

The Latest Advances in the Development of Vaccines and Drugs for COVID-19

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Keywords: COVID-19; Vaccine; Drugs; Latest Advances; Inactivated Vaccine; Adenovirus Vaccine; Remdesivir.

Abstract: The outbreak of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 [COVID-19]) has led to the unprecedented public health crisis. With the rapid spread, the hospitalization and death rate were surge worldwide. In response to the COVID-19 pandemic, several vaccine candidates were developed to control the spreading. The mechanism, advantages, and disadvantages of vaccines techniques used in the production of vaccines against COVID-19, including inactivated, nucleic acid-based, adenovirus, and subunit approaches, were discussed. Currently, vaccine candidates based on various platforms have entered phase III trials and have been widely used in many countries. Moreover, there are medications used to eliminate the severe respiratory symptoms of COVID-19, including Remdesivir and Monoclonal Antibodies. However, with the emergence of new variants of COVID-19, such as Delta variants, there is a need for the ongoing development of vaccines and medications to overcome the potential new outbreak of COVID-19 in the future.

1. Introduction

The novel coronavirus SARS-CoV-2 was first identified as the causative agent of a series of atypical respiratory diseases in Wuhan, China [1]. This pathogen, also known as covid-19, was officially declared a pandemic by the World Health Organization on 11 March 2020.

In the context of the Covid-19 pandemic, the increasing number of patients and complications of the disease have imposed a significant healthcare burden on patients, the healthcare system, and the government in terms of patient care costs, hospital beds, beds in ICU wards and special care services [2].

Due to the risk of acquiring the critical disease and the fact that some special needs care requires hospitalization for treatment, patients with COVID-19 occupy a specific percentage of bed space. Taking a study of 138 COVID-19 patients in Wuhan, China, as an example, there were 26.1% of patients received special treatment, with 41.6% receiving non-invasive ventilation and 47.2% receiving invasive ventilation, respectively [3]. In terms of the elderly population, COVID-19 infection would increase the risk of serious illness and death

In reaction to COVID-19, certain health care institutions have a tendency to decrease the availability of certain outpatient services aiming to lower the risk of exposure and provide additional health care resources for pandemic control, but this can delay the treatment of some patients [2]. Thus, a COVID-19 pandemic places a significant strain on the public health care system and has a detrimental effect on the population's health.

On the other hand, the pandemic has had a significant economic impact on the world. The United States GDP plummeted by 11.2% from the fourth quarter of 2019 to the second quarter of 2020 due to the outbreak, the greatest loss since the Great Depression [4]. In the UK, output contracted by a similar magnitude, falling by a record 20.4 per cent from April to June, following a 2.2 per cent decline from

January to March [4]. During the early stages of the outbreak, various physical containment measures, such as mask use, social isolation, quarantine, and isolation [5, 6], indicated national governments' efficient prevention and control of the COVID-19 pandemic. However, when the outbreak spreads, some rigorous health restrictions, such as city closures, can have a considerable detrimental impact on local economies, resulting in the closure of some enterprises and job losses [7, 8]. The unemployment rate in the United States increased from 3.5% in February 2020 (the lowest level in nearly 60 years) to 14.7% in April, the highest level in 80 years [5]. Additionally, such precautions may worsen some social conflicts and have a considerable detrimental impact on local economies since the virus is widespread. Some residents are afflicted and do not cooperate with and take these preventive steps. As a result of severe health policies and physical prevention and control measures, countries' economic development and social livelihoods have become extremely susceptible throughout the pandemic.

Due to the lack of effective medication to alleviate the burden, countries have agreed to rely on vaccines to create herd immunity in response to the increasing disease. Due to the lack of effective drugs to alleviate the pandemic's burden, countries have come to rely on vaccines to acquire herd immunity and halt the spread of epidemics, a case in point being the elimination of smallpox [8]. For patients infected with COVID-19, medications act as a second line of defense against the epidemic, perhaps saving their lives and restoring their health. As a result, efficient vaccines for population prevention and clinical treatment are urgently needed to conclude the epidemic and restore normalcy to society.

