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Existing drugs as treatment options for COVID-19: A brief survey of some recent results

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ABSTRACT

The novel coronavirus, namely SARS-CoV-2, emerged from central China in December 2019 and then spread rapidly worldwide. It has infected hundreds of thousands of people and killed several thousand thus far. The illness caused by this coronavirus is called COVID-19 and has been declared a global emergency by the World Health Organization (WHO) on January 30, 2020. Although a series of existing drugs have shown some promise in treating COVID-19, there is currently no approved medication that treat this disease. In this focus-review, we aim to summarize the available literature on the potential usefulness of existing drugs against COVID-19.

1. Introduction

Coronaviruses are a large family of viruses that cause illness ranging from the common cold to much more serious diseases such as severe acute respiratory syndrome and Middle East respiratory syndrome [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the most recently discovered member of this family which was first reported on 31 December 2019 [2]. The vision shape of this novel virus is essentially a spiky ball, with a diameter of approximately 60–140 nm [3] (Figure 1).

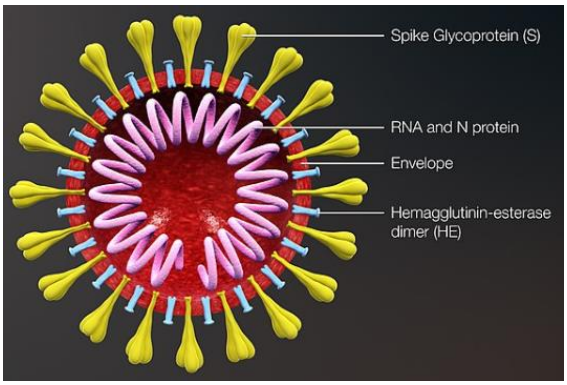

Figure 1. Structure of Coronavirus

The disease it causes is called coronavirus disease 2019 (COVID-19) and the most common symptoms of this disease are fever, cough, shortness of breath and fatigue, while other symptoms include muscle pain, sputum production, headache, loss of smell and taste, sore throat, and diarrhea [4]. The findings show that SARS-CoV-2 is not transmitted through the airways, and through major infection control measures, including wearing surgical masks, hand and environmental hygiene, hospitalization can be prevented [5]. Globally, the virus has infected hundreds of thousands of people since its emergence (Figure 2) [6]. The fatality rate for people with COVID-19 disease is between 3%-4% and by 29 March, more than 31000 people have died worldwide [7]. Unfortunately, there's currently no treatment specifically approved for COVID-19, and scientists are working to develop new and effective medicines to treat this disease. However, new interventions are likely to require months to years to develop. On the other hand, number of clinical researches are underway to repurpose existing drugs for

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this emerging virus infection, this strategy could shorten the time and reduce the cost compared to de novo drug discovery. Herein, we aim to review the recent results on the potential usefulness of existing drugs against COVID-19.

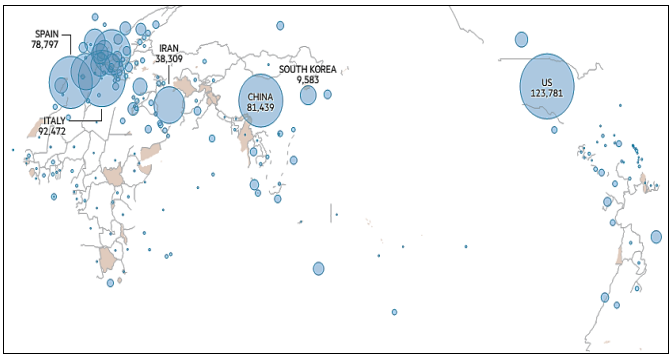
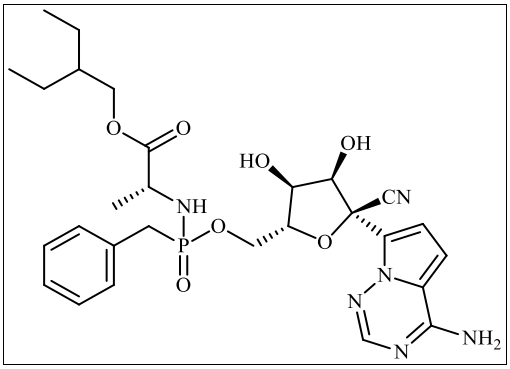


