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Review Article

Therapeutic Strategies in the Fight against COVID-19: From Bench to Bedside

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Abstract

In December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China. This virus rapidly spread worldwide and was declared a global pandemic by the World Health Organization (WHO) in March 2020. High incidence, long incubation period, and diverse clinical signs of the disease posed a huge challenge globally. The efforts of health systems have been focused on repurposing existing drugs or developing innovative therapies to reduce the morbidity and mortality associated with SARS-CoV-2. In addition, most of the large pharmaceutical companies are intensely working on vaccine development to swiftly deliver safe and effective vaccines to prevent further spread of the virus. In this review, we will discuss the latest data on therapeutic strategies undergoing clinical trials. Additionally, we will provide a summary of vaccines currently under development.

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What's Known

- The coronavirus disease 2019 (COVID-19) is a complex and challenging disease with an enormous impact on global health.
- Proposed therapeutic strategies have been based on the inhibition of virus replication and tissue damage associated with hyperactivation of the immune system.

What's New

- Remdesivir is the only medication approved by the American food and drug administration (FDA) for severe cases of COVID-19 patients. A combination of immunomodulators and remdesivir is recommended. Other therapeutic agents can be utilized only in clinical trials.
- The most successful vaccines are based on adenoviral vectors and mRNA technology.

Introduction

In December 2019, a cluster of patients with pneumonia emerged in Wuhan (China) as a result of the novel coronavirus (2019-nCoV).[1] The reported cases were identified in Wuhan's seafood market.[2] The virus is officially known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19). According to the report by the National Health Commission of China, the virus can transmit from human to human, chiefly via respiratory particles.[3] Soon after, the disease rapidly spread to other countries to such an extent that in January 2020, the World Health Organization (WHO) declared it the sixth public health emergency of international concern, and in March 2020 as a global pandemic.[4]

Common symptoms of COVID-19 are fever and dry cough. Epidemiological studies have indicated that people with comorbidities and the elderly are more vulnerable to the disease.[2] SARS-CoV-2 belongs to the beta coronavirus of group 2B and causes the disease by infecting host cells through angiotensin-converting enzyme 2 (ACE2) receptors.[1, 5] This virus is a member of the same family as the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), which have caused outbreaks of epidemic proportions in the past two decades.[2, 5] Currently, most of the treatments are based on repurposing existing drugs and supportive therapy. The most

important pathophysiological processes of COVID-19 include high virus load, hyper-inflammation, and tissue damage.[6] To date, multiple therapeutic strategies have been planned based on inhibiting at least one of these mechanisms.

Due to the importance of preventing the spread of the virus, many pharmaceutical companies have put all their efforts into developing novel COVID-19 vaccines with high safety and efficacy. The present review provides the latest achievements in therapeutic strategies such as pharmacotherapy, cell therapy, and convalescent plasma therapy. Finally, candidate vaccines in development are summarized.

Pathogenesis of COVID-19

The SARS-CoV-2 virus infects the lower respiratory tract and causes pneumonia. However, clinical signs and mortality rates are lower than with MERS and SARS. SARS-CoV-2 infection is divided into three phases, namely (i) asymptomatic state, (ii) upper airway and conducting airway response, and (iii) hypoxia, ground-glass infiltrates, and progression to acute respiratory distress syndrome (ARDS).[4, 7]

Phase I: Asymptomatic State (Initial 1-2 Days of Infection)

Infected host cells are mediated by the interaction between the spike (S) protein of the virus and ACE2, the primary receptor for SARS-CoV-2 located in the lungs. *In vitro* studies on SARS-CoV have indicated that the ciliated cells are the primary target cells in the conducting airways. Due to the limited spread of the virus, the immune response is weak in this phase. Although the viral load is low in this stage, people are infected, and the virus can already be detected using polymerase chain reaction (PCR). Samples are taken using the throat or nasal swabs; however, nasal swabs might be more sensitive than throat swabs.[8]

Phase II: Upper Airway and Conducting Airway Response (Next Few Days)

The virus spreads to the lower respiratory tract and triggers a robust immune response. Infected cells secrete interferon and the levels of some cytokines, such as C-X-C motif ligand 10 (CXCL10), increase. CXCL10 has also been reported to be useful as a disease marker in SARS. The disease is mild in this phase and is limited to the airways. Patients are monitored and treated at home.[8]