The purpose of this review is to provide an overview of the current state of development of various vaccines and therapeutics, including their design principles, manufacturing processes, and the benefits and drawbacks of various vaccine platforms, as well as to propose new approaches and recommendations for future vaccine research. Firstly, we discuss the current stage of development of the COVID-19 vaccine, covering vaccine design concepts, manufacturing techniques, and the advantages and disadvantages of various vaccine platforms. Second, we assess the safety and efficacy of treatment approaches currently under investigation. Finally, we summarize the characteristics of the vaccinations and medications, providing some pharmacological recommendations for further COVID-19 prevention and control.

2. Vaccine

2.1 Inactivated Vaccine

Inactivated or killed vaccines are the types of vaccine containing killed pathogen of interest that remain the immunogenic structure, which triggered the immune response [9]. Currently, inactivated vaccines are primarily developed against viruses, including polio and influenza, also bacteria such as pertussis and cholera [9, 10]. To ensure the safety and efficacy of vaccines, the inactivation process that destroying the pathogens' ability to replicate while maintaining the integrity of pathogens' antigenic structure is crucial in the production [11]. Historically, insufficient inactivation had caused an adverse event. For instance, 380,000 doses of poliovirus vaccines that failed to inactivate the replication of poliovirus were administered to healthy children, who eventually caused 40,000 to contract abortive poliomyelitis, several cases of permanently paralyzed and died in 1955 [12]. Today, several methods like heat, chemicals or radiation are used to inactivate the pathogen in the production [13]. Chemicals like Formaldehyde or β -propiolactone (BPL) are widely used as inactivating agents for vaccine propose that ensure the antigenic structure while destroying the viral ability to replicate by inflicts the irreversible modification [12, 14]. Besides, new inactivation techniques that aim to reduce the damage of pathogenic antigen structure are developed, such as hydrogen peroxide treatment and gamma irradiation [15].

After administration, inactivated virus elicits the immune system, MHC-II pathway would be activated to generate helper T cells and initiate humoral immune response [15]. In addition, since cytotoxic T cell immunity is usually generated by live viral infection via the MHC-I pathway, inactivated vaccines have limited cellular immune response [11, 15]. In comparison, inactivated

vaccines are more stable and safer than live vaccines since the killed viruses cannot mutate back to the pathogenic form[11]. Moreover, inactivated vaccines are easy to store since they are usually transported in a freeze-dried form and do not require refrigeration, making them cheaper and more accessible to developing countries [13]. In addition, a study has demonstrated that inactivated vaccines are capable of remaining antigenicity under the change of temperature simulated by the kinetic-based model [16]. However, it is recommended to store at $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ for the freeze-dried vaccine for long-term stability in the shelf life [16]. The disadvantage of inactivated vaccines includes the weaker immune response than live vaccines, and thus they require multiple booster doses to maintain the protective immunity level[15]. Besides, many unrelated antigenic structures present in the microbes could lead to allergic reactions [11].

In response to the pandemic of covid-19, several inactivated vaccine candidates are in pre-clinical and clinical evaluation. BBIBP-CorV is an inactivated vaccine candidate developed by Sinopharm's Beijing Institute of Biological Products [17]. It has completed phase III trials in Argentina, Bahrain, Egypt, Morocco, Pakistan, Peru, and the United Arab Emirates (UAE) [18]. Moreover, phase III trials in UAE have shown a 78.1% effectiveness of BBIBP-CorV against symptomatic cases and 100% effectiveness against severe cases (40 382 participants) [18].