Figure 2. Mapping the coronavirus outbreak as of 29 March 2020

2. Remdesivir

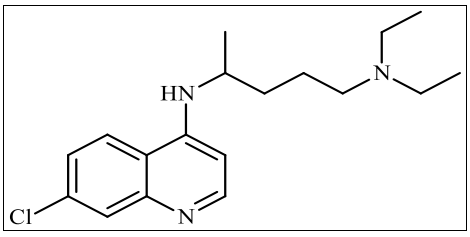
Remdesivir (Scheme 1) is a novel synthetic antiviral drug in the class of nucleotide analogs. It was developed by the pharmaceutical company Gilead as a treatment for Ebola virus disease and Marburg virus infections [8]. The drug has been recently recognized as a promising antiviral drug against a wide array of single stranded RNA viruses such as Junin virus, Lassa fever virus, Nipah virus, Hendra virus, etc. [9]. Mechanistically, it works by blocking of the RNA polymerase of the viruses and so prevents their replication [10]. In late January 2020, Wang *et al.* revealed that remdesivir is highly effective in the control of COVID-19 infection in vitro (EC_{50}= 0.77 μM in Vero E6 cells) [11]. Importantly, a US patient with confirmed SARS-CoV-2 was treated in Seattle after receiving intravenous remdesivir and appeared to respond well with no side effects [12]. Recently, Gilead began laboratory testing of remdesivir for the treatment of a small number of patients infected by the new coronavirus in collaboration with Chinese medical authorities [13].



Scheme 1. Chemical structure of remdesivir

3. Chloroquine

Chloroquine (Scheme 2) is a lysosomotropic antimalarial drug that used to prevent and treat malaria [14]. It is also used to treat infection caused by a different type of parasite (ameba) by killing the ameba [15]. Very recently, in the same paper describing the possible benefits of using remdesivir in the treatment of COVID-19 [11], Wang *et al.* reported that chloroquine could act effectively against COVID-19 in vitro (EC_{50}= 1.13 μM in Vero E6 cells). After these results, at least fifteen clinical trials had been registered in the Chinese Clinical Trial Registry to test whether COVID-19 infections could be treated with chloroquine [16]. Pleasingly, the primary results from more than 100 patients have demonstrated that this old drug is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virusnegative conversion, and shortening the disease course according to the news briefing from more than 10 hospitals in Wuhan, Jingzhou, Guangzhou, Beijing, Shanghai, Chongqing, and Ningbo. Very recently, the results of a clinical study at La Timone hospital in France on a small group of patients, also confirmed the usefulness of chloroquine in the treatment of COVID-19 [17]. Notably, on 27 March, the Italian national healthcare system announced that chloroquine and hydroxychloroquine could be used to treat all COVID-19 patients.

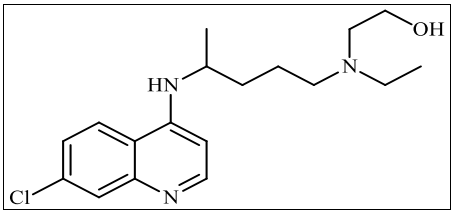


Scheme 2. Chemical structure of chloroquine

4. Hydroxychloroquine

Hydroxychloroquine (Scheme 3) with trade name Plaquenil is an antimalarial medicine marketed worldwide for the treatment of malaria in areas where malaria remains sensitive to chloroquine [18]. The drug is also recently studied as an experimental treatment for COVID-19. In vitro studies by Chinese and Iranian scientists in cell cultures demonstrated that hydroxychloroquine was more potent than chloroquine

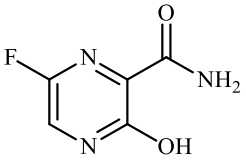
against the new virus [19, 20]. Following this results, at least 20 clinical studies were launched in China. The early results obtained from more than 100 patients indicated the superiority of chloroquine compared with hydroxychloroquine in the treatment of COVID-19 [21]. A study of 36 patients (6 patients were asymptomatic, 22 had upper and 8 had lower respiratory tract infection symptoms) in Marseille, France, showed a considerable reduction in viral load by using hydroxychloroquine in combination with azithromycin. Interestingly, at day6 post-inclusion, all of patients treated with this combination [22]. Despite this successes, more clinical data is required before the drug can be approved for use.