Phase III: Hypoxia, Ground-glass Infiltrates, and Progression to ARDS

In this phase, the virus reaches the respiratory exchange units of the lung and infects type II pneumocytes. About 20% of the infected people enter this phase and can become seriously ill. Virus involvement in host cells leads to cell death and tissue damage. In addition, lymphopenia occurs at this stage due to the infection of T cells and macrophages by the virus.[4] In severe cases with high viral load, patients develop ARDS.[4, 8] The main reason for ARDS is the cytokine storm, an uncontrolled release of pro-inflammatory cytokines (particularly interleukin (IL)-16), which leads to tissue damage and organ failure.[9] Immunopathogenesis of coronavirus is depicted in figure 1.[10]

Therapeutic Strategies for COVID-19
Pharmacotherapy

In terms of disease pathogenesis, different therapeutic agents have been suggested based on targeting viral replication and tissue damage associated with cytokine storms. The spectrum of therapeutics for COVID-19 is evolving rapidly. Most of the efforts have focused on repurposing the existing drugs to reduce the morbidity and mortality associated with virus complications. In the following section, we summarize the current evidence for pharmacotherapy in patients with confirmed COVID-19.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine are being used worldwide for about 70 years, and are part of the WHO Model List of Essential Medicines. They have a long-standing history in the prevention and treatment of malaria and the treatment of chronic inflammatory diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[11, 12] These drugs can exert antiviral effects by different mechanisms. Since they are weak base therapeutic agents, they can, for example, increase endosomal pH in host intracellular organelles, resulting in inhibition of autophagosome-lysosome fusion and inactivation of enzymes required for replication.[13] Additionally, they can affect the glycosylation of ACE2.[14] Different doses of both drugs have been suggested to treat patients with confirmed COVID-19. However, the latest report from Tang and colleagues showed no beneficial effects in COVID-19 patients.[15] Moreover, a meta-analysis reported that hydroxychloroquine is associated with increased mortality in COVID-19 patients, and chloroquine had no beneficial effects.[16]

Ribavirin

Ribavirin is a guanine analog that inhibits viral RNA-dependent RNA polymerase (RdRp)

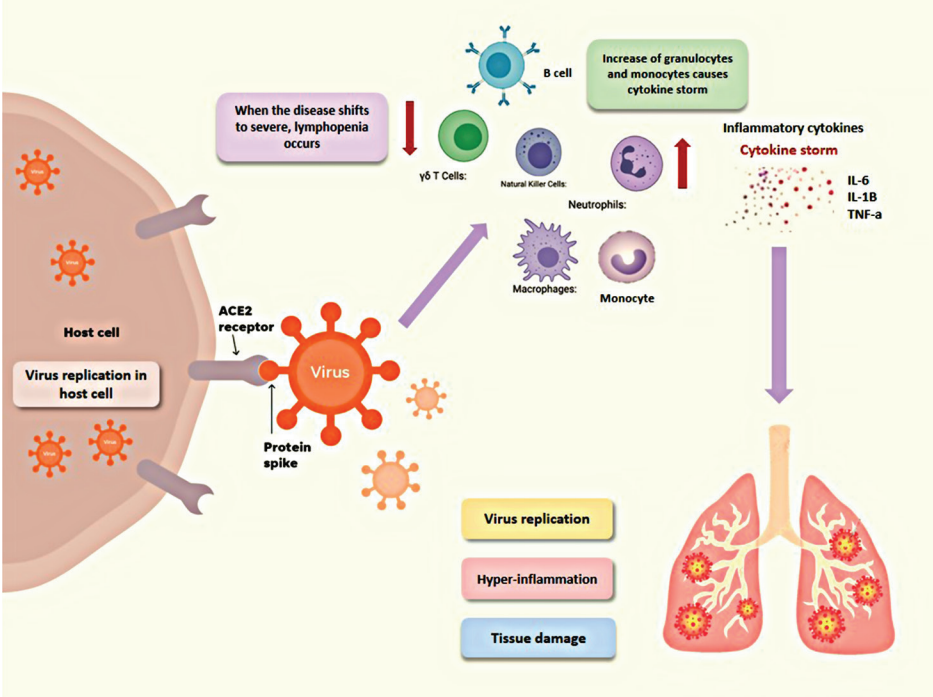

Figure 1: The immunopathogenesis of coronavirus is illustrated. Coronavirus infects host cells through binding to angiotensin-converting enzyme 2 receptor (ACE2). Virus replication in host cells leads to cell death and tissue damage. In addition, coronavirus induces the innate and adaptive immune response. Over time, the infection disturbs adaptive and innate immune responses. It eventually causes lymphopenia and hyper-inflammation. Hyper-activation of immune cells, predominantly neutrophils, and considerable release of IL-6, TNF-α, and IL-1β lead to cytokine storm syndrome resulting in tissue damage.

