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Recent Advances on Drugs and Vaccines for COVID-19

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Abstract

The current situation of Coronavirus Disease 2019 (COVID-19) worldwide is still very severe. Presently, many breakthroughs have been accomplished in the research and development of drugs for the treatment of COVID-19, especially vaccines; however, some of the so-called COVID-19-specific drugs highlighted in the early stage failed to achieve the expected curative effect. There is no antiviral therapy available, by stimulating protective immunity vaccine is the best choice for the future management of infection. Therefore, we aimed to identify the latest developments in the research and development of these drugs and vaccines and provide a reference for the prevention and treatment of COVID-19.

Keywords

COVID-19, SARS-CoV-2, antiviral drugs, anti-SARS-CoV-2 antibody, vaccines, coronavirus

Highlights

What do we already know about this topic?

At present, severe acute respiratory syndrome coronavirus 2 is still spreading worldwide and has a serious impact on the health, economic development, and social stability of all mankind. In general, injecting safe and effective vaccines to form herd immunity is currently the most economical and effective means to control the spread of Coronavirus Disease 2019 (COVID-19).

How does your research contribute to the field?

Our research helps people quickly understand the latest research progress of COVID-19 treatment drugs and vaccines, and provides references for the prevention and treatment of COVID-19.

What are your research's implications towards theory, practice, or policy?

Our research can provide references for researchers to develop drugs and vaccines. In terms of the prevention and treatment of COVID-19, our research can provide medical workers with a reference so that they can choose safe and effective treatment drugs and inject safe and effective vaccines into humans to form herd immunity.

Introduction

The outbreak of coronavirus disease (COVID-19), which began in December 2019, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The epidemic has spread worldwide. At present, more than 200 million COVID-19 patients have been confirmed and more than 4 million deaths have been recorded, seriously endangering human health and public safety.[2] The clinical trial results of many of the so-called COVID-19-specific drugs have failed to achieve the expected effect, and some drugs may even increase mortality. At the beginning of the pandemic, researchers highlighted the importance of research and development of vaccines. Presently, there are more than 200 vaccines under development worldwide, of which more than 100 vaccines have been approved for clinical trials.[3] Therefore, we have reviewed the characteristics of SARS-CoV-2 and the progress of the current treatment drugs and vaccines for COVID-19 to provide references for the clinical prevention and vaccine development of SARS-CoV-2.

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Brief Introduction of the Coronavirus (CoV)

General Characteristics and Infection of CoV. CoV belongs to the genus CoV in the system classification of CoVs. It is a Ribonucleic Acid (RNA) virus with an envelope and a linear single-stranded positive-strand genome. It can be divided into 4 genera: α, β, γ, and δ.[4] The diameter of the CoV is about 80–120 nm, the 5′ end of the genome has a methylated cap structure and the 3′ end has a poly(A) tail. The full length of the genome is approximately 27–32 kb, which is the largest of the known RNA viruses,[5] with multiple open reading frames.[6] Among these, only the α and β genera have virus strains that are pathogenic to humans. According to phylogenetic analysis, SARS-CoV-2 and SARS-CoV belong to the CoV subfamily of the CoV family. The S proteins of SARS-CoV-2 and SARS-CoV are closely related to phylogeny. The amino acid sequence homology of the 2 viruses is approximately 77%.[7] CoV is closely related to many human respiratory infectious diseases. SARS-CoV-2 is the seventh CoV that can infect humans. The remaining 6 are HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV (causing severe acute respiratory syndrome),[8] and MERS-CoV (causing Middle East respiratory syndrome).[9] SARS-CoV-2 infection mainly involves the respiratory system, with typical clinical symptoms including fever, dry cough, and dyspnea.[10]

Biological Structure and Pathogenic Mechanism of CoV

The spike (S) protein on the surface of the CoV is a type I transmembrane protein composed of 2 subunits, S1 and S2. S1 is responsible for receptor binding and S2 is responsible for membrane fusion.[11] S1 interacts with the specific cell receptor-angiotensin–converting enzyme 2 (ACE2) to change the structure of the S2 subunit, resulting in the fusion between the virus envelope and the host cell membrane.11 Therefore, the spike protein plays a vital role in the life cycle of CoV, and there is no homologous protein of spike protein in the human body, which makes spike protein an ideal target for the development of antiviral drugs.

Compared with SARS-CoV and MERS-CoV, SARS-CoV-2 is more infectious and seriously endangers human health. Therefore, the development of effective anti-SARS-CoV-2 drugs and vaccines is urgently needed.