Scheme 3. Structure of hydroxychloroquine

5. Favipiravir

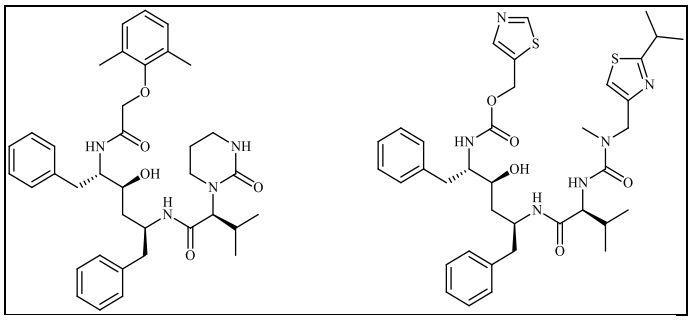
Favipiravir (Scheme 4) is an antiviral drug developed by Fujifilm Toyama Chemical in Japan with activity against many RNA viruses (e.g., alphavirus, arenavirus, bunyavirus, filovirus, flavivirus, norovirus) [23]. In 15 February 2020, it was approved for treatment of novel influenza in China [24]. Mechanistically, this drug inhibits RNA-dependent-RNA-polymerase activity of the viruses and prevents their propagation [25]. It was suggested that this novel drug may potentially have an antiviral effect on SARS-CoV-2 which is classified into the RNA viruses [26]. On the middle of February 2020, several clinical trials on favipiravir for the treatment of patients sickened by COVID-19 initiated in China and the drug has been tested in 340 individuals in Wuhan and Shenzhen [27]. Surprisingly, patients who were given the medicine in turned negative for the virus after a median of four days after becoming positive, compared with a median of 11 days for those who were not treated with the drug. The drug also seemed to shorten the duration of a patient's fever from an average of 4.2 days to 2.5 days. In addition, X-rays confirmed improvements in lung condition in about 91% of the patients who were treated with favipiravir, compared to 62% or those without the drug. The results of this investigation has yet to be published in a peer-reviewed science journal. The relatively same results were also obtained by Wang and colleagues after evaluation of the efficacy and safety of the drug in 120 patients with COVID-19 [28].



Scheme 4. Chemical structure of favipiravir.

6. Kaletra

Kaletra is a fixed dose combination of two antiviral drugs, lopinavir/ritonavir (Scheme 5), normally used for the treatment and prevention of HIV/AIDS [29]. On 17 February 2020, one small study by Korean researchers reported that Kaletra reduced viral loads and improved clinical symptoms during the treatment of a COVID-19 patient [30]. Inspired by this work, Chinese researchers tested the efficacy and safety of this drug in 99 adult patients, but found no benefit beyond standard care [31]. The authors suggested that combining kaletra with other antiviral agents might enhance antiviral effects of this drug against SARS-CoV-2. Along this line, a new trial looking at the effectiveness of kalera, as well as low dose dexamethasone, has started at the University of Oxford.



Scheme 5. Chemical structures of lopinavir (left) and ritonavir (right)

7. Tocilizumab

Tocilizumab (Figure 3) with brand name of actemra is an injectable synthetic immunosuppressive drug that binds to interleukin-6 (IL-6) in the body and blocks the effects of interleukin 6 (IL-6) in patients with rheumatoid arthritis [32]. According to research published on 19 March 2020 in European Radiology, the patients with COVID-19 tend to have high levels of C-reactive protein (CRP) and IL-6 [33]. Therefore, it is likely that IL-6 or IL-6 receptor blocking antibodies used in cancer treatment (e.g., tocilizumab, sarilumab, and siltuximab) be useful in treating this disease. In this context, the FDA has just approved a randomized, double-blind, placebo-controlled phase III clinical trial

to evaluate the safety and efficacy of intravenous (IV) tocilizumab for COVID-19 pneumonia [34].