activity. Ribavirin has previously been used to treat patients with SARS and MERS. In MERS, ribavirin (generally combined with interferons) demonstrated no tangible effect on clinical outcomes or viral clearance.[17] Ribavirin was also used to treat SARS (in combination with other drugs such as corticosteroids), and no conclusive results were obtained.[18] Recent studies have shown no significant difference in mortality rates and length of hospital stay between the group treated with ribavirin and the control group.[19]

Lopinavir/Ritonavir

Lopinavir/ritonavir is a combination drug for the treatment of human immunodeficiency virus (HIV). In 2003, the drug showed inhibitory activity against SARS-CoV *in vitro* via inhibition of 3CL protease, a critical enzyme for virus replication.[20] Several systematic review meta-analyses have shown that lopinavir/ritonavir has no significant effect on the recovery of patients with COVID-19.[21-23]

Remdesivir

Remdesivir is an antiviral drug, an adenosine analog, which exerts its effect by binding to the viral RdRp leading to inhibition of viral replication. Remdesivir was synthesized by Gilead Sciences in 2017 for the treatment of Ebola virus disease. *In vitro* studies have shown that remdesivir could inhibit coronaviruses such as SARS-CoV and MERS-CoV replication. Remdesivir is the only antiviral drug approved by the American Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients. To date, many clinical trials have evaluated the use of remdesivir for the treatment of COVID-19. Although some studies have reported the ineffectiveness of remdesivir, most completed clinical trials strongly recommend the use of remdesivir in hospitalized patients.[24-28] For instance, an adaptive COVID-19 treatment trial (a randomized, double-blind, placebo-controlled trial) has shown that remdesivir could shorten the time to recovery, and the positive effects of remdesivir were confirmed in the hospitalized patients on supplemental oxygen.[29] It is noteworthy that the safety and efficacy of co-administration of remdesivir and corticosteroids have not been thoroughly evaluated in clinical trials. However, there are theoretical arguments in favor of the beneficial effects of such a combination therapy in some patients with severe COVID-19. Therefore, it can be used as adjuvant therapy in severe patients who require supplemented oxygen.[30]

Baricitinib is a selective Janus kinase (JAK) 1 and 2 inhibitors capable of inhibiting the pathways of cytokine production. Baricitinib combined with

remdesivir were shown to be more effective than remdesivir alone in reducing recovery time with no serious side effects in patients receiving high-flow oxygen or noninvasive ventilation (clinical trial: NCT04401579).[31] According to preliminary reports, remdesivir can be used in pregnant patients. It has been reported that among 86 pregnant and postpartum hospitalized patients with severe COVID-19, remdesivir therapy was well tolerated, and the rate of serious side effects was low.[32]

Favipiravir

Favipiravir is an antiviral agent that inhibits the RdRp of the virus, similar to remdesivir. Favipiravir is effective against a wide range of influenza viruses. Most of the preclinical data on favipiravir are derived from its anti-influenza and anti-Ebola activity. There are a few studies on the efficacy of favipiravir in COVID-19. In a two-arm, open-label control study, patients with laboratory-confirmed COVID-19 were divided into two groups, namely patients in the favipiravir arm received oral favipiravir (day 1: 1,600 mg twice daily, days 2-14: 600 mg twice daily) plus IFNα, and patients in the control arm were treated with lopinavir/ritonavir plus IFN-α.[33] According to this study, favipiravir showed considerably better therapeutic effects on patients with COVID-19 in terms of disease progression, viral clearance, and improvement in chest imaging (91.43% versus 62.22%) than the control group. Furthermore, the favipiravir arm showed fewer adverse reactions than the control arm.[33] In contrast, a clinical trial revealed that favipiravir was ineffective in treating patients with COVID-19 and reducing the viral load.[34]