New Use of Old Medicine

Currently, there is no specific drug that can effectively treat COVID-19; therefore, medical practitioners must find effective drugs against SARS-CoV-2 from antiviral drugs. These drugs were originally designed for other pathogens and have rapidly changed their use in current anti-CoV trials.[12]

Lopinavir/Ritonavir. Lopinavir/ritonavir is a protein inhibitor used to treat human immunodeficiency virus (HIV) infection. Studies have shown that these 2 drugs can inhibit 3C-like proteases, thus showing activity against other new CoVs in vitro, and SARS-CoV 3C-like protease is a key enzyme in the processing of SARS-CoV-2 polyprotein.[13] In vitro, lopinavir/ritonavir has the activity of anti-SARS-CoV-2 virus.[14] Pharmacokinetic analysis indicates that the predicted therapeutic dose of lopinavir and ritonavir concentrations in plasma and lung concentrations can inhibit the SARS-CoV-2.[15] In the ferret infection model of SARS-CoV-2 infection, the clinical score of the lopinavir/ritonavir group improved compared to that of the control group; however, there was no difference in the virus titer.[16] However, according to Cao et al.[17] in terms of mortality, clinical improvement time, viral RNA load of patients after medication, adverse drug reactions, and clinical deterioration time, compared with standard treatment, lopinavir/ritonavir has no significant effect on the treatment of COVID-19. A study by Ader et al.[18] also showed that lopinavir/ritonavir had no significant effect on the clearance rate of SARS-CoV-2, and the incidence of serious adverse events in the lopinavir/ritonavir group was even higher. Therefore, the use of lopinavir/ritonavir alone is not recommended.

Interferon Beta-1b, Ribavirin, and Lopinavir/Ritonavir. Interferons are multifunctional glycoproteins that can be divided into type I (IFN-α and IFN-β), type II (IFN-γ), and type III (IFN-λ). IFN-α can produce proteins with antiviral effects by binding to cell surface receptors, and it concurrently enhances immune response and produces antiviral effects; therefore, it is widely used in clinical practice.[19] In addition, IFN-β also shows strong antiviral activity against SARS-CoV and MERS-CoV.[20,21] Therefore, it has become a drug candidate for the treatment of COVID-19.

Ribavirin is a nucleoside analog that is activated by intracellular phosphatase to inhibit the synthesis of guanosine monophosphate, thereby inhibiting virus replication. Ribavirin can effectively inhibit the activity of human CoV in vitro.[21] However, its in vitro anti-SARS-CoV activity is limited, high concentrations are required to inhibit viral replication, and large doses and combination therapy are required.[22]

In a multicenter, randomized, open phase 2 trial for patients with COVID-19, injection of interferon (interferon beta-1b), oral protease inhibitor (lopinavir/ritonavir), and oral nucleoside analog (ribavirin) triple combination drug can effectively inhibit the shedding of SARS-CoV-2.[23] Moreover, early triple therapy based on interferon β-1b, ribavirin, and lopinavir/ritonavir can effectively reduce 28-day mortality. Therefore, ribavirin is often used in combination with other antiviral drugs to achieve the optimal effect, and it is recommended to use it in combination with interferon or lopinavir/ritonavir.[24] However, in patients with severe COVID-19, ribavirin treatment failed to demonstrate improvement in the negative transition time of SARS-CoV-2 testing, including improvement in mortality.[25] Therefore, the use of triple therapy is not recommended for critically ill patients.

Chloroquine and Hydroxychloroquine. Chloroquine and hydroxychloroquine are drugs used for malaria, allergy, and autoimmune diseases, and chloroquine and hydroxychloroquine may prevent the virus from entering the cell by interfering with the glycosylation of the virus ACE2, inhibiting glycosylation, proteolytic processes, and endosomal acidification of the host receptor. These drugs also exert immunomodulatory effects by reducing the production of cytokines and inhibiting the autophagy and lysosome activity of host cells.[26,27] Previous studies found that chloroquine can effectively inhibit SARS-CoV-2 in vitro,[28] and hydroxychloroquine can inhibit SARS-CoV-2 more effectively than chloroquine in vitro.[29] During that time, COVID-19 had rapidly spread globally; therefore, hydroxychloroquine was highly regarded. However, the study by Cavalcanti et al.[30] showed that in patients hospitalized with mild-to-moderate COVID-19, hydroxychloroquine alone or in combination with azithromycin did not improve the clinical condition at 15 days compared with standard treatment. Pre-exposure prophylaxis with hydroxychloroquine once or twice a week did not significantly reduce laboratory-confirmed COVID-19 or COVID-19-compatible diseases among health care workers.[31,32] Therefore, the use of hydroxychloroquine in COVID-19 is not recommended.

