Different methods in COVID-19 treatments

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Abstract. COVID-19 is a global pandemic starting from China in late 2019 and spread over the world dramatically rapid. A lot of methods were tried by experts to find treatments of COVID-19. Compared with COVID-19, not only the death rate but also spread rate is lower, as well as its existing time. It is also possible that transmitted the virus through eyes, noses and ears. Vaccination has been used as precaution treatment. And some small molecules are used to treat patients who have positive results in severe situation. Adults and pediatric patients who infect COVID-19 pandemic in mild to moderate situation, can use small molecule treatments in emergency only. However, vaccination is unable to protect people 100% and small molecules, such as paxlovid, have not been approved, but have been authorized for emergency use by Food and Drug Administration (FDA). This review focused on methods and mechanism of different treatments of COVID-19.

Keywords: Clinical, Covid-19, Treatment.

1. Introduction

The COVID-19 pandemic is caused by the coronavirus SARS-CoV-2 [1]. It's originated from a "wet market" in Hubei, Wuhan, China, which sells live animals for eating. In the beginning, the virus mutated from a coronavirus common in animals and jumped over to humans causing infected person cough and sneeze. Followed by transmission among humans through expelled droplets. There are 8,098 Severe Acute Respiratory Syndrome (SARS) cases with 10% death rate showed on WHO in 2003, which influenced Asia in the largest scale [2].

Compared with COVID-19, not only the death rate but also spread rate is lower, as well as its existing time. Middle East respiratory syndrome (MERS) pandemic, which happens in 2012, is the second widely spread coronavirus occurring in the 21st century. The interval between all three viruses decreased from 9 years to around 7 years, and on the other hand, the duration of each pandemic was prolonged. Generally, all those diseases were caused by coronavirus that belong to Coronaviridae family [3].

As the spike glycoprotein (S) of COVID-19 virus and SARS virus, which mainly affect the diseases, share some similarities, the COVID-19 virus is highly related with SARS virus in 2003.

The Covid-19 is transmitted by contaminated air and has higher risk of indoor condition even with long distance. It is also possible that transmitted the virus through eyes, noses and ears. People without any symptoms can also transmit virus through air [4]. Generally, prevent spreading, washing hands thoroughly for a minimum of 20 seconds with soap and hot water regularly, avoiding gathering with people in a less ventilated place, wearing masks when outside home.

Vaccination, the precaution method, is the best way to get the immune system which allows the body's defense against infection. The development of a new vaccine is a time-consuming, costly and complicated process. Adults and pediatric patients who infect COVID-19 pandemic in mild to moderate situation, can use small molecule treatments in emergency only.

However, vaccination is unable to protect people 100% and small molecules, such as paxlovid, have not been approved, but have been authorized for emergency use by Food and Drug Administration (FDA) under Emergency Use Authorization (EUA). The major challenges are for clinicians because of the presence of transmission risk between intravenous (IV) and oral drugs.

This review focused on different treatments of COVID-19. In comparison with the SARS-CoV, the SARS-Cov-2 genome presents a high sequence identity (96%) [5].

2. Vaccination

Covid-19 are mRNA virus, all mRNA virus will evolve and change gradually. The mutation of this kind of virus is expected. The most well-known variant is Omicron. This variant is highly contagious and easily spread from person to person. It contributes the largest increase number of infection population in 2020 typically in some counties without critical social distance control. What is more, Omicron is able to be controlled by 3 doses of mRNA vaccines, so government highly recommend to take the dose of vaccines to reduce the 90% risk of infection of Covid-19 [6].

Vaccination is mature developed and widely used precaution treatment for COVID-19. Different types of Vaccines are shown in table 1. Recommend to take the dose of vaccines to reduce the 90% risk of infection of Covid-191.

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Table 1. The different examples of vaccines used to treat COVID-19.

Name	Doses	Types of Vaccine	How it works
Pfizer-BioNTech	2	mRNA	mRNA spike protein (S) on the surface of virus break down mRNA and remove it; immune system regcognize S produce antibodies; able to protect against future infection from the virus
Moderna	2	mRNA	
Johnson & Johnson's Jassen	1	Viral Vector	vetor virus spike protein (S) on the surface of virus; immune system regcognize S produce antibodies; able to protect against future infection from the virus

Both moderna vaccine and Pfizer-BioNTech vaccine are mRNA vaccine, which containing the material of virus to give instructions to cell to make unique protein. The genetic material of virus will be destroyed. After human cell have copies of the unique protein, the vaccine can prevent human body from virus in some extent.

Viral Vector is another potential target, which Johnson & Johnson's Jassen vaccine focused on. Cells are guided to make and copy a unique protein to break the progress of virus. These vaccines may cause the same but mild symptoms of Covid-19 and allergy [7].

3. Small Molecules as Anti-Viral Drugs

Small molecules, which have low molecular weight, are able to inhibit viral protein or enzyme. Large molecules that are used in drug therapy, like biologics, are natural products derivatives used to deal with diseases [8].

Compared with large molecules anti-viral therapy, small molecules anti-viral therapy has many advantages. Small molecules have a low production cost and are easily manufactured, but large molecules need more expensive methods of production, and most of them are difficult, time-consuming to collect.

The oral bioavailability of small molecules are relatively better than that of large molecules as large molecules are focused on proteolytic degradation by injection instead. The diffusion abilities of the two ways of therapies are also different, small molecules can diffuse easily, which allows small molecules to access intracellular targets, which large molecules are unable to access. Small molecules will not respond to immune system, but large molecules influence on immunogenicity by modifying antibodies to reduce large molecules' half-life. Small molecules are able to test on rodents as the species independence, however, as large molecules are species-specific, the toxicity studies of large molecules related to humans by primates.