Janus Kinase (JAK) Inhibitors

JAK inhibitors can exert an anti-inflammatory effect by interfering with the signal transduction leading to immune stimulation and inflammation.[35] Therefore, immunosuppression induced by JAK inhibitors can potentially reduce the hyper-inflammation observed in COVID-19 patients. Moreover, JAK inhibitors, particularly baricitinib, can directly possess antiviral properties by inhibiting endocytosis of the virus.[36] A systemic review meta-analysis concluded that JAK inhibitors could significantly reduce mortality risk in hospitalized patients with COVID-19.[37] According to the COV-BARRIER trial, baricitinib combined with corticosteroids could significantly decrease mortality.[38] In addition, tofacitinib may be an appropriate alternative in the absence of baricitinib, as it exhibited beneficial effects in the STOP-COVID clinical trial.[39] As a result, baricitinib and tofacitinib are recommended by the American National Institutes of Health (NIH) to manage inflammation in hospitalized patients requiring high-flow oxygen or noninvasive ventilation. It should be noted that other JAK inhibitors cannot be administered to patients except in clinical trials. Because of the potential for fetal malformations, the risks of use in pregnant patients must be weighed against the potential benefits.[40]

Adjunctive Therapies

Corticosteroids

The main reason for using corticosteroids is to reduce host inflammatory responses in the lungs, resulting in ARDS. However, this benefit may be outweighed by undesired side effects, including increased risk of secondary infection and delayed viral clearance.[41] It has been reported that corticosteroids did not improve outcomes during the SARS and MERS outbreaks, but delayed viral clearance and increased the rate of secondary infections.[42, 43] In a clinical study of 31 COVID-19 patients, 11 received corticosteroids. The results showed that corticosteroid therapy had no considerable effect on virus clearance time, hospital length of stay, and duration of symptoms.[44] Corticosteroids can however reduce pulmonary fibrosis in patients with severe ARDS and avoid progressing pathological deterioration, the reason why some patients with SARS infection benefited from corticosteroids.[45] Evidence showed that a low-to-moderate dose of corticosteroids (e.g., methylprednisolone) may increase survival in COVID-19 patients with clinical indications such as refractory ARDS, sepsis, or septic shock.[4, 46, 47]

A large multicenter open-label randomized controlled trial conducted in the United Kingdom reported that the administration of up to 10 days of dexamethasone combined with standard care significantly reduced mortality in patients on mechanical ventilation or requiring supplemental oxygen on admission. In contrast, in another study, patients requiring supplemental oxygen on admission did not benefit from dexamethasone administration.[48] Based on many clinical trials, NIH recommended short-term low-to-moderate dose administration of corticosteroids as adjuvant therapy to improve the survival of patients with severe COVID-19. However, a randomized clinical trial showed that an early high-dose of steroids could preserve pulmonary fibrosis and long-term pulmonary consequences in critically ill patients. Therefore, more studies are needed to determine the most effective steroids dose.[49] As in non-pregnant patients, administration of a short course of dexamethasone is recommended for

hospitalized pregnant patients due to reduced maternal mortality and low risk of fetal adverse effects.[50]

Monoclonal Antibodies

As mentioned, the S protein on the surface of SARS-CoV-2 mediates the entry of the virus into the host cell by binding to ACE2. Specific monoclonal antibodies (mAbs) that block the S protein can act as an effective agent in preventing the spread of the virus and host infection.[51] Since the onset of the COVID-19 pandemic, several of these mAbs have been the subject of clinical trials.[52] In November 2020, FDA authorized the emergency use of bamlanivimab to treat mild to moderate COVID-19 patients over the age of 12 with chronic diseases. Bamlanivimab is not recommended for hospitalized patients, because its beneficial effects have not been proven and may even aggravate the symptoms of the disease. It should therefore only be prescribed in the early stages of the disease. The current recommended dose is a 700 mg single dose as an intravenous infusion over at least 60 minutes.[53] Reported side effects of bamlanivimab, similar to other mAbs, include allergic reactions, pain, and bruising at the injection site.[54] Several clinical studies have been performed on its efficacy. These studies have shown that patients who receive bamlanivimab are more likely to survive and are less likely to need hospitalization. For example, a study of 1,392 patients with mild to moderate COVID-19 showed that the mortality rate (1.7% vs. 2.8%) and hospitalization (6.4% vs. 14.8%) were higher in the control group than in the bamlanivimab group.[55]