Arbidol. Arbidol is an antiviral drug for the treatment of influenza caused by influenza A and B viruses and can effectively block the trimerization of SARS-CoV-2 S protein, thereby preventing the fusion of virus and host cell membrane, and blocking the trimerization of SARS-CoV-2 spike protein can also lead to the formation of naked or immature viruses, which are less infectious.[33-35] The results of Lanjuan Li et al.'s study showed that in an in vitro cell test, Arbidol effectively inhibited the CoV by 60-fold compared with the control group at a concentration of 10-30 μmoL and significantly inhibited the pathological effect of the virus on cells; in mouse experiments, Arbidol significantly reduced the area of pulmonary fibrosis in the mouse model and improved lung function (reduced inspiratory resistance, lung dynamic compliance, and increased forced lung capacity).[35] Furthermore, treatment with Arbidol can reduce the severity of sepsis within 48 hours after the induction of sepsis.[35] The early combined use of Arbidol and Lianhua Qingwen (LHQW) can reduce the time to conversion to nucleic acid negativity, the time of chest computed tomography (CT), and the length of hospital stay, thereby significantly accelerating the recovery of patients with moderate COVID-19. However, no benefit was observed in patients with severe COVID-19 who received a combination therapy of LHQW + Arbidol.[36] In another study, Arbidol contributes to clinical and laboratory improvements, including requiring ICU admissions, peripheral oxygen saturation, duration of hospitalization, chest CT involvements, white blood cell, and erythrocyte sedimentation rate.[37] Moreover, Arbidol monotherapy is superior to lopinavir/ritonavir in the treatment of COVID-19.[38] Therefore, it is recommended to use Arbidol in COVID-19 in China.[24]

Remdesivir. Remdesivir (RDV, code GS-5734) is a new experimental broad-spectrum antiviral drug developed by Gilead Sciences. Although it failed in Ebola clinical trials,[39] it was once considered one of the most potential anti-novel CoV drugs because it can effectively inhibit the replication of SARS-CoV[40] and MERS-CoV[41] in respiratory epithelial cells. The core element of CoV replication and transcription mechanism—RNA-dependent RNA polymerase—is the primary target of the antiviral drug RDV.[42,43] The study showed that the use of RDV therapy in the early stage of infection has obvious clinical benefits to rhesus monkeys infected with SARS-CoV-2.[44] These data support early RDV treatment of COVID-19 patients to prevent the development of severe pneumonia.

Among adult hospitalized patients with COVID-19 and evidence of lower respiratory tract infection, RDV is superior to placebo in shortening the recovery time, and the median recovery time of patients receiving RDV is 10 days.[45] Among patients with moderate COVID-19, there was no statistically significant difference in the clinical status between patients randomized to receive a 10-day course of RDV and standard care 11 days after the start of treatment. Compared with standard care, there is a statistically significant difference in the clinical status of patients randomized to receive a 5-day course of RDV treatment, but the difference has uncertain clinical significance.[46] Among patients with symptoms lasting 10 days or less, patients who received RDV experienced clinical improvement much faster than those who received placebo. However, in a study of adult patients hospitalized with severe COVID-19, RDV was not associated with a statistically significant clinical benefit.[47]

Another clinical study of 53 COVID-19 patients revealed that 36 of them showed improvement in clinical symptoms after 10 days of medication, but the side effects were also obvious. Among 32 (60%) patients with elevated liver enzymes, diarrhea, skin rash, renal dysfunction, and hypertension, 12 patients (23%) had serious side effects, such as multiple organ dysfunction syndrome, septic shock, acute kidney injury, and hypertension.[43] These studies proved that RDV can effectively combat SARS-CoV-2. The differences in the results of different studies may be related to factors such as the research subjects and sample size selected by the researchers. Further research is needed on the treatment of RDV in the treatment of COVID-19.

Favipiravir. Favipiravir (FPV) is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. It can be transformed into a nucleoside triphosphate form similar to the purine structure in the cell and inserted into the viral RNA chain, thereby blocking the extension of the RNA chain and virus replication.[48] Most of the preclinical data of favipiravir comes from its anti-influenza activity and anti-Ebola activity.[49,50] In this open-label before-after controlled study: compared with the control group, the FPV group had a faster virus clearance, a significant improvement in chest CT,

with an improvement rate of 91.43% vs 62.22% (P = 0.004). In addition, fewer adverse events were found in the FPV arm than in the control arm.[51] In another randomized trial of asymptomatic to mildly symptomatic patients with COVID-19, taking FPV did not significantly improve virus clearance in the first 6 days; however, there is a tendency to clear the virus early. A study by Doi et al. showed that FPV can reduce the time to fever, and all patients did not have disease progression or death.[52]

Ivermectin. Ivermectin is a broad-spectrum antiparasitic drug that can be used for diseases caused by soil-borne helminths and can also be used to treat scabies. In India, ivermectin is used by many Indian officials and medical workers to prevent and treat the COVID-19. However, the World Health Organization (WHO) does not recommend the use of ivermectin to treat or prevent COVID-19 outside of clinical trials.[53] The results of a double-blind, randomized trial conducted in Cali, Colombia showed that compared with placebo, there was no significant improvement in symptom relief in adults with mild COVID-19 (a 5-day course of ivermectin) time.[54] This finding also does not support the use of ivermectin to treat mild COVID-19. The U.S. Food and Drug Administration (FDA) stated that ivermectin is not an antiviral drug, and it is dangerous to take in large doses and may cause serious adverse reactions. The FDA does not recommend the use of ivermectin to treat or prevent COVID-19.[55]