2.2 mRNA Vaccine

mRNA vaccines are a type of nucleic acid vaccine[19]. In recent years, the mRNA vaccine has been studied as effective in the fields of cancer immunotherapy and treatment for infectious diseases [20]. In addition, many countries have carried out clinical trials for mRNA vaccines against viral diseases such as Zika, Ebola and influenza [21, 22]. mRNA vaccines contain antigen-coding mRNA that simulates the natural infection by initiating protein synthesis once it enters the cell's cytosol [19]. Subsequently, these proteins could act as extracellular secreted proteins to stimulate helper T cell and B cell via the MHC-II pathway to induce humoral response [13]. Also, inducing a cell-mediated immune response by presented to cytotoxic T cells via intracellular MHC-I pathway [23]. Besides, mRNA is the main pathogen-associated molecular pattern (PAMPS) of RNA virus which could induce an innate immune response after being recognized by its pattern recognition receptors (PRRs) [23, 24]. Also, the recognition allows the maturation of dendritic cells (DCs) and enhance the following adaptive response [23].

To overcome the challenge of crossing the cell membrane, several methods, including injecting naked mRNA, conjugating with lipid-based carriers, polymers, or peptides, and transfection of dendritic cells, are used in the design [25]. Although injecting naked mRNA in the conventional mRNAs and self-amplifying forms could induce an immune response, factors like insufficient cell uptake or extracellular exonucleases present in the target tissue may limit mRNA delivery [23]. Besides, the most prevalent delivery tool is Liposomes or lipid nanoparticles (LNPs), and LNPs mediated mRNA vaccines have been produced against various pathogens such as Zika and influenza[23, 26]. The components of LNPs, including the precise molar ratios of phospholipids, cationic-ionizable amino lipids and poly(ethylene) glycol (PEG) lipids, has shown the ability to enhance the endosomal escape and stability of vaccine both in vivo and vitro [26]. Facing the pandemic of covid-19, Bnt162 vaccines are mRNA- based that developed by companies including BioNTech (Germany), Fosun Pharma (Shanghai, China), and Pfizer (Canada) [13]. Three Bnt162 vaccines utilized the LNP technique, including BNT162a1, BNT162b1 and BNT162b2[13]. Among them, BNT162b2 is widely used worldwide, with Israel, the United Kingdom and the USA having a high administration rate [27].

Compared to traditional techniques such as an inactivated vaccine, the mRNA technique is more targeted because it would only express the specific antigen to induce the direct immune response [23]. In addition, this characteristic also eliminates the risk of allergic reactions caused by other antigenic features in the inactivated vaccine [28]. Moreover, mRNA vaccine is produced via in vitro cell-free transcription reaction, ensuring safety by minimising the probability of cell-derived impurities and viral contaminants [23]. Besides, mRNA vaccine could result in a stronger protective immunity level than inactivated vaccine. It could induce additional cell-mediated immune response via MHC-I

pathway cytotoxic T cell response [19]. Besides, mRNA vaccines are more effective than DNA vaccines since they do not require entering the nucleus to initiate the expression [23]. Moreover, entering the nucleus has reduced the chance of random genome integration [23, 26]. However, due to the single-stranded structure feature of RNA, mRNA is fragile and highly demanded on and uninterrupted refrigeration in storage and transport [29]. Currently, several methods have been developed to enhance the stability of mRNA. In particular, the liquid or lyophilized version mRNA vaccines have shown longer stability in storage [25].

2.3 DNA Vaccine

DNA vaccines are also nucleic acid vaccines that contain antigen-encoding plasmid DNA [19]. Previously from the mice experiment, DNA vaccines were effective in inducing a cellular response. Notably, Cytolytic T Lymphocytes against an influenza strain distinct from the strain that encoded antigen derived [30, 31]. After administration of DNA vaccines, plasmid DNA enters the cell's nucleus. It translates new peptides, which are presented to the naive T cell in the lymph node via MHC-I and MHC-II restricted pathway and following with the activation of the T and B lymphocytes [31, 32]. In addition, new peptides could also induce humoral immune responses [11]. There are three ways to elicit the MHC-I restricted Cytolytic T Lymphocytes via injecting plasmid DNA including mediating by transfected muscle cells, transfected professional Antigen-presenting cells, or cross priming [32]. When DNA vaccines produce Cytolytic T Lymphocyte since it could a higher antibody level compared to other routes such as subcutaneous [32, 33].