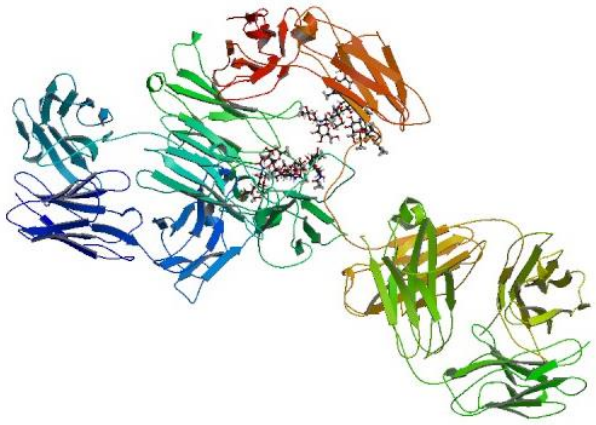


Figure 3. Structure of tocilizumab.

8. SNG001

Interferon beta 1-alpha (IFN-beta-1a) with trade name of Rebif (Figure 4) is a cytokine in the interferon family which produced by mammalian cells (Chinese hamster ovary cells) and used to treat multiple sclerosis (an autoimmune diseases) in adults [35]. SNG001 is a formulation of rebif for direct delivery to the lungs *via* nebulization and could increase the production of IFN-beta (a naturally occurring protein, which orchestrates the body's antiviral responses) [36]. Two Phase II clinical trials in asthma showed that inhaled SNG001 treatment activated antiviral pathways in the lung along with improving lung function in patients with a respiratory viral infection. In the UK, pharmaceutical company Synairgen had begun a trial in over two hundred COVID-19 patients using SNG001 [37]. A successful outcome from this trial would be a major breakthrough in the fight against this novel virus. Of note, FDA has also launched a clinical trial to test rebif as COIVD-19 therapy [38].

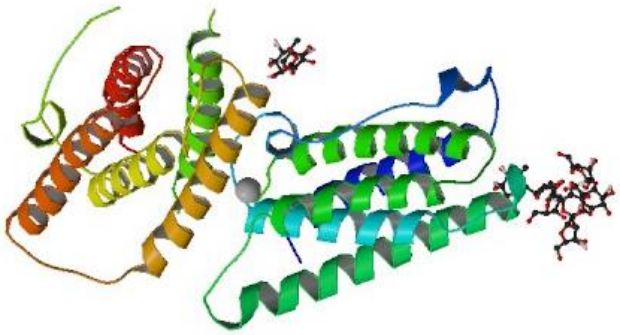


Figure 4. Structure of Rebif

9. Blood pressure drugs

Without doubt, angiotensin-converting enzyme 2 (ACE2) is a functional receptor for the coronavirus [39]. Therefore, it is possible that angiotensin II receptor blockers (such as common drugs for hypertension) block the SARS-CoV-2 spike protein (receptor) and prevent the virus from infecting cells [40-42] (Figure 5). Currently, there is limited evidence on the safety or efficacy of this class of drugs in clinical treatment of COVID-19 and further studies should be performed.