Baricitinib. Baricitinib is an oral Janus activated kinase (JAK) inhibitor discovered by Incyte and licensed to Lilly. New data from Phase 3 COV-BARRIER sub-study indicates one death prevented for every 6 baricitinib-treated patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) compared to placebo. Data showed 46% risk reduction in mortality by Day 28 and 44% risk reduction in mortality by Day 60.[56] On July 28, 2021, the U.S. FDA broadened the Emergency Use Authorization for baricitinib to allow for treatment with or without remdesivir. The EUA provides for the use of baricitinib for treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, non-invasive or invasive mechanical ventilation or ECMO.[57]

Progress in the Development of Antibodies and Antibody Drugs

Monoclonal antibody therapy has been used for viral infections, such as respiratory syncytial virus pneumonia and Ebola virus disease. In the current pandemic of COVID-19, the early efficacy signals of convalescent plasma therapy have encouraged the research and development of anti-SARS-CoV-2 monoclonal antibodies.[58] On January 28, 2020, Ying et al reported for the first time the human monoclonal antibody CR3022 against SARS-CoV, which can bind to the receptor binding domain (RBD) on the S protein of SARS-CoV-2.[59] Therefore, it is believed that CR3022 has the potential to be used alone or in conjunction with other antibodies as a candidate therapy for the prevention and treatment of COVID-19. However, the study by Yuan et al[60] found that when CR3022 binds to SARS-CoV-2, it does not compete with ACE2 to bind to the RBD of the virus, and it cannot neutralize SARS-CoV-2 in vitro. It also revealed the structural basis for the binding of CR3022 antibody to the RBD hidden epitope of the CoV S protein. The availability of hidden epitopes not only makes the development of SARS-CoV-2 vaccines possible, but also the development of universal antibodies using hidden epitopes, blocking infection.

Sotrovimab (VIR-7831) is a fully human anti-SARS-CoV-2 monoclonal antibody developed by GSK and Vir Biotechnology. This antibody binds to the epitope on the SARS-CoV-2 spike protein to inhibit the binding of the virus to human cells, thereby blocking infection.[61] The results of the phase 3 COVID-19 Monoclonal Antibody Efficacy Test-Early Intentional Care trial demonstrated that sotrovimab significantly reduced the risk of hospitalization or death in high-risk adult outpatients with mild-to-moderate COVID-19. Compared with placebo, hospitalization for more than 24 hours or death from any cause were reduced by 79% with sotrovimab, and the main adverse events were skin rash (1%) and diarrhea (2%).[62] On May 26, 2021, the drug received emergency use authorization from the FDA for the treatment of COVID-19.[63]

Progress in Vaccine Research and Development

At the beginning of the COVID-19 epidemic, the research and development of vaccines have received the attention of scientific researchers. Vaccination has always been the most effective way to prevent infectious diseases. For SARS-CoV-2, which may coexist with humans for a long time in the future, vaccine development is particularly important. According to the overview of COVID-19 vaccine candidates announced by the WHO, as of October 3, 2021, there are a total of 317 COVID-19 vaccine candidates worldwide. Among them, 194 candidate vaccines are in the pre-clinical research stage, and 123 candidates have entered the clinical trial stage (Figure 1).[3] The COVID-19 vaccines can be administered in 3 planned doses. Figure 2 shows that 19 (15%) vaccines were administered in a single dose (grey). The double-dose vaccines (light blue to dark blue) are 76 (62%) and are vaccinated regularly on 2 different days, for example, on day 0 and day 14 (6%), day 0 and day 21 (23%) as well as day 0 and 28 (33%). In addition, only one candidate vaccine is administered in 3 doses on days 0, 28, and 56 (yellow).There are also 27 (22%) vaccines that have not yet cleared the dose and vaccination plan (green).[3] The research and development of COVID-19 vaccines cover almost all existing vaccine technologies. According to the different research platforms, the types are mainly divided into the following types.