In comparison to mRNA vaccines, DNA vaccines require a plasmid vector that is normally derived from bacteria with the insertion of heterologous genes (transgenes) under the control of a eukaryotic promoter to ensure protein expression in the host body [11]. DNA vaccines are highly specific with the antigen inserted into the plasmid, and the expression of immunizing antigen is the same as the natural route [19, 32]. Therefore, inducing direct cellular and humoral immune responses that are stronger than inactivated vaccines [13]. Moreover, DNA vaccines have shown potential chronic viral infections since they allow the continuous expression of antigen exposed to the antigen-presenting cells [19]. Besides, multiple variants of antigen could insert in a single array of the plasmid, DNA vaccines could against multiple strains of the virus in a single dose [32]. This process does not require setting up the recombinant proteins for each expressed antigen, thus allow rapid manufacture and lower cost compared to recombinant vaccines [32]. Besides, plasmid DNA is temperature-stable, allowing easier storage and transport than mRNA vaccines [19]. However, there are several concerns relating to the safety of DNA vaccines related to the immunizing DNA, which has the potential to elicit anti-DNA antibodies and the oncogenes [32]. Facing the COVID-19 pandemic, several DNA vaccines such as INO-4800 and Plasmid DNA oral vaccine are currently in phase I trial [33].

2.4 Adenovirus Vaccine

Virus vector vaccines make use of a modified virus as a vector capable of transmitting antigens from one infectious agent to another. After the vaccination, the cell in the human body is then encouraged to produce a specific harmless spike protein found on the surface of the infectious pathogen. When the immune system recognizes this protein, it will produce antibodies and activates other immune cells to combat it. This process generates memory cells that act as a defense against future infections.

Numerous viruses have been used as vectors, including Alphavirus, Rhabdovirus, and Measles virus [34]. Nonetheless, there are still some concerns about the efficacy and safety of certain virus-vectored vaccinations. In a clinical phase I investigation, it was discovered that an MV vector vaccine administered to a self-amplifying RNA virus elicited a poorer immune response in immunized volunteers than in COVID-19 patients [34]. Another example is the replication-competent VSV SARS-CoV-2 vaccine candidate V590, which demonstrated that while volunteers tolerated the vaccination well, the immune response was still weaker than in COVID-19 patients [34].

Comparatively, the adenoviral vector-based vaccine can promote innate immune responses and antigen expression in various ways, promoting humoral and cell-mediated immune responses to

vaccination antigens [35]. On the other hand, because Adenovirus (Ads) are epithelial tending, they can be employed to control mucosal and systemic immunity [35]. More precisely, when Ads are used to construct vaccines, most vectors are altered by deleting the E1 or E1/E3 genes, which increases the ability to integrate exogenous antigens and decreases viral replication [36, 37]. Thus, Ads are attractive vectors for vaccine creation due to their potent infectivity, broad host cell tropism and great gene expression potential [20, 38].

However, there are several disadvantages related to the adenovirus vector vaccine. Firstly, due to early gene deletions, adenoviral vector vaccines may not express late coat proteins *in vivo*, and consequently, replication-deficient adenoviruses may require larger dosages than live RCA vaccines [39]. Finally, there is the possibility of pre-existing immunity against adenovirus [38], as Ads are a frequent pathogenic virus type in humans, and there is a risk of exposure in daily life. Therefore, persons who have been previously infected with adenovirus are more immune to adenovirus, which can diminish the effectiveness of vaccine immunity.

To address the pre-existing immunity, researchers have switched the target adenovirus vectors to rare human adenoviruses (such as HAd6, HAd11 and HAd19a) and other non-human adenoviruses [40], including chimpanzee Ad (chAd), porcine Ad (PAd), Canine Ad (CAAd), and others. In addition to discovering additional adenoviral vectors, approaches such as encapsulating Ad vectors in microparticles, encapsulating vectors in polyethylene glycol, and modifying Ad capsid proteins [40] can be utilized to physically circumvent pre-existing vector immunity without compromising Ad vector activity.

In response to the global COVID-19 epidemic, several adenovirus-based vaccines have been put into use.