IL-6 appears to be a key inflammatory cytokine in inducing systemic inflammation and hypoxemic respiratory failure in COVID-19 patients.[56] IL-6 receptor-inhibiting mAbs block IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors.[57] Several randomized clinical trials demonstrated that tocilizumab, an IL-6 receptor inhibitor, in combination with standard COVID-19 care improved the recovery time and had clinical benefits.[58-60] Other IL-6 receptor inhibitors such as siltuximab and sarilumab have also shown promising results for treating patients with COVID-19. According to the NIH guideline, sarilumab and tocilizumab can be used only in combination with a course of dexamethasone or an alternative corticosteroid in the hospitalized patients requiring supplemental oxygen, high-flow oxygen, noninvasive ventilation, or invasive mechanical ventilation. Although there are no data on the use of these mAbs during pregnancy, they can be indicated in pregnant patients considering the safe use of other immunoglobulins G (IgG) mAbs in this target population.[61]

Stem Cell-based Therapies

Regenerative medicine is another approach that can be applied to reduce the complications of COVID-19. Stem cells offer a promising method to suppress coronavirus lethality. The capacity of mesenchymal stem cells (MSCs) in inhibiting hyper-inflammation has been revealed in the animal model of the influenza virus.[62]

MSCs exhibit anti-inflammatory and immune-regulatory effects by concurrent activation of T lymphocytes and provoking macrophages' differentiation into anti-inflammatory macrophages and regulatory T cells.[63] MSCs can decrease IL1α, TNFα, IL-6, IL-12, and IFNγ concentration in the lungs and prevent a cytokine storm.[63, 64] In addition, these cells reduce the level of hydrogen peroxide production by neutrophils and thus prevent further activation of the immune cells. MSCs are useful in both acute and chronic lung injury.[65] According to a recent study, MSCs were able to reduce acute lung injury and ischemia-reperfusion caused by lipopolysaccharide.[66] Interestingly, the immunomodulatory function of MSCs can be potentiated by cytokines produced by lymphocytes.[67] MSCs can modify the abnormal function of both innate and adaptive immune responses, such as hyper-inflammation and lymphopenia.[68, 69]

The safety and efficacy of MSCs have been confirmed in clinical studies. In a recent study, lymphocyte count was augmented and inflammatory markers decreased in patients treated with MSCs. In addition, levels of the anti-inflammatory cytokine IL-10 were elevated too.[70] Moreover, regeneration of damaged tissues caused by COVID-19 can be improved by immunomodulatory, regenerative, pro-angiogenic, and anti-fibrotic properties of MSCs.[71] Due to complications of stem cell therapy, secreted exosomes from stem cells can be utilized instead of cell therapy.[72] Exosomes are extracellular vesicles secreted by different cells, which play an essential role in cell communication. MSCs-derived exosomes contain various macromolecules which can participate in the regulation of immune cell function.[72] Altogether, stem cell-based therapy is a promising approach to COVID-19 treatment, but more large-scale trials are needed.

Convalescent Plasma Therapy

The use of convalescent plasma (CP) or hyper-immune immunoglobulin is one of the potential

promising adjuvant therapies for patients with COVID-19.[73] The rationale for using human blood products in the treatment of COVID-19 emanated from its use in the H1N1 influenza pandemic in 2009, during which patients derived a clinically significant mortality benefit and improved viral clearance by using blood products.[74] Duan and colleagues observed a significant clinical improvement in 10 COVID-19 patients treated with convalescent plasma transfusion, leading to complete viremia resolution in seven days. These results suggest that CP may be a promising option for the treatment of COVID-19, but more randomized trials are needed.[75]

CP refers to passive antibodies obtained from individuals who have recovered from COVID-19, especially those with an adequate titer of neutralizing antibodies (NAbs) in their plasma. According to previous findings on various viral respiratory diseases, CP can be utilized as an effective and emergency treatment for COVID-19 to confer immediate immunity to severe patients and decrease the viral load.[76, 77] It was shown that administration of CP with a higher titer of IgG antibody decreased the risk of mortality compared to CP with a lower titer.[78] Two studies supported these findings. One concluded that CP reduced the mortality rate among the patients,[79] and the other found an inverse correlation between transfusion of CP and deaths occurring within 14 days after transfusion.[80] IgG level after CP administration could be a promising parameter for measuring treatment success in immunosuppressed patients who are at the early stage of the infection and have no detectable IgG.[81]

Some studies demonstrated that CP therapy in COVID-19 patients can considerably improve disease symptoms and clinical parameters such as pulmonary lesions. They also reported that CP can be used for prophylactic purposes by minimizing the virulence of the illness through the neutralization of virus antigens with particular antibodies, thereby reducing the mortality rate.[82] After CP administration, antibodies (especially NAbs) increase in a time-dependent manner in the recipients. These antibodies bind to the viral particles and neutralize them by blocking access to host target cells. Furthermore, other antibody action pathways such as antibody-mediated cellular cytotoxicity, complement activation, and phagocytosis can promote the effect of CP. Plasma contains not only NAbs, but also non-neutralizing antibodies such as IgG and IgM, which can contribute to prophylaxis and recovery enhancement through binding to the virus, but the presence of NAbs is critical.[76, 82]