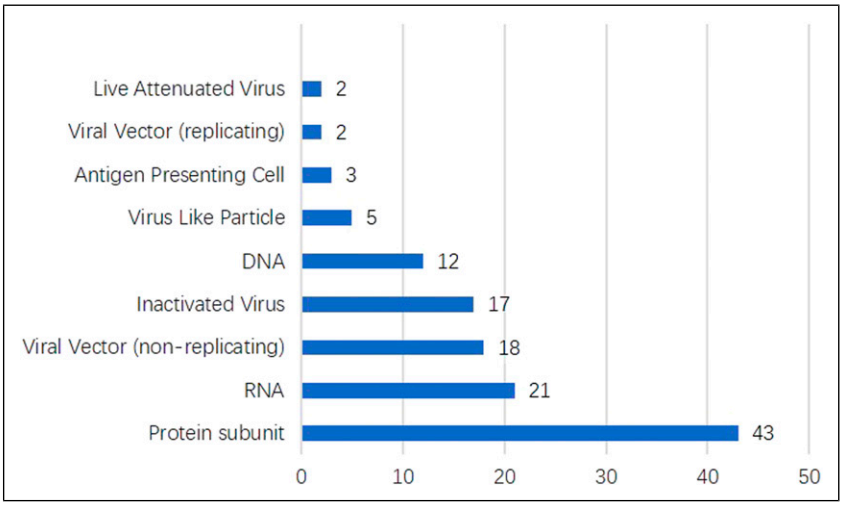

Figure 1. Candidate vaccines in clinical development.

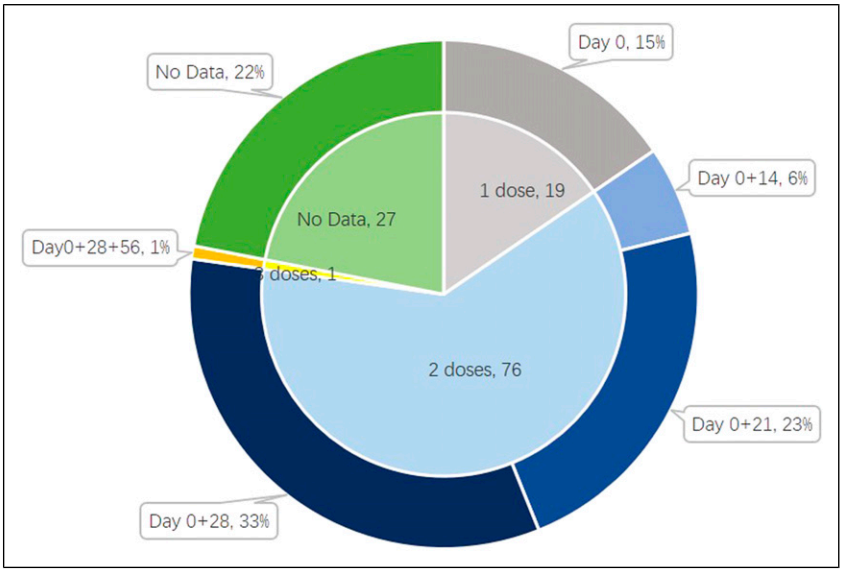

Figure 2. Dosage and schedule of COVID-19 candidate vaccines in clinical development.

Inactivated Vaccine. Inactivated vaccine means that the pathogenic microorganisms are cultivated first, and then the pathogenic microorganisms are inactivated by heating or by chemical agents. After inactivation, the entire virus or bacteria can form an inactivated vaccine, and their split fragments are formed into a split vaccine. After vaccination with an inactivated vaccine, the recipient can produce an immune response based on humoral immunity, so that the body can produce neutralizing antibodies that neutralize and eliminate pathogenic microorganisms and their toxins. There are currently 17 inactivated vaccines in the clinical research phase, of which 10 are in phase III or IV clinical trials.[3] Results have shown that the safety and tolerability of the SARS-CoV-2 inactivated vaccine have satisfied the relevant WHO standards in several unblinded phase III clinical trials.[64,65] In addition, according to randomized clinical trials, inactivated vaccines can significantly reduce the risk of COVID-19 infection in adults, and serious adverse events are rare.[66,67] Inactivated vaccines are easy to store and are inexpensive, but their immune activation ability is weak, and multiple vaccinations may be required to boost immunity and may cause allergic reactions due to antigen recombination.[68] We need to perform long-term monitoring of vaccine safety, especially in elderly people with underlying diseases.[69]

Live Attenuated Vaccine. Live attenuated vaccine refers to the structural change of the toxic subunit after the pathogen has been genetically modified or chemically treated and its toxicity is weakened. However, the activity of the binding subunit remains unchanged, that is, a type of vaccine that

Table 1. Some Vaccine Candidates in Clinical Phase.