Sputnik V, a COVID-19 vaccination based on two adenovirus vectors (rAd26 and rAd5) produced by the Gamaleya National Center for Epidemiology and Microbiology, was launched in Russia for the first time on 11 August 2020 [41-43]. Notably, to date, only Sputnik V has designed vaccines using two different serotypes of adenoviral vectors [41, 44], administered as the first and second dose to induce an immune response *in vivo*, respectively. In an interim report of a randomized, double-blind, placebo-controlled phase 3 trial, two doses of Sputnik V were shown to be 91.6% effective against COVID-19 and 100% effective against severe COVID-19 [45].

The ChAdOx1 nCOVID-19 vaccine, commonly known as the AZ vaccine, was developed in partnership with AstraZeneca Pharmaceuticals and the University of Oxford in the United Kingdom. The AZ vaccine is a replication-deficient simian adenovirus vector containing a full-length code-optimized sequence encoding the SARS-CoV-2 spike protein and a tissue fibrinogen activator (tPA) guide sequence [46]. Based on a summary of four randomized trials, the researchers reported efficacy of 66.7% for the AZ vaccine beyond 14 days after the second dose [47]. For the COVID-19 variant, the AZ vaccine produced lower titres of neutralizing antibodies after vaccination. However, efficacy was observed clinically in 70.4% of symptomatic COVID-19 [48], implying that the vaccine still provides some protection against infection with the new variant. Regarding post-vaccination adverse effects, many incidences of aberrant thrombotic events and thrombocytopenia have been documented following AZ vaccination [49]. Although these adverse effects are uncommon, they highlight the importance of paying attention to their safety.

Janssen COVID-19 vaccine, developed by Johnson & Johnson in the USA and Janssen Vaccines in Leiden, Netherlands, is an adenovirus-based design of the COVID-19 vaccine [50]. The Janssen COVID-19 vaccine consists of a recombinant, replication-free human adenovirus type 26 vector, requiring only one dose and not cryopreservation [50]. In terms of efficacy, interim results from an international phase 3 clinical trial showed that the efficacy of the Janssen COVID-19 vaccine against symptomatic, laboratory-confirmed COVID-19 was 66.3% at 14 days post-vaccination, compared to 65.5% [50, 51]. Concerning adverse responses, a number of cases of Cerebral Venous Sinus Thrombosis (CVST) have been documented in vaccinated people, as have cases that did not present with CVST but were consistent with thrombocytopenia syndrome (TTS) [52]. Although insufficient evidence suggests a connection between the disease and vaccination, this serious adverse reaction to vaccination merits clinician care and assessment of potential health consequences.

There is also a recombinant adenovirus type 5 vector vaccine, Ad5-nCoV vaccine, that lacks the E1 and E3 genes, developed by the Institute of Military Medicine of the Chinese People's Liberation Army Academy of Military Sciences and CanSino Biologicals [46]. Ad5-nCoV vaccine is tolerated up to 28 days post-vaccination, and the humoral response to SARS-CoV-2 in healthy adults peaks at day 28 post-vaccination [53]. Evidence from their phase 2 study suggests that the candidate Ad5 vector COVID-19 vaccine has a good safety profile, with only minor, transient adverse events associated with vaccination and no serious adverse events [54]. Its phase 3 clinical trial of an Ad5 vector vaccine is underway in Pakistan (NCT04526990).

2.5 Subunit Vaccine

Subunit vaccines frequently use purified antigens, such as toxoid, cell fragments, or surface molecules [55] rather than employing complete microorganisms as the principal immunologically active component. Subunit vaccines that use proteins as antigens, such as methyl protein vaccines, frequently elicit a T cell-dependent adaptive immunological response[55]. This protein does not reproduce independently in the human body and thus poses no danger of pathogenicity [56]. It has considerable advantages in terms of vaccine safety and side effect minimization[57].

In addition, subunit vaccines have the advantages of targeting specific, well-defined neutralizing epitopes with higher immunogenicity [57]. On the other hand, the production of subunit vaccines usually requires the purification of immunogens from many pathogenic microorganisms, which is nevertheless dangerous and expensive compared to other active vaccines [56].

