Chapter

Therapeutic Interventions for COVID-19

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Abstract

SARS-CoV-2, a novel coronavirus, is currently represented a major public health concern. The high transmission rate of this virus increases the mortality rate worldwide. To date, significant efforts and restricted regulations were performed around the world to control this crisis effectively, but unfortunately, there is no specific and successful therapy for COVID-19. Many approaches have been repurposed for SARS-CoV-2 treatment such as antivirals and anti-inflammatories. Furthermore, antibody therapies are one of the main and important approaches of SARS-CoV-2 infection treatment. In recent trials, various immunotherapeutic interventions such as convalescent plasma therapy and monoclonal antibodies, as well as immunomodulatory agents are being proposed. However, the development of a vaccine that provides durable protective immunity will be the most effective therapy for controlling possible epidemics of this virus. The current review summarized all the proposed therapeutic approaches together with information on their safety and efficacy in treating COVID-19, as well as the vaccine candidates. The provided comprehensive information regarding the applied therapeutic strategies against COVID-19 might help the scientific community in any progress toward the treatment of COVID-19 infection.

Keywords: SARS-CoV-2-immune response, vaccine, therapeutic interventions, antiviral drugs, immunity

1. Introduction

To date (August 2022), over 600,114,721 have been detected worldwide as positive COVID-19 cases with more than ~6,470,118 deaths in 228 countries [1]. In 2002–2003, the globe was first exposed to coronavirus through severe acute respiratory syndrome (SARS), and in 2011, it was first exposed to middle east respiratory syndrome (MERS) [2]. Then, toward the end of 2019, the current coronavirus (SARS-CoV-2) COVID-19 emerged in Wuhan, China [3]. COVID-19 is a contagious respiratory disease caused by the coronavirus 2 (SARS-CoV-2) that causes severe acute respiratory syndrome [4]. The virus is mostly transmitted by droplets and direct contact [5].

The disease's clinical symptoms are diverse, ranging from asymptomatic to severe illness, up to 20% of symptomatic individuals facing a high risk of mortality [6].

Critical illnesses include acute respiratory distress syndrome, septic shock, coagulopathies, refractory metabolic acidosis, and multi-organ dysfunction [7, 8]. Worse clinical outcomes have been linked to older age, male sex, and comorbidities [9]. To date, the factors associated with the disease severity of COVID-19 have not been clearly identified. It was demonstrated that both viral and host factors are implicated in treatment outcomes [10]. However, the pathogenesis of COVID-19 is closely associated with host factors, particularly cellular immunity in patients [11].

2. Genomics of SARS-CoV-2

SARS-CoV-2, such as other coronaviruses, is an enveloped, single-stranded, and positive-sense RNA virus with a non-segmented genome of 30 kb (**Figure 1**) [12]. The viral genome encodes 16 nonstructural proteins (NSPs) needed for pathogenesis and virus replication, four structural proteins including envelope (E), membrane (M), nucleocapsid (N), and spike (S) glycoproteins, all of which are important for virus genotyping and therapeutic strategies, and nine other accessory genes (**Figure 1**) [13]. There is a huge similarity between the first published SARS-CoV-2 genome and SARS-CoV, especially in the spike protein revealing the high transmission rate from human to human [14].

There is a huge data rising on the viral genomics and its transcriptomic level involving the virus-host protein interactions. These data are highly needed for the drug discovery, vaccine development, and public health strategies.

The ACE2 gene expresses the angiotensin-converting enzyme-2 in several human cells. Several studies reported that the spike protein has a 10–20 times higher affinity for binding