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Editorial

Current Therapeutic Options for the COVID-19

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EDITORIAL

Since the outbreak of the Coronavirus Disease (COVID-19), which is caused by the new Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), the epidemic has spread rapidly. In general, when a sudden infectious epidemic encounters, people will look for effective treatment options from existing drugs before a vaccine against the new virus is developed [1]. In this editorial, I will update the status of current therapeutic options for the COVID-19.

As for today, the selected anti-SARS-CoV-2 drugs mainly came from three directions: the first is a nucleoside inhibitor that targets the viral replication key enzyme (RNA dependent RNA polymerase, RdRp); the second is a SARS-CoV-2 protease inhibitor, and the third is an inhibitor to block the interaction of the virus with human host protein angiotensin-converting enzyme 2 (ACE2).

Nucleoside inhibitors that target the RdRp

According to the news released by the Chinese Ministry of Science and Technology on February 15, favipiravir, chloroquine phosphate and remdesivirare the three top-choice medicines for the treatment of COVID-19 since they have showed higher efficacy and lower side effects. Among these, favipiravir and remdesivir are RdRp inhibitors.

Favipiravir, (also named as T-705 or avigan), developed by the Toyama (Fujifilm Group) Chemical Industry Co., belongs to a broad-spectrum antiviral drug [2]. It is currently used to treat COVID-19 patients both in China and Japan.

Remdesivir, an antiviral drug candidate developed by an American biopharmaceutical company Gilead, belongs to the type of nucleoside inhibitors targeting RdRp. The Washington State Regional Hospital announced on February 3, 2020, that the first COVID-19 patient in the United States has been discharged after receiving intravenous treatment with remdesivir. This is the first case in the world that uses remdesivir to cure the COVID-19.

SARS-CoV-2 protease inhibitors

Darunavir is a common AIDS treatment drug, a protease inhibitor that inhibits the production of mature infectious HIV. In early January 2020, darunavir has been used to treat patients and was recommended to be included in the sixth edition of the Chinese National Health Commission's diagnostic guidelines [3]. However, the biological activity of darunavir for COVID-19 is low and thus it was difficult to achieve a virus suppression effect in the body.

Lopinavir/ritonavir (sold under the brand name Kaletra), is a combination of HIV protease inhibitors and used as an antiviral drug to treat AIDS [1]. It is recommended for anti-COVID-19 treatment by the Chinese National Health Commission and has shown efficacy for certain patients, but not seems to apply to the vast majority of patients. This is similar to the result when lopinavir/ritonavir was used to treat SARS and MERS patients. Also, when it is used alone, the virus may soon develop resistance.

On February 19, 2020, the Chinese National Health Commission issued the "New Coronary Virus Pneumonia Diagnosis and Treatment Program (Sixth Trial Version)". In the new version, the lopinavir/ritonavir and ribavirin in the original protocol have been retained. Besides, chloroquine phosphate has been included as a trial drug for antiviral treatment.

Chloroquine was originally used to treat malaria and autoimmune diseases and it is a protease inhibitor. After the outbreak of SARS in 2003, researchers found that chloroquine also inhibited coronavirus. A report published on February 3, 2020 showed that in the *in vitro* cell tests of 7 drugs including remdesivir, the performance of chloroquine was only slightly lower than that of remdesivir [4]. Also, considering its insignificant side effects and its capability to prevent severe cytokine storm, chloroquine is probably one promising medicine to treat COVID-19. Several Chinese hospitals have recently launched clinical trials of chloroquine. Science and Technology Daily reported on February 14 that, in a chloroquine phosphate treatment trial of 19 patients conducted by the Beijing You' an Hospital and the Second Affiliated Hospital of Sun Yat-sen University, all patients had clinical symptoms alleviated or improved and 17 patients had a negative nucleic acid test. The clinical result clearly showed the safety and effectiveness of chloroquine in the treatment of COVID-19. However, the mechanism is not clear at this moment.

Inhibitors to block the interaction of SARS-CoV-2 with

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human ACE2

Umifenovir (sold under the brand name Abidol) is an anti-influenza drug but not approved by FDA. Umifenovir prevents contact between the virus and target host cells ACE 2 [5]. In early January 2020, Abidol has also been used to treat patients in China and were recommended to be included in the sixth edition of the Chinese National Health Commission's diagnostic guidelines. However, the biological activities of these drugs are low and the anti-influenza medication has no clear effect on the SARS-CoV-2, and it is currently only used as a symptomatic treatment in some areas. Furthermore, there is currently no published experimental data to prove that a combination of abidol and oseltamivir is effective against the SARS-CoV-2 coronavirus, SARS virus, and MERS virus.

So far, there is no sufficient evidence of efficacy and safety of any drugs based on this mechanism.

Combination

Several combination drugs have been used to treat COVID-19 patients. For example, on February 2, 2020, the Institute of Emergency Medicine and Disaster Medicine of Sichuan Provincial People's Hospital suggested using lopinavir/ritonavir in combination with entricitabine (FTC)/Tenofovir Alafenamide Fumarate tablets, (TAF or Vemlidy) for the early treatment of COVID-19 patients. FTC and TAF are two anti-AIDS drugs that mimic human nucleotides to introduce defection during the synthesis of the RNA virus. The results are not known yet. The most promising combination is hydroxychloroquine and azithromycin, which has shown a 100% recovery of a group of 20 patients reported on March 16, 2020 [6].

Medicine not suggested from the clinical trials in China

The lung images of COVID-19 patients did not change significantly after using hormones, such as glucocorticoids. So, hormone treatment is not recommended [7]. Gamma globulin has no obvious effect, and thus it is not recommended for use as well. Some patients who have used the lopinavi/ritonavir tablets in the early stage have experienced side effects such as diarrhea and the clinical effect was not obvious and is no longer recommended. The combination of abidol, ribavirin, oseltamivir, and some Chinese medicine capsules or antibiotics is just a comfort medication, and there is no evidence to prove their effectiveness.

Modeling work

On February 3, scholars from Tongji Medical College of Huazhong University of Science and Technology and Wuhan Children's Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology announced five possible antiviral drugs, beclabuvir, saquinavir, bictegravir, lopinavir and dolutegravir, for COVID-19 based on a computation of 8506 drugs on the market or in clinical trials. They found that beclabuvir can not only bind to the mpro protein, but also a potential inhibitor that targets the RdRp; saquinavir not only binds well to the mpro protein, but also combines with the S protein of the new coronavirus.

More modeling work had been conducted by multiple groups. We have also conducted some work based on inhibition of the protease and inhibition of the virus with ACE2. Our results showed that the following medicines may be used to fight the disease [8,9], cangrelor, Dpnh (NADH), Flavin Adenine Dinucleotide (FAD) adeflavin, iomeprol, coenzyme A, tiludronate, Flavin Adenine Dinucleotide (FAD) adeflavin, zanamivir, bortezomib, saquinavir, cangrelor, carfilzomib, indinavir, remdesivir, tadalafil, rivaroxaban, sildenafil, dasatinib, vardenafil, montelukast, indinavir, ergotamine, amphotericin b, vancomycin, zafirlukast, and lanicor.

This editorial was submitted in Feb. As for April 21, It seems clear that the lower-cost combination of hydroxychloroquine and azithromycin is great for patients with mild and moderate symptoms, and remdesivir works great for patients with severe symptoms.

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