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Short Review

COVID-19: Immune System and Chemotherapeutic Agents

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A B S T R A C T

Pandemic is the worst-case scenario in the realm of infectious disease. It has been part of human life since the beginning of human colonization on earth. It becomes worse and spreads more easily as human social interaction increases drastically in this modern time. COVID-19 is the newest and latest pandemic that has affected millions of people all over the world. More than one million people have died due to this disease. Meanwhile, an effective and robust chemotherapeutic agent against COVID-19 has yet to be found. Similarly, an effective vaccine has not been produced and implemented yet. It is most likely that the effective therapeutic agents and the vaccines will be available by the end of 2020 or around the first quarter of year 2021. This article discusses the structures, transmission pathways, and types of infections caused by SARS-CoV-2, the causative agent of COVID-19 disease. It also discusses the availability of therapeutic agents and vaccines for COVID-19.

Keywords: Pandemic, COVID-19, Chemotherapeutic agent, Vaccine

1. Introduction

Communicable diseases have existed since human colonization on earth. They existed during the hunter-gatherer times and became more prevalent when society shifted into agrarian life. It is even becoming more serious in the millennial time due to the increase of human population and interactions. Malaria, leprosy, smallpox, and tuberculosis appeared during the agrarian life about 10,000 years ago. As the population started to move from one place to another due to war and other events, new pandemics were becoming widely distributed in the middle-age. The earliest pandemic recorded was in 430 BC in Athens during the Peloponnesian War. The outbreak was believed to be transmitted from Ethiopia, Libya, and Egypt. It was suspected that it was Typhoid fever, which killed more than two-third of Athens's population. As human interactions become more intensive over time, the pandemics also spread more, and accordingly taking more victims around the world. The most notorious pandemic known in human civilization was the black death or bubonic plague, which spread for more than 1,000 years and killed millions of victims (Editors, 2020). Fortunately, with the advancement of science and medicine, most of the pandemics have been controlled and eradicated.

In this modern era, communicable diseases are becoming easier to spread among global population as people now can travel more easily among countries and places. As a result, global outbreaks and pandemics are more prevalent. The outbreak of the novel coronavirus disease, COVID-19, represents a pandemic threat to global public health nowadays. This outbreak is caused by the new coronavirus 2019-nCoV that is now officially designated as severe acute respiratory syndrome-related coronavirus SARS-CoV-2 (Gorbalenya, 2020; Kupferschmidt and Cohen, 2020).

2. SARS-CoV-2 structure, transmissions, and infections

Coronaviruses (CoVs) are relatively large viruses that contains single-stranded positive-sense RNA genome protected and strengthened by nucleocapsid protein and encapsulated within a membrane envelope. The viral envelope is studded with glycoprotein spikes that give coronaviruses their crown-like appearance (Figure 1). Coronavirus carries a single-stranded positive sense RNA that has three functions during its life cycle. First, it functions as the initial RNA of the infectious cycle, second

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as a template for replication and transcription, and third, as a substrate for packaging into the progeny virus (Lim, et al., 2020). Coronavirus spike proteins attach to special receptor proteins ACE2 of the target cells. Most of cells that carry ACE2 receptors are located on the lining of respiratory tract and digestive tract, making these two systema as the primary sites for coronaviruses infections (Nguyen, et al., 2020; Smith, 2020).

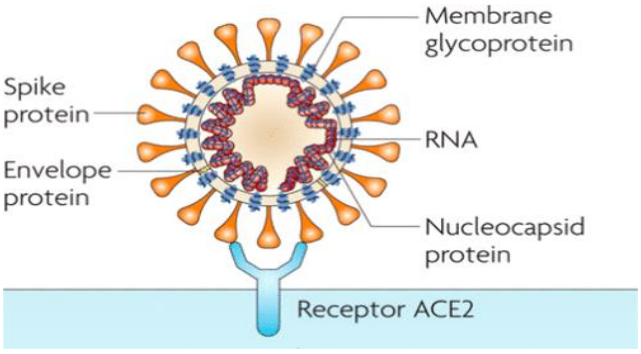

Figure 1. Structure of a corona virus and target cell receptor ACE2 (Nguyen, et. al., 2020).

Coronaviruses infect both humans and animals. Many animals are known to be reservoir for the coronaviruses such as palm civets, bats, rhesus macaque, dogs, racoon dogs, red foxes, Chinese ferret-badgers, cats, and others. Certain types of animals such as bats that host the largest variety of coronaviruses appear to be immune to coronavirus-induced illnesses (Shi, Z. and Hu Z., 2008).