Researchers have used recombinant technology to generate subunit protein vaccines in heterologous hosts to overcome the challenges of immunogen purification. This method entails inserting an antigen gene from a target virus or bacterium into another vector to form a recombinant pathogen, then extracting the antigen as an essential component of the vaccine from the vector. This manufacturing technique is not only cost-effective, but it also investigates the prospect of using bacteria and viruses as vectors to transport protein subunits [56], opening up a wider range of possibilities for future vaccine development.

Recombination strategies that have been used to simplify protein subunit vaccines include the following: *ab initio* synthesis of gene fragments to produce only immunodominant subfragments of the target immunogen, use of fusion proteins to enhance immunogenicity, protein engineering to improve solubility and stability, and direct incorporation of recombinant subunit immunogens into vaccine adjuvants [58]. The proteins used to design SARS-CoV subunit vaccines include, full-length S proteins, receptor binding domains (RBDs), non-RBD S protein fragments and non-S structure-based proteins [37], and the development of S proteins and their fragments (e.g. RBDs) is a major target for subunit vaccines against both highly pathogenic human CoVs, as they are responsible for binding viral particles to receptors on host cells and for inducing the production of more effective subunit vaccines. Similar areas have been shown to stimulate the formation of more effective neutralizing antibodies[59], suggesting that they could be used to build subunit vaccines against covid-19.

In response to the global pandemic of COVID-19, researchers have developed a number of protein subunit vaccines, including the already licensed ZF2001, Sovereign II, and a number of vaccine candidates in clinical trials such as Novavax Pharmaceuticals NVX-CoV2373 in the USA and CIGB-66 in Abudala, Cuba [60].

The ZF2001 protein subunit vaccine is a recombinant dimer receptor binding domain vaccine created by Anhui Zhifei Longcom and the Chinese Academy of Sciences' Institute of Microbiology. The researchers changed the RBD structure into a tandem repeating single chain dimer (sc-dimer) form without inserting exogenous sequences, in contrast to the usual RBD vaccination [61]. This modification significantly increased immunogenicity against SARS-CoV-2 infection and allowed production in high yields (g/L levels) in the industry-standard Chinese hamster ovary (CHO) cell system [61]. In Phase 1 and Phase 2 trials of ZF2001, researchers found the vaccine to be well tolerated at 25 or 50 µg doses and in two- or three-dose regimens [62]. ZF2001 is currently being tested in phase 3 clinical studies with 29,000 people in five countries, and it has been approved for use in China and

Uzbekistan. Notably, the neutralisation titres of ZF2001 are substantially unchanged but slightly reduced against several forms of the current SARS-CoV-2, indicating that these variants are not immune to the entire virus or RBD [63].

FINLAY-FR-2 is a conjugate vaccine produced by the Finlay Institute from Cuban. This vaccine consisted of the receptor binding domain of the SARS-CoV-2 spike protein conjugated chemically to tetanus toxoid [64]. According to a press release from the Cuban biopharmaceutical company BioCubaFarma, its secondary injection of Soberana 2 vaccine in combination with a booster shot dubbed Soberana Plus demonstrated 91.2% efficacy against coronavirus in late-stage clinical studies.

Covovax is a COVID-19 subunit vaccine being developed by Novavax in collaboration with the Coalition for Epidemic Preparedness Innovations (CEPI). The vaccine contains Matrix-M1 adjuvant and a recombinant SARS-CoV-2 (rSARS-CoV-2) nanoparticle vaccine derived from the full-length (i.e., including the transmembrane structural domain) wild-type SARS-CoV-2 spike-in glycoprotein and expressed in Sf9 insect cell lines [65-67]. It can also generate multifunctional CD4+ T cell responses to IFN-, IL-2, and TNF- α [68]. It promotes viral attachment to the human angiotensin-converting enzyme 2 (hACE2) receptor on host cells for entrance [66]. A two-dose regimen of the Covovax vaccine administered 21 days apart was found to be safe and effective in 89.7% of symptomatic Covid-19 caused by both B.1.1.7 and non-B.1.1.7 variants, according to its phase 3 report [65].