Vaccine	Type of Candidate Vaccine	Doses	Schedule	Route	Developers	Clinical Phase
Inactivated vaccine	CoronaVac	2	Day 0 + 14	IM	Sinovac Research and Development Co., Ltd	Phase 4(NCT04756830)
	Inactivated SARS-CoV-2 vaccine (Vero cell)	2	Day 0 + 21	IM	Sinopharm +Wuhan Institute of Biological Products	Phase 3(ChiCTR2000034780)
	BBIBP-CorV	2	Day 0 + 21	IM	Sinopharm + Beijing Institute of Biological Products	Phase 4(NCT04863638)
	SARS-CoV-2 vaccine (vero cells)	2	Day 0 + 28	IM	Institute of Medical Biology + Chinese Academy of Medical Sciences	Phase 3(NCT04659239)
	QazCovid-in®-COVID-19 inactivated vaccine	2	Day 0 + 21	IM	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Phase 3(NCT04691908)
	BBV152	2	Day 0 + 14	IM	Bharat Biotech International Limited	Phase 3(NCT04641481)
Live attenuated virus	COVI-VAC	1-2	Day 0 or Day 0 + 28	IN	Codagenix/Serum Institute of India	Phase 1(NCT04619628)
	MV-014-212	1	Day 0	IN	Meissa Vaccines, Inc	Phase 1(NCT04798001)
Protein subunit	NVX-CoV2373	2	Day 0 + 21	IM	Novavax	Phase 3(NCT04611802)
	Recombinant SARS-CoV-2 vaccine (CHO cell)	2-3	Day 0 + 28 or Day 0 + 28 + 56	IM	Anhui Zhifei Longcom Biopharmaceutical	Phase 2(NCT04466085)
	VAT00002	2	Day 0 + 21	IM	Sanofi Pasteur + GSK	Phase 3(PACTR202011523101903*)
	FINLAY-FR-2 anti-SARS-CoV-2 vaccine	2	Day 0 + 28	IM	Instituto Finlay de Vacunas	Phase 3(RPCEC00000354)
Viral vector	ChAdOx1-S-(AZD1222)	1-2	Day 0 + 28	IM	AstraZeneca + University of Oxford	Phase 4(NCT04760132)
	Recombinant novel coronavirus vaccine	1	Day 0	IM	CanSino Biological Inc/Beijing Institute of Biotechnology	Phase 4(NCT04892459)
	Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S)	2	Day 0 + 21	IM	Gamaleya Research Institute; Health Ministry of the Russian Federation	Phase 3(NCT04530396)
	Ad26.COV2.S	1-2	Day 0 or Day 0 +56	IM	Janssen Pharmaceutical	Phase 4(EUCTR2021-002327-38-NL)
Virus-like particle	CoVLP	2	Day 0 + 21	IM	Medicago Inc	Phase 2/3 (NCT04636697)
	SARS-CoV-2 VLP vaccine	2	Day 0	SC	The Scientific and Technological Research Council of Turkey	Phase 2 (NCT04962893)
DNA-based vaccine	INO-4800	2	Day 0 + 28	ID	Inovio Pharmaceuticals + International Vaccine Institute	Phase 2/3(NCT04642638)
	AG0301-COVID19	2	Day 0 + 14	IM	AnGes + Takara Bio + Osaka University	Phase 2/3(NCT04655625)
	nCov vaccine	3	Day 0 + 28 + 56	ID	Zydus Cadila	Phase 3(CTRI/2020/07/026352)
RNA-based vaccine	mRNA-1273	2	Day 0 + 28	IM	Moderna	Phase 4(NCT04760132)
	BNT162b2	2	Day 0 + 21	IM	Pfizer/BioNTech + Fosun Pharma	Phase 4(NCT04760132)
	CVnCoV vaccine	2	Day 0 + 28	IM	CureVac AG	Phase 3(NCT04674189)
	mRNA-1273.351	3	Day 0 or day 0 + 28 or day 56	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4(EUCTR2021-000930-32)

The original data are as follows, these data are from the World Health Organization (https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines). We used Excel to complete the production of the 2 pictures.

maintains antigenicity. The live attenuated vaccine enters the body to stimulate the body to produce specific memory B cells and memory T cells, which play a role in obtaining long-term or lifetime protection.[70] According to the latest WHO report on SARS-CoV-2 live attenuated vaccines, there are 2 live attenuated vaccines entering clinical trials: COVI-VAC developed by Codagenix and Serum Institute of India and MV-014-212 developed by Meissa Vaccines, Inc Both COVI-VAC and MV-014-212 are used for immunization through nasal drops (Table 1).[3] Currently, they are undergoing phase I clinical trials in London and Kansas, respectively. Live attenuated vaccines are very similar to wild-type pathogens. Compared with inactivated vaccines, they are more immunogenic and have longer action times. However, these vaccines may undergo secondary mutations, revert to wild-type strains, and restore toxicity in the body.[70] Therefore, people with weakened immunity cannot be vaccinated with live attenuated vaccines.