Coronaviruses can be designated into four classes including alpha, beta, gamma, and delta. The causative agent of COVID-19, the SARS-CoV-2, is a beta type coronavirus. Included in the class of beta coronavirus are severe acute respiratory syndrome (SARS) virus (SARS-CoV), Middle East respiratory syndrome (MERS) virus (MERS-CoV), and SARS-CoV-2. Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 attacks the lower respiratory system that cause viral pneumonia. It may also affect the gastrointestinal system, heart, kidney, liver, and central nervous system leading to multiple organ failure. (Chauhan, et.al. 2020; Saar, et. al, 2020; Petrosillo, et. al., 2020). Current scientific information indicates that SARS-CoV-2 is more contagious than SARS-CoV (Petrosillo, et. al., 2020; Kumar, et. al., 2020). The World Health Organization (WHO) estimated the reproductive number (R_0) for SARS-CoV-2 is between 2–2.5. This range is higher than the R_0 for SARS-CoV, which is between 1.7–1.9 and MERS-CoV, which is below 1 (Petrosillo, et. al., 2020). These numbers explain why MERS-CoV infections were limitedly spread in the Middle East area, while SARS-CoV-2 are spreading all over the world.

Genomic analysis evidence suggests that SARS-CoV-2 infects the host tissue by binding to ACE2 receptors (Wan, et. al., 2020). After binding to the receptors, the viral genome enters the host cell and exploits the host cell machinery to enable their own replication, which allows it to spread. The process involves a cycle of infection starting from attachment, entry into the host cell, uncoating of genome, synthesis, which includes viral RNA replication and viral protein synthesis, assembly, and release from the host cell to start a new cycle on the other host's cells (Lim, et. al., 2016; Chess, 2021). There are varieties of clinical signs and symptoms caused by SARS-CoV-2 infection. Table 1 shows some clinical characteristics of SARS-CoV-2 infection and the number of cases (%) found in each clinical analysis.

Table 1. Clinical characteristics of COVID-19 (Petrosillo, et. al., 2020)

Characteristics	% of case
Signs and symptoms	
Fever	*81 – 91*
Cough	*48 – 68*
Dyspnoea	*19 – 31*
Sore throat	*29*
Dizziness and confusion	*22*
Diarrhoea	*16*
Nausea and vomiting	*6*
Laboratory findings	
Leukopenia	*35*
Lymphopenia	*35 – 72*
Thrombocytopenia	*12*
Elevated aminotransferases	*28 – 35*
Radiological chest findings on admission	
Unilateral infiltrate	*10*
Bilateral infiltrate	*84 – 90*
No findings	*14*
Complications	
Intensive care unit admission	*24*
Acute respiratory distress syndrome	*18 – 30*
Acute kidney injury	*3*
Death in hospitalized patients	*10 – 11*

3. Therapeutic agents and vaccines against COVID-19

Development of therapeutic agents against COVID-19 is mainly based on the structure and the life cycle of coronavirus in the host cells. The main primary targets for the agents are mostly the viral proteins, the viral genome, and the receptors on the host's cell membrane. The viral proteins targets include spike glycoprotein, viral membrane proteins, and the viral capsid (Liu, et. al., 2020). Table 2 shows the main target for therapeutic agents and their roles during viral infection.

There have been hundreds of drug candidates available and suggested to be effective against COVID-19 (Table 3). Based on the data, the *3CLpro, RdRp, S-protein*, and *ACE2* receptor are the target proteins that have been chosen as the most favorite targets for the developing therapeutic agents. Many of these drugs are available and have been used for other diseases caused by other types of viruses or

microorganisms. Most of them are still required to have more rigorous clinical tests specifically for COVID-19. Currently, some of them are being studied in the last stage of clinical trials (Liu, et. al., 2020).

Table 2. Target candidates for therapeutic agent development and their roles during coronavirus infection (Liu, et. al., 2020).

Target	Roles during viral infection
3CLpro	A protease for the proteolysis of viral proteins
PLpro	A protease for the proteolysis of viral proteins
RdRp	An RNA-dependent RNA polymerase
S protein	A viral surface protein for binding to host cell
TMPRSS2	A host-cell protease that prime the S protein
ACE2	A viral receptor protein on the host cell
AT2	A viral receptor protein on the host cell

Table 3. Existing drugs with therapeutic potentials for COVID-19 (Liu, et. al., 2020).

Drug candidate	Target
Baricitinib	*JAK-kinase*
Lopinavir	*Viral proteases: 3CLpro / PLpro*
Ritonavir	
Darunavir	
Favipiravir	*RdRp*
Remdesivir	
Ribavirin	
Galidesivir	
BCX-4430	
Arbidol	*S-protein / ACE2*
Chloroquine	*Endosome / ACE2*
Nitazoxanide	

Like COVID-19 therapeutic agents, COVID-19 vaccines have been developed in a fast mode. Scientists are racing to produce safe and effective COVID-19 vaccines by next year (Corum, et. al., 2020). Usually it takes several years to have a vaccine available for full use. The process starts with pre-clinical trial, phase I clinical trial, phase II clinical trial, phase III clinical trial, patent and approval, and finally production. Several countries such as the USA, China, Russia, Germany, and others compete to develop and produce COVID-19 vaccine as soon as possible (Gallagher, 2020). There have been several COVID-19 vaccines developed (Table 4). Many of them have passed phase III clinical trial and are being used in limited areas.