A recent randomized study showed that although CP was utilized extensively in treating severe COVID-19, no significant clinical improvement was observed in the treatment group.[83] Besides, it was reported that CP could not reduce the risk of mortality in moderate to severe COVID-19 patients, while there are even uncertainties about its effect on mild and asymptomatic patients.[84] Therefore, more studies are required to clarify uncertainties about CP therapy. Despite the mentioned benefits, CP has some limitations, such as a lack of standardization, availability, and clinical evidence to advocate its efficacy.[85]

Designed Vaccine

Vaccination is the most promising approach to stop and control infection. Recently, due to the outbreak of COVID-19, the need for an effective vaccine against SARS-CoV-2 has become extremely urgent. Most pharmaceutical companies and academic institutions worldwide have focused on developing vaccines against SARS-CoV-2. By October 2021, 128 vaccine candidates have undergone clinical trials, and 194 are in the pre-clinical phase.[86] The only COVID-19 vaccines approved by the WHO are Pfizer-BioNTech, Moderna, Janssen, Sinopharm, Sinovac, and AstraZeneca COVID-19 (table 1).[87, 88] Vaccine technology has been considerably improved in recent years.[89] It includes RNA and DNA vaccines, recombinant protein vaccines, live vector vaccines, whole-cell inactivated vaccines, live-attenuated vaccines, and subunit vaccines. The type and percentage of COVID-19 vaccine candidates under clinical trials are presented in figure 2.[86]

COVID-19 Vaccines Under Development
Whole Virus Vaccines

Live-attenuated or inactivated whole virus vaccines are a classic strategy to induce the secretion of immune effectors against the virus.[90] A major advantage of whole virus vaccines is the stimulation of toll-like receptors (TLRs), including TLR 3, TLR 7/8, and TLR 9.[91] Live-attenuated vaccines can elicit both humoral and cellular immune responses. These vaccines are easily produced, and typically two doses provide a strong lifelong immune response. Live virus vaccines are shown to cause some complications, including lung damage and infiltration of eosinophils in a mouse model and liver injury in ferrets.[92-94] Therefore, this type of vaccine needs extensive additional testing to prove its safety. However, inactivated vaccines produce a lesser immune response than live-attenuated vaccines, and adjuvants are required

Table 1: A Summary of the WHO-approved SARS-CoV-2 vaccine candidates

Vaccine type	Name	Developer	Antigen	Immunogenicity in human	Number of doses	Schedules
Inactivated virus	Vaccine BBIBP-CorV	Beijing Institute of Biological Products, Sinopharm, and Institute of Viral Disease Control and Prevention	The whole virus	79%	2	Day 0 and day 21
	CoronaVac (formerly PiCoVacc)	Sinovac Biotech and National Institute for Communicable Disease Control	The whole virus	51%	2	Day 0 and Day 14
Adenoviral vector	AZD1222 (also known as ChAdOx1)	The University of Oxford and AstraZeneca	Full-length spike protein	63-90%	2	Day 0 and day 60 or 90
	Ad26.COV2.S	Johnson&Johnson and Beth Israel Deaconess Medical Center	-	85.4%	1-2	Day 0 or day 0 and day 56
mRNA vaccine	Comirnaty (also known as tozinameran or BNT162b2)	Pfizer and BioNTech	Full-length spike protein with two proline substitutions	Very high (95%)	2	Day 0 and day 21
	mRNA-1273	Moderna	Full-length spike protein with two proline substitutions	Very high (94.5%)	2	Day 0 and day 28