Generally, small molecules are easier to be manufactured with large amounts of trials. The potency of small molecules is easier to be enhanced by strengthen the enzyme-molecule interaction. Not only small molecules but also vaccine antigens is commonly used in early global pandemic treatment research stages. Currently vaccines for COVID-19 pandemics are relatively mature, but finely developed small molecules are able to achieve a better potency to promote the efficiency with a lot of trials and even future preclinical and clinical trials during drug development stages.

RNA polymerase (RNAP or RNApol), is an enzyme that synthesizes RNA that is either for protein-coding or non-coding from a DNA template. RNAP opens the double-stranded DNA by using the enzyme helicase, so one strand of the exposed nucleotides is able to be used as RNA synthesis template, where the process is known as transcription. The factor and mediator complex of transcription should be attached to the promotor region before RNAP can initiate the DNA unwinding at that position [9].

4. SARS-CoV-2

The coronavirus SARS-CoV-2 arouses COVID-19 pandemic, which is highly related with SARS virus [10,11]. Not only the main protease (Mpro, also known as 3C-like protease (3CLpro)), but also the papain-like protease (PLpro), which allows a functional replicated complex and enable virus transmission, are vital in the viral proteases' activities [12].

The polyprotein cleavage sites modified by a cysteine protease, which is the main protease of SARS-CoV-2, to obtain functional proteins that essential for viral replication as shown in Fig. 1.

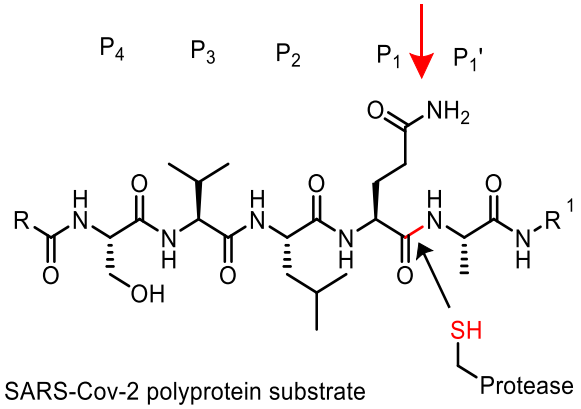


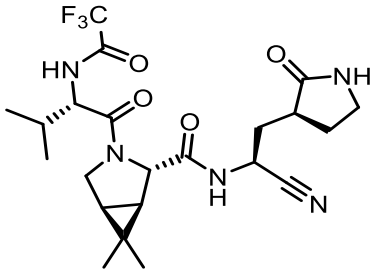
Fig. 1 Catalytic cleavage of cysteine protease in polyprotein substrate

The design challenges for converting intravenous (IV) to oral include that the peptidomimetics are a tough challenge for oral drug space, and where the AV requires EC90, uCmin and an associated therapeutic index. Considering oral bioavailability for SARS-CoV-1, there are 5 H-bond donors for PF-835231, which means <0.5% oral bioavailability.

The challenge for the oral drug is the permeability, metabolic stability and anti-viral activity. Remaining other parts of the chemotepy as a control factor, modifing the cysteine trap with different functional groups attached to see how the physicochemical propertie will be affected.

Both PF-7321332 (as shown in Fig.2) and Ritonavir are small molecules discovered by Pfizer to be used as treatment of COVID-19. PF-7321332 is the first oral small molecules as antiviral Mpro inhibitor to treat COVID-19 together with Ritonavir to maintain the function of PF-7321332 in metabolism.

The selective inhibitor, PF-07321332, of the SARS-CoV-2 protease does work for COVID-19 together with Ritonavir to extend the strength of maintaining this inhibitor in body [13].



H Bonds	3
Enz IC_{50}	19nM
Cell EC_{50}	74nM
HLM	22 ul/min/mg
RPCK	1.7 P_{app} AB (10^{-6} cm/sec)
LogD	1.7
Rat F_{oral}	30-50%
MWt	499

Fig. 2 PF-7321332: Oral SARS-CoV-2 Mpro Inhibitor Candidate

5. Limitation and future development

Vaccine treatment and small molecule treatment are focused on different treatment groups, where vaccine aims to protect no symptom public away from infected, and small molecule aims to treat mild-to-moderate infected patients.

To inject a vaccine, a specialized person required and generally, injected people feel uncomfortable in the following days, but having a small molecule is relatively easy. Although small molecule is unable to prevent COVID-19, it provides an opportunity to cure infected people instead of using placebo.

Table 2. The advantages and disadvantages of different treatments.

Treatment	Advantage	Disadvantage	Treatment groups
Vaccine	Gain protection without ever having to risk the potentially serious consequences of getting sick	Specialized person required for doing injection; Discomfort experienced after getting the vaccine	No symptom public
Small molecule	Easy to obtain; No specialized person required; Oral	Unable to prevent getting COVID-19	Mild-to-moderate patients

For further drug discovery, more small molecules are able to be discovered in the aim of prevent COVID-19.

6. Conclusion

COVID-19 is a global pandemic with a high spreading speed, the main protease of COVID-19 is cysteine catalytic proteases. The Covid-19 is transmitted by contaminated air and has higher risk of indoor condition even with long distance. The transmitted methods of COVID-19 are various. Vaccination and small molecules are two main ways to treat COVID-19 with different target groups in different target responses. The major challenges are for clinicians because of the presence of transmission risk between intravenous (IV) and oral drugs. For small molecule like Paxlovid is still not approved but only in emergency use under personal doctor's suggestion, more experiments should

be undertaken to continue further analysis with more clinical practices to complete the development phases of new drug discovery. Although still many challenges included to find a better treatment way, new drugs should be discovered in future.

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