Vaccines are known to cause productions of specific antibodies in host tissues. The increase production of these antibodies will cause the individual to be immune to the original SARS-CoV-2 virus, the causing agent of COVID-19 disease. There are several ways to create a vaccine for specific disease. The most common methods are genetic vaccine, viral vector vaccine, protein-based vaccine, inactive or attenuated virus vaccine, and repurposed vaccine (Corum, 2020).

Table 4. Several vaccine candidates for COVID-19 and their development phases (Corum, et. al., 2020).

Vaccine candidate [1)]	Development phase	Country
Sinovac	Approved for limited use	China
Cansino	Approved for limited use	China
Sputnik V	Approved for limited use	Russia
Sinopharm	Approved for limited use	UAE
EpiVacCrona	Approved for limited use	Russia
Moderna	Phase III	USA
Covaxin	Phase III	India
Johnson&Johnson	Phase III	Israel
Novavax	Phase III	USA
BRACE	Phase III	Australia
Pfizer/BiNTech	Combined phase II/III	USA
Astra-Zenca	Combined phase II/III	UK
Zydus	Phase II	India
CureVac	Phase II	Germany/USA
Zhifei Bio	Phase II	China
Inst. of MedBio	Phase II	China
Imperial college	Combined phase I/II	UK
Anges	Combined phase I/II	Japan
Arcturus	Combined phase I/II	USA
Soberana 1	Combined phase I/II	Cuba
Sanofi-gsk	Combined phase I/II	French
SpyBiotech	Combined phase I/II	UK
Chumakov	Combined phase I/II	Russia
Genexine	Phase I	Korea
ArCov	Phase I	China
Chula VRC	Phase I	Thailand
Entos Pharm	Phase I	Canada
Symvivo	Phase I	Canada
GRAd-COV2	Phase I	Italy
Vaxart	Phase I	USA
Merck	Phase I	USA
Wantai nasal spray	Phase I	China
MVA	Phase I	Germany
Merck-2	Phase I	USA
ImmunityBio	Phase I	USA
Brilife	Phase I	Israel
Clover-gsk-Dynavax	Phase I	USA
UofQ-CSL	Phase I	Australia
Medicago	Phase I	Canada
Vaxine	Phase I	Australia
Ky-BioProcessing	Phase I	USA
Medigen	Phase I	China
Adimmune	Phase I	China
Covaxx	Phase I	China
UofTubingen	Phase I	Germany
Sovereign 2	Phase I	Cuba
QazCovid	Phase I	Kazakhtan
Shenzen Kangtai	Phase I	China
Sanofi	Preclinical	French
Novartis	Preclinical	Swiss
PittCoVac	Preclinical	USA

[1)] Name of vaccine or name of developer/producer

In addition to drugs and vaccines, scientists are developing therapeutic antibodies and RNA therapies (Table

5). Therapeutic antibodies are mostly developed from human body proteins such as cytokines, chemokines, interferons (IFNs), interleukins (IL), and lymphokines. The RNA therapies are mostly developed by using RNA interference (RNAi). The RNAi is known to interfere to a specific mRNA, such as SARS-Cov-2 mRNA. The interference will inhibit gene expression and genetic translation of the target mRNA (Liu, C., et. al., 2020). A new generation of therapeutic antibody is monoclonal antibody cocktail that combine several antibody proteins in the solution. This type of therapeutic antibody was used to treat the President of the United States during the infection of COVID-19 on October 2nd (Herper, 2020; PRNewswire, 2020).

Table 5. Candidates of therapeutic antibodies and RNA therapies for COVID-19 (Liu, et. al., 2020).

Candidates	Types
Renegeron	Monoclonal antibody cocktail
LY-CoV555	Monoclonal antibody cocktail
rSIFN-co	Cytokine/Interferon
IFN-w(rhIFN-w)	Cytokine/Interferon
HAS-IFN fusion	Human-albumin-serum/Interferon
siRNAs (28 patents)	RNA therapies

4. Conclusions

For years coronaviruses (CoVs) have been identified as mild respiratory pathogens, especially in human. However, the emergence of SARS-CoV, MERS-CoV, and SARS-CoV-2 has changed the attitude of people toward the CoVs. With its fatality rate of about 3%, infection rate (R_0) of above 2.0, and widespread impact in the world, SARS-CoV-2 has become the center of research development. Most research has focused on the development and production of therapeutic agents and vaccines for COVID-19, the newest pandemic caused by SARS-CoV-2.

There have been hundreds of therapeutic agents developed, tested, and used in limited areas to treat COVID-19. Hence, no single therapeutic agent has been truly identified as the best miracle drug for the disease. Meanwhile, the development of COVID-19 vaccines has been relatively faster than those of other regular diseases. It is hoped that both therapeutic agents and vaccines for COVID-19 will be available very soon by the end of 2020 or by the first quarter of 2021.

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