Subunit Vaccine. Subunit vaccines are vaccines made by extracting the special protein structure of bacteria and viruses through chemical decomposition or controlled proteolysis and screening out immunologically active fragments. Compared with other types of vaccines, subunit vaccines eliminate the concerns of incomplete virus inactivation, restoration of virulence, and pre-existing anti-vector immunity and have fewer side effects.[71] It can be used for patients with weakened immune function. However, due to the low immunogenicity of this type of vaccine, it needs to be combined with an adjuvant to exert better immune protection.[72] The production of this vaccine is slow and requires cold chain transfer and storage. At present, 43 protein subunit vaccines have entered different stages of clinical trials.3 The results of phase III trials of the subunit vaccine NVX-CoV2373 developed by Novavax in 33 locations in the UK showed that the efficacy rate of the vaccine was 89.7%; the protection rate against the original strain of COVID-19 was 96.4% and the protection rate against the B.1.1 variant was 86.3%.[73] In South Africa's phase 2a-b clinical trials, the vaccine's protection rate in HIV-infected populations was 60.1%, and the post hoc vaccine efficacy against B.1.351 was 51.0% among HIV-negative participants.[74] The recombinant SARS-CoV-2 vaccine (CHO Cell) jointly developed by the Chinese Academy of Sciences is also undergoing phase III clinical trials. It has been approved for emergency use in China and is the first SAR-CoV-2 recombinant subunit protein vaccine approved for clinical use worldwide.

Viral Vector Vaccine. Viral vector vaccines are vaccines obtained by inserting genes encoding effective pathogens into non-pathogenic viral vector genome species. After vaccination with this type of vaccine, antigen expression can be observed in cells, and the proliferation of the vaccine strain in the body can activate the body's humoral immunity and cellular immunity and have the advantages of high immunogenicity, long action time, and high safety. Viral vector vaccines can be divided into replicating and non-replicating types. It is a specially designed virus that carries the main structural genes of the SARS-CoV-2 vaccine candidate, such as the spike protein.[75]

Most replicating vector vaccines are in the early stages of development (19 species), and only 2 are undergoing clinical trials.3 Among them, DelNS1-2019-nCoV-RBD-OPT1 is based on influenza virus vector developed by University of Hong Kong, Xiamen University, and Beijing Wantai Biological Pharmacy; the safety of the influenza virus carrier platform nasal spraying was evaluated in the phase I experiment.[76] In the phase II trial, the immunogenicity of the nasal spray influenza virus vector COVID-19 vaccine was evaluated according to different immunization procedures.[77]

A non-replicating vector refers to a viral vector that has been genetically modified to cause replication defects. In this state, it can still trigger the required human immune response but cannot replicate in human cells. The results of a phase III clinical trial of non-replicating adenovirus vector vaccine Ad26.COV2.S showed that a single dose of Ad26.COV2.S (5×10^{10} viral particles) has an efficacy of 73.1% and 81.7% for severe COVID-19 patients on 14 and 28 days, respectively, showing high safety.[78] It is currently undergoing phase IV clinical trials. Adenovirus type 5 vector, jointly developed by CanSino Biological Inc and Beijing Institute of Biotechnology, has completed phase II clinical trials and is well tolerated, with only mild and transient fever and other adverse reactions, and induces a rapid immune response. On the 28th day after vaccination, the neutralizing antibody titers of the participants who received 1×10^{11} and 5×10^{10} virus particles against live SARS-CoV-2 were 19.5% and 18.3%, respectively.[79] Currently, Adenovirus type 5 vector is undergoing phase III clinical trials in Russia, Pakistan, Mexico, Chile, and Argentina at the same time[80] and phase IV clinical trials in China.[81]

Virus-Like Particle (VLP). VLP vaccines are composed of hollow particles that refer to one or more structural proteins of a certain virus. They do not contain viral nucleic acids, cannot replicate autonomously, and are the same or similar in shape to real virus particles. Compared with live attenuated vaccines, VLP vaccines do not contain viral nucleic acids and they do not replicate in the host. Therefore, VLP vaccines must be repeatedly immunized. This is because of the loss of the basic genetic components of this type of vaccine that renders it non-infectious and relatively safe. The CoV-Like Particle COVID-19 (CoVLP) vaccine developed by Medicago Inc has entered phase II/III clinical trials (Table 1). According to the results of the phase I test of the vaccine, this plant-derived VLP vaccine has good tolerance and immunogenicity and can exert better immune protection when combined with adjuvants.[82] According to the latest updated list from the WHO (October 3, 2021), 5 VLP vaccines have entered the stage of clinical trials.[3]

Nucleic Acid Vaccine. Nucleic acid vaccines include DNA vaccines and RNA vaccines, which refer to the direct introduction of DNA or RNA encoding a certain antigen

protein into the host cell to synthesize the antigen protein in the host cell body, thereby inducing the host cell's antigen protein to produce an immune response to achieve the purpose of preventing and curing diseases. At present, the design, preparation, and activity detection of nucleic acid vaccines are supported by corresponding mature platforms, which can flexibly and quickly respond to the expression of different infectious pathogens, with relatively little production time and cost, and have the potential for emergency vaccine development and production. As non-viral vectors, these vaccines are safer than viral vectors.[83]