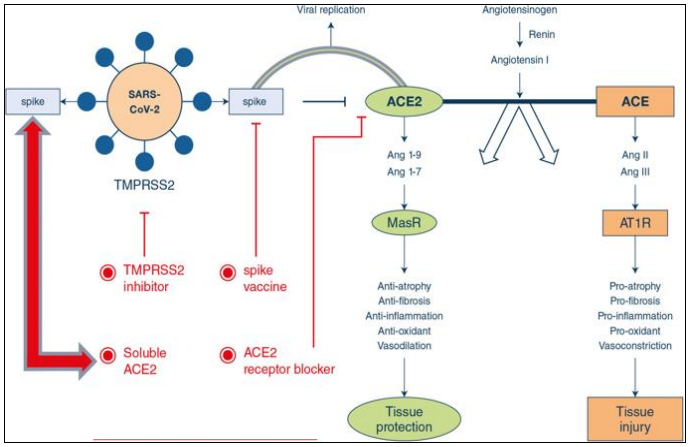


Figure 5. Therapeutic approaches *via* angiotensin II receptor blockers

10. Carbon quantum dots (CQDs)

Carbon quantum dots (CQDs) are important options for interacting with viruses and preventing them from entering cells. Recently, a team of researchers from the University of Lille, France, and Ruhr-University Bochum, Germany, showed that the functionalized CQDs with boronic acid ligands, interfered with the function of coronavirus's S protein and significantly inhibited its entry into the host cells. Their studies demonstrated that the addition of these nanomaterials to the cell culture medium, before and during infection with coronavirus, considerably reduced the infection rate of the cells (Figure 6). Surprisingly, after one viral life cycle – which is 5.5 hours for coronavirus – a great inhibition activity was also observed at the viral replication step [43].

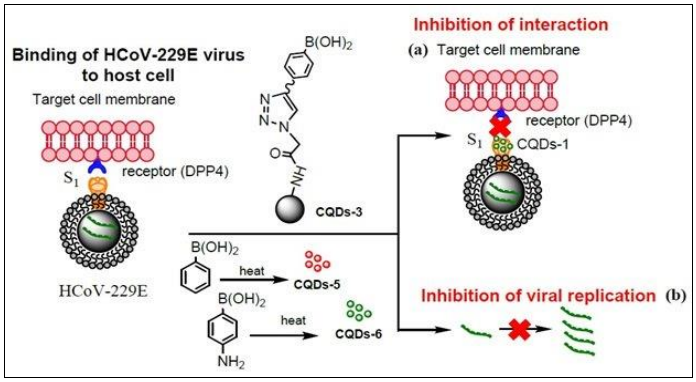


Figure 6. Interacting of carbon quantum dots (CQDs) with viruses

11. Human Recombinant Soluble ACE2 (hrsACE2)

What protects the lungs from SARS-CoV-2 injury, is an enzyme called ACE2 (Angiotensin converting enzyme 2), which also explains the severe lung failure and death from it. ACE2 has been known as a basic receptor for SARS-CoV-2 infections and it has been suggested that inhibition of this interaction may be utilized in the treatment of patients with COVID-19. Human recombinant soluble ACE2 (hrsACE2) blocks significantly the early stages and the growth of SARS-CoV-2 infections [44].

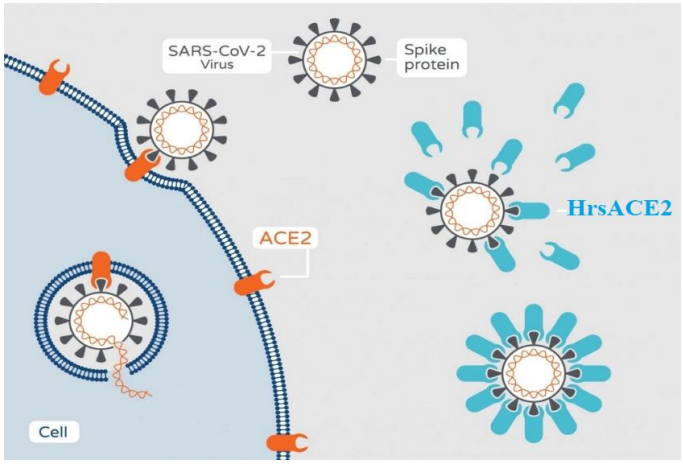


Figure 7. HrsACE2 protects cells against SARS-CoV-2 Virus

12. Conclusion

The current pneumonia outbreak caused by a new coronavirus, has evolved into a global health emergency declared by the WHO. Unfortunately, there is no confirmed effective medicine to treat the disease caused by this virus to date and there is a desperate need for new or redeveloped medicines to treat COVID-19. Currently many research teams are working worldwide to either develop a new drug or repurpose an existing medication for the treatment of this disease. As showed in this review, a variety of existing drugs are being tested whether they can be repurposed as a possible treatment for COVID-19. However, there is still limited evidence on the safety or efficacy of the drug candidates in clinical treatment of COVID-19 and further studies should be performed.

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