3. Medicine

Although vaccines have been shown to be more effective at preventing the new coronavirus, the more fundamental solution focuses on treatment, which is critical medication. Due to the new coronavirus's continued and widespread prevalence, patients and medical communities worldwide are confronted with significant medical challenges and hazards. Now, there are no specific medications that are effective against COVID-19. Scientists are continually discovering new medications as effective treatments while also repurposing current ones.

3.1 Remdesivir

3.1.1 Basic Information

Remdesivir is a novel class of antiviral nucleoside compounds created by Gilead Sciences. It is antiviral on a broad spectrum, including Ebola virus (EBOV) and respiratory disease MERS-CoV, SARS-CoV and SARS-CoV-2 [69]. The FDA approved the use of remdesivir in severe hospitalized COVID-19 patients under an emergency use authorization (EUA) on May 1st, 2020. Afterwards, on August 28th, 2020, the letter was reissued with revisions to expand the authorized remdesivir administration to the non-severe COVID-19 patients. Finally, on October 22, 2020, remdesivir became the first drug with the FDA approval for the treatment of COVID-19. Following the FDA's approval of Remdesivir for the treatment of COVID-19, the World Health Organization's (WHO) SOLIDARITY treatment trial, which enrolled approximately 12,000 patients in 500 hospitals across more than 30 countries, demonstrated that Remdesivir has a broad antiviral spectrum in vitro, including EBOV, Marburg infection, respiratory syncytial infection (RSV), HCV, and some paramyxoviruses [70-72]. To be more specific, it illustrated movement against MERS-CoV and SARS-CoV [73, 74]. Favorable in vitro results bolstered assist assessment in EBOV-infected macaques, where remdesivir inhibited viral proliferation and improved survival, clinical manifestations of the disease, and pathophysiological blood indicators. After its disclosure, remdesivir was managed beneath compassionate utilize to patients with ebolavirus infection (EVD) but halted after and between times investigation of the primary randomized controlled clinical trial (RCT) appeared an inadequacy of remdesivir to medications with monoclonal antibodies (Mab114 and REGN-EB3). The experiment evaluated the efficacy of a variety of investigational medicines in the treatment of EVD. Following the intervals investigation, the remdesivir arm was discontinued for the remainder of the trial [75, 76].

3.1.2 Drug Performance and Effectiveness Controversy

The therapeutic effect of remdesivir on COVID-19 is still controversial. It was suggested that Remdesivir against COVID-19 and other viral diseases written by Malin JJ, Suárez I, Priesner V, Fätkenheuer G and Remdesivir J. that "because there is no placebo control in the study, it is impossible to conclude the efficacy of EVD. In contrast, the data of placebo-controlled trials showed that it was beneficial for patients with COVID-19. Remdesivir shortens the recovery time of hospitalized patients requiring oxygen supplements and may have a positive impact on mortality outcomes with good safety." [76]. This means that there is a major breakthrough in the fight against COVID-19, but at the same time, there are problems that approval of this drug is not enough to solve the public health problems caused by the continuing pandemic of COVID-19. This requires further scientific exploration to evaluate the full potential of nucleoside analogues as a treatment or prevention of viral respiratory infection and to develop effective antiviral drugs for oral bioavailability.

The experimental data and analysis clearly presented that the effect of remdesivir on covid-19 still lacks more favorable data support, and there are still many influencing factors that have not been fully studied. (Due to limited clinical experience with remdesivir, robust clinical data evaluating the adverse drug reactions and possible drug-drug interactions is limited.) Therefore, the effect of this drug is controversial. The drug is not banned in China, and its use in clinical treatment can be seen

Within patients with moderate COVID-19, there was no statistically significant difference in the clinical status of patients who were randomized to receive a 10-day course of remdesivir at 11 days after treatment initiation compared to standard care. Compared to standard care, there was a statistically significant difference in the clinical status of patients randomized to a 5-day course of remdesivir. However, the clinical significance of this difference was not established [77].