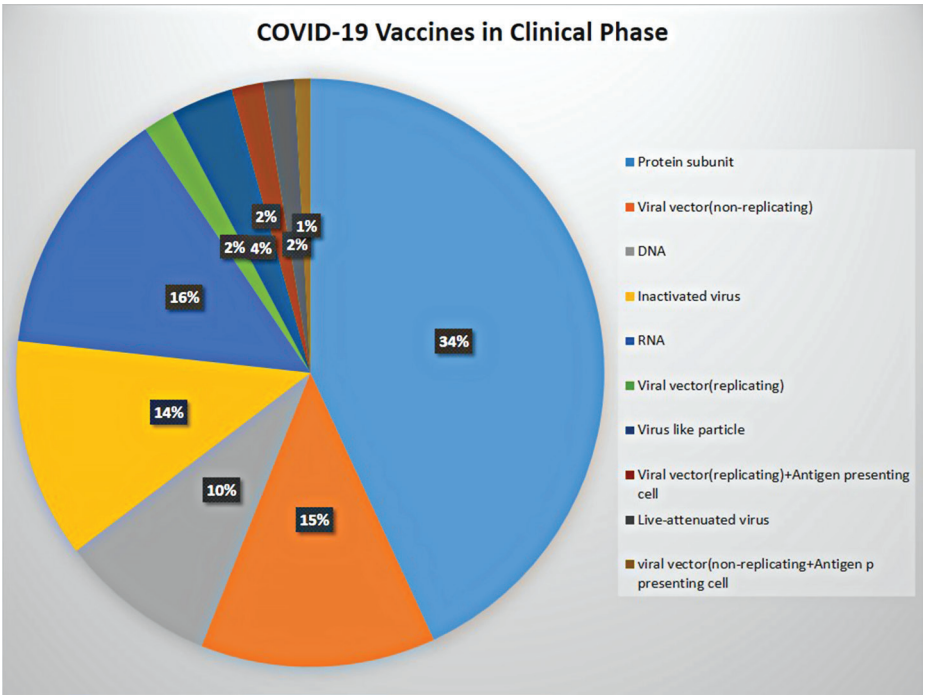

Figure 2: The pie chart shows the type and percentage of COVID-19 vaccine candidates currently under clinical trials.

to boost immune response.[95] It is notable that Sinopharm and Sinovac, recently approved by the WHO, are based on an inactivated virus platform.

Subunit Vaccine

Subunit vaccines contain one or more antigens that can induce a strong immune response. Almost all subunit vaccines contain S protein as the immunogenic agent to activate the immune system to prevent interaction with the host ACE2 receptor. Several institutions have started programs on the COVID-19 subunit vaccine. For instance, the University of Queensland is synthesizing a subunit vaccine based on the "molecular clamp" technology to expose viral surface protein more easily to the immune system.[96] Clover Biopharmaceuticals is using their patented Trimer-Tag® technology to produce a recombinant COVID-19 S protein subunit-trimer vaccine (S-Trimer) via a rapid mammalian cell-culture based expression

system.[97] Moreover, Novavax published that they have produced virus-like nano-particles based on S protein.[98] However, some studies have reported that the SARS full-length S proteins can increase infectivity and eosinophilic infiltration. In a recent study, it has been demonstrated that SARS-CoV-2 receptor-binding domain (RBD) protein has the potential to enhance cross-reactive or cross-neutralizing antibodies against SARS-CoV-2 or SARS-CoV and also inhibits the virus entry into ACE2 expressing host cells by blocking these receptors.[99] For instance, ZF2001 is a subunit vaccine using a dimeric form of the RBD of the S protein. According to the phase I and II trials, ZF2001 was well tolerated and immunogenic.[100] Indeed, using RBD as an antigen can provide high protective immunity, but also minimize hyperactivation of the immune system, the adverse effect of full-length S protein.[91]

Nucleic Acid Vaccines

mRNA vaccines represent a promising approach to vaccine development. This type of technology is based on transferring mRNA encoded viral antigen into host cells. Then, host cells express antigens and activate immune cells. The advantages of mRNA vaccines include high efficiency, capacity for rapid expansion, and potential for low-cost fabrication and safe administration.[101] Considering the achieved clinical success, mRNA vaccines developed by Pfizer-BioNTech and Moderna were approved by the FDA.

DNA vaccines usually contain plasmid DNA molecules that encode immunogenic antigens. Providing drug product stability is easier to achieve in DNA vaccines than in mRNA vaccines. However, they may increase the risk of mutations in the host genome as the result of vector integration.[102] So far, two SARS-CoV-2 DNA vaccines are under development.[103] INO-4800 and AG0302-COVID19 are DNA plasmid vaccines encoding SARS-CoV-2 S protein, which are under phase 2/3 clinical trials (NCT04642638 and NCT04655625).[104]