DNA Vaccines. DNA vaccines refer to a type of vaccine that transfers the DNA vector to the nucleus, transcribes it into messenger RNA (mRNA), and finally translates it into the target antigen, thereby activating immune protection in the body.[84] DNA vaccine candidate INO-4800 showed excellent safety and tolerability in phase I clinical trials, and by inducing humoral or cellular immunity, it showed immunogens in 100% (38/38) of the vaccinated subjects.[85] It has entered phase 2/3 clinical trials to further evaluate the immunogenicity and safety of the vaccine and determine the optimal dose of the vaccine.[86] In addition, AG0301-COVID19 and nCov vaccine have also entered phase 2/3 clinical trials (Table 1).[3] Because DNA vaccine production does not involve virus replication and protein expression, the production cycle is short, the cost is low, and the development is faster than their inactivated equivalents. Although DNA vaccines are generally well tolerated, the risk of insertional mutations cannot be ignored.

RNA Vaccines. RNA vaccines generally refer to mRNA vaccines composed of mRNA molecules encoding the selected antigen in vitro. Transcription was not required. The immunogen sequence only needs to be translated to produce the antigen of interest.[87] After the RNA vaccine enters the human cells, it stimulates the synthesis of immunogens by inducing humoral and cellular immune responses.[88] The mRNA-1273 jointly developed by Moderna and National Institute of Allergy and Infectious Diseases has completed phase III clinical trials, and the results showed that the mRNA-1273 vaccine showed 94.1% effectiveness in preventing COVID-19 illness, including severe disease. No safety concerns were identified in addition to transient local and systemic reactions. Except for short-lived local and systemic reactions, serious adverse events are rare.[89] The vaccine has now entered phase IV clinical trials. In addition, BNT162b2, jointly developed by Pfizer/BioNTech and Fosun Pharma, has obtained phase III clinical trial data, and the effectivity rate in preventing COVID-19 is 95%; it has entered phase IV clinical trials.[90] Compared with DNA vaccines, mRNA vaccines do not need to be transported to the nucleus for transcription, which greatly improves the transfection efficiency and eliminates the possibility of random integration into the host DNA to cause carcinogenic events.[91] Although RNA vaccines generally exhibit strong humoral immunity and a high seroconversion rate, the inconsistent cell-mediated immune response generated by them after they enter cells cannot be ignored. More safety tests should be conducted to ensure that there are no unexpected side effects.[83]

At present, there are 123 SARS-CoV-2 vaccines in clinical research, including 17 inactivated vaccines, 2 attenuated vaccines, 43 subunit vaccines, 5 VLP vaccines, 20 viral vector vaccines, 12 DNA vaccines and 21 RNA vaccines, and 3 Antigen Presenting Cell vaccines (Figure 1). The representative vaccines entering the middle and later stages of clinical research are shown in Table 1.[3]

Conclusion

At present, SARS-CoV-2 is still spreading worldwide and has a serious impact on the health, economic development, and social stability of all mankind. Because the development of new drugs takes a long time, medical practitioners and scientific researchers have to scrutinize drugs to treat COVID-19 among the "old drugs." Some of the drugs with high prestige in the early stage have been found to produce serious adverse reactions while demonstrating antiviral properties after clinical trials, and some may even increase mortality. Therefore, more formal and large-sample studies are needed to verify the effectiveness of the drugs. Hence, it is necessary to pay close attention to the adverse effects of the drugs in clinical use. In general, injecting safe and effective vaccines to form herd immunity is currently the most economical and effective means to control the spread of COVID-19. In the past few decades, the development of vaccine technology platforms has expanded the scope and shortened the time from pathogen identification to the deployment of candidate vaccines for clinical trials. Various types of vaccines have mature product candidates entering the clinical trial stage. Many vaccines have been approved for emergency clinical use, but there are still many challenges in the development of vaccines. The first challenge is virus mutation. SARS-CoV-2 variants have been detected in many countries, such as P.1, B.1.1.351, B.1.1.7, and B.1.617.2. The Delta mutant strain includes 3 main subtypes (B1.617.1, B.1.617.2, and B.1.617.3). It was first discovered in India in October 2020. This strain has a stronger immune evasion ability than other mutant viruses, and it spreads faster than other strains.[92] The Delta mutant strain is less sensitive to antibody neutralization.[92-94] Therefore, as the virus mutation develops expeditiously, the effectiveness and timeliness of vaccines are greatly challenged. Second, for many countries and regions, meeting the demand for vaccine production is difficult, and vaccination is obviously unfair among different groups of people. These will promote the spread and mutation of SARS-CoV-2 in some areas. How to address political issues and produce sufficient doses of vaccines are another challenge in controlling the spread of COVID-9. The final breakthrough of COVID-19 still depends on the development of targeted antiviral drugs and vaccines. Countries worldwide

should keep up with the times and strengthen cooperation to develop and produce antiviral drugs and vaccines.

Declaration of Conflicting Interests

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Supplemental Material

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