3.2 Monoclonal Antibodies

3.2.1 Basic Information

In addition to remdesivir, monoclonal antibodies are also one of the drugs currently receiving a lot of attention. The development of monoclonal antibody drugs began in 1975. 1986, the first anti-transplantation immune rejection of murine monoclonal antibody muromonab-CD3 (OKT3), approved by the FDA market, but due to technical reasons, produced serious adverse reactions

With the development of recombinant DNA technology, the generation of fully human monoclonal antibodies became possible, and the first fully human antibody, adalimumab, was marketed in 2002.

Monoclonal antibodies have a wide range of therapeutic promise in medicine and are used to treat various diseases such as oncology, autoimmune diseases, infectious diseases and transplant rejection. Adalimumab is used to alleviate moderate to severe rheumatoid arthritis (RA) with structural damage that has failed to respond to anti-rheumatic drug (DMARD) therapy.

Among the various potential therapeutic interventions, monoclonal antibodies (mAbs) represent one of the most promising classes of molecules due to their longstanding track record of safety in humans, their exceptional specificity to the virus (which minimizes the risk of off-target effects), and their ability to coordinate the immune defense in the fight against infection. Technological advances over the past two decades in sequencing and single cell screening, as well as manufacturing, have positioned mAbs to quickly respond to the COVID-19 pandemic. In this review, first, we highlighted important pathophysiology associated with SARS-CoV-2, protective functions of antibodies in mucus, and some of the leading mAb under development for SARS-CoV-2. [78]

3.2.2 Challenges

Although this approach has shown promising results, large-scale production of monoclonal antibodies is costly, labor- and resource-intensive, and time-consuming, especially for emerging pathogens. Zhejiang College group detailed the useful characteristics of 11 viral segregates from COVID-19 patients, all with at slightest one transformation [79]. This concept demonstrates how alterations happening within the SARS-CoV-2 genome can affect viral pathogenicity. For instance,

the infectivity of SARS-CoV-2 is amplified when the aspartic acid at position 614 of the S protein in the viral genetic material becomes glycine (D614G) [80].

Overall, there are significant challenges in demonstrating the benefits of monoclonal antibodies in clinical trials. Because most people with the early infection will recover, the clinical goals needed to demonstrate benefit relative to placebo are not easily achieved. Similarly, it may be difficult to demonstrate a role for patients with more severe diseases, where inflammation and clotting disorders may be more important than viral replication. As the COVID-19 pandemic develops in the United States and worldwide, the clinical research infrastructure will need the flexibility to deliver short-term monoclonal antibodies to populations or facilities at high risk of infection.

Another potential challenge is the ability to produce sufficient monoclonal antibody products, as noted above.

3.3 Other Medications

As no specific medicine has been developed so far, the principle of treatment is still based on symptomatic treatment.

4. Conclusion

Vaccines based on various platforms have entered phase III clinical trials and have been licensed for community use. Still, their efficacy and safety continue to warrant investigation, particularly given the present predominance of certain variant strains. Certain new SARS-CoV-2 variants are more infectious and immunological evasive and have the capacity to overcome the original immune defenses. There is an increasing risk of new variant infection following vaccine completion. Additionally, because vaccinations are expensive and have poor production, it is difficult to cover a substantial proportion of the population in a short period. In this context, the next critical part of vaccine development is addressing the predominance of COVID-19 variant strains to boost human immunity and lower infection risk. Whether it is the immune effect of vaccines or the therapeutic effect of drugs, the treatment of COVID-19 is still breaking through and improving, and there are still many challenges to be faced. The high cost of the vaccine, the complexity of the production process, and the demanding level of technology required are the direct reasons for the low yield of the vaccine. The emergence of mutated strains nowadays also raises doubts about the effectiveness of vaccines. In terms of drugs, we are now eager to develop specific drugs for COVID-19 that can treat the disease more directly and effectively. It still requires scientific exploration and continuous experiments to find the best way to relieve and cure coronavirus infections.

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