Synthetic Peptide or Epitope Vaccine

In contrast to subunit vaccines, these vaccines contain certain antigen fragments and usually cause low immunogenicity. To increase the ability of these vaccines to stimulate the immune system, structural modifications, delivery systems, and adjuvants are needed.[105] However, they are easier to produce than other types of vaccines. Recently, a group of scientists has discovered a highly conserved set of B and T cell epitopes from S and nucleocapsid (N) proteins of SARS-CoV-2 that may be useful in developing an epitope vaccine against COVID-19.[106] Currently, Generex Biotechnology is using the patented NuGenerex Immuno-Oncology Ii-Key technology for a COVID-19 vaccine. They employ synthetic peptides that are chemically linked to the 4-amino acid Ii-Key to potentiate immune response.[107]

Live Vector Vaccines

Live vector vaccines refer to live viruses that contain the complex antigen(s). These viral vectors are divided into two types: replicating (replicate in the host's body) and non-replicating. The presence of heterogeneous antigens in live viruses can cause robust immunogenicity, but its safety is comparable to that of subunit vaccines. Adenoviral vectors are the most common delivery vehicles in gene therapy. They are non-enveloped double-stranded DNA viruses causing mild self-limiting respiratory tract infections in humans.[108] Adenoviral vector-based vaccines have some advantages over mRNA vaccines, including low cost, thermostability, and ease of scale-up.[109] Currently, Oxford/AstraZeneca and Johnson & Johnson are using adenoviral vectors for encoding the full-length S protein of SARS-CoV-2. The efficiency of these vaccines is relatively high, but they may not be effective in people with recessive infectious viruses.[110]

COVID-19 Vaccine and Challenges due to SARS-COV-2 Variants

One of the major issues facing global health is the emergence of various variants of the coronavirus. For instance, even within a year, several variants appeared in different countries, such as the United Kingdom, South Africa, and Brazil.[111] It has been shown that mutations can influence transmission rates, susceptibility to mAbs, and vaccine-induced neutralization of antibodies.[112] However, current variants cannot entirely resist the existing vaccines due to the similarity of the antigenicity with the original virus. Thus, extensive vaccination of populations with available vaccines is needed, besides developing new vaccines with high efficacy against variants. The main target for designing COVID-19 vaccines is the S protein of the virus.[113] Although mutations in the S protein may affect the efficacy of original vaccines, the development of vaccines for the variants is always based on targeting the S protein. Fortunately, updating nucleic acid vaccine, protein subunit vaccine, and adenoviral vector-based vaccine for new variants is easy and can be achieved by adjusting the gene sequence of

the S protein. In the fight against variants, three principles should be observed: (i) designing new vaccines based on the original vaccine to maintain immunological memory fresh, (ii) developing multivalent vaccines as they stimulate immunity against multiple variants and are preferred over monovalent vaccines, and (iii) re-vaccination with the initial vaccine is highly recommended to gain high titers of antibody. Therefore, institutions and pharmaceutical companies should collaborate to achieve high immunity against new variants and resolve practical limitations.[114]

Conclusion

Today we are faced with a dreadful virus with superior infectivity. To hold the spread of the virus, accelerating the diagnosis and treatment of patients is critical. It is essential that all the research centers, pharmaceutical companies, and governments collaborate to control this disease. Among antivirals, only remdesivir is approved by the FDA for hospitalized patients. Considering the NIH recommendation, adjuvant therapy with corticosteroids, JAK inhibitors, and IL-6 inhibitors can be helpful in severe cases to suppress the overactivation of immune cells. Furthermore, the use of anti-SARS-CoV-2 mAb products is recommended in non-hospitalized patients with mild to moderate COVID-19 at increased risk of clinical progression.

In contrast, other therapeutic agents can only be administered in clinical trials. Despite all the achievements in developing therapeutic strategies, we need to know a lot more about this virus and its complications to discover more effective treatments. In addition, further well-designed large sample studies are needed to prove the efficacy of these new therapeutic approaches and their safety. Thus far, it has been proven that vaccination is the most important weapon against COVID-19. To date, many vaccines have entered clinical trials, and the most successful vaccines are based on mRNA and adenoviral vectors. While emerging new variants can affect the efficacy of original vaccines, updating these vaccines can be done quickly if the genome sequence of the new variant is detected rapidly. To accelerate the process of overcoming this disease, the respective institutes and pharmaceutical companies should collaborate.

Authors' Contribution

B.A, A.H.A.J, H.F, L.D, K.R.S, and H.F: Study concept and design, Acquisition, and interpretation of data, Drafting and critical revision of the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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