously. Active symptomatic support remains key to treatment. These drugs above would be helpful and the efficacy needs to be further confirmed.

#### Acknowledgement

This research was funded by the 13<sup>th</sup> Five-Year National Science and Technology Major Project from Ministry of Science and Technology of the People's Republic of China (Grant No.: 2017ZX09304027).

#### References

1. National Health Commission of the People's Republic of China. Pneumonia epidemic situation of new coronavirus infection on January 23, 2020. <http://www.nhc.gov.cn/yjb/s3578/202001/5d19a4f6d3154b9fae328918ed2e3e8a.shtml> (accessed January 23, 2020).
2. Natsuko Imai. Report 2: Estimating the potential total number of novel Coronavirus cases in Wuhan City, China. <http://www.imperial.ac.uk/mrc-global-infectious-disease-analysis/news--wuhan-coronavirus/> (accessed January 23, 2020).
3. Lu H, Stratton CW, Tang YW. Outbreak of Pneumonia of Unknown Etiology in Wuhan China: the Mystery and the Miracle. *J Med Virol*. 2020. doi: 10.1002/jmv.25678.
4. Kim Y, Liu H, Galasiti Kankanamalage AC, Weerasekara S, Hua DH, Groutas WC, Chang KO, Pedersen NC.

- Reversal of the Progression of Fatal Coronavirus Infection in Cats by a Broad-Spectrum Coronavirus Protease Inhibitor. *PLoS Pathog.* 2016; 12:e1005531.
5. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *J Immunol.* 2017; 198:4046-4053.
  6. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. *Nat Rev Drug Discov.* 2016; 15:327-47.
  7. National Health Commission of the People's Republic of China. Notice on printing and distributing the diagnosis and treatment plan of pneumonia with new coronavirus infection (trial version 3). <http://www.nhc.gov.cn/yzygj/s7653p/202001/f492c9153ea9437bb587ce2ffcbee1fa.shtml> (accessed January 23, 2020).
  8. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, Kao RY, Poon LL, Wong CL, Guan Y, Peiris JS, Yuen KY; HKU/UCH SARS Study Group.. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax.* 2004; 59:252-256.
  9. Arabi YM, Allothman A, Balkhy HH, *et al.* Treatment of Middle East Respiratory Syndrome with a combination of lopinavir-ritonavir and interferon- $\beta$ 1b (MIRACLE trial): study protocol for a randomized controlled trial. *Trials.* 2018;19:81.
  10. Wang Y, Fan G, Salam A, Horby P, Hayden FG, Chen C, Pan J, Zheng J, Lu B, Guo L, Wang C, Cao B; CAP-China Network. Comparative effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection. *J Infect Dis.* 2019; pii: jiz656.
  11. 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.
  12. Agostini ML, Andres EL, Sims AC, *et al.* Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *mBio.* 2018; 9: pii: e00221-18.
  13. Chow EJ, Doyle JD, Uyeki TM. Influenza virus-related critical illness: prevention, diagnosis, treatment. *Crit Care.* 2019 ; 23:214.
  14. Bleibtreu A, Jaureguiberry S, Houhou N, Boutolleau D, Guillot H, Vallois D, Lucet JC, Robert J, Mourvillier B, Delemazure J, Jaspard M, Lescure FX, Rioux C, Caumes E, Yazdanapanah Y. Clinical management of respiratory syndrome in patients hospitalized for suspected Middle East respiratory syndrome coronavirus infection in the Paris area from 2013 to 2016. *BMC Infect Dis.* 2018; 18:331.
  15. Xia S, Yan L, Xu W, Agrawal AS, Algaissi A, Tseng CK, Wang Q, Du L, Tan W, Wilson IA, Jiang S, Yang B, Lu L. A pan-coronavirus fusion inhibitor targeting the HR1 domain of human coronavirus spike. *Sci Adv.* 2019; 5:eaav4580.
  16. Coleman CM, Sisk JM, Mingo RM, Nelson EA, White JM2, 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.
  17. Ji S, Bai Q, Wu X, Zhang DW, Wang S, Shen JL, Fei GH. Unique synergistic antiviral effects of Shufeng Jiedu Capsule and oseltamivir in influenza A viral-induced acute exacerbation of chronic obstructive pulmonary disease. *Biomed Pharmacother.* 2020;121:109652.
  18. Ding Y, Zeng L, Li R, Chen Q, Zhou B, Chen Q, Cheng PL, Yutao W, Zheng J, Yang Z, Zhang F. The Chinese prescription lianhuaqingwen capsule exerts anti-influenza activity through the inhibition of viral propagation and impacts immune function. *BMC Complement Altern Med.* 2017; 17:130.

Received January 23, 2020; Accepted January 27, 2020.

\*Address correspondence to:

Hongzhou Lu, Shanghai Public Health Clinical Center, Fudan University, No.2901, Caolang Road, Jinshan District, Shanghai 201508, China.

E-mail: luhongzhou@fudan.edu.cn

Released online in J-STAGE as advance publication January 28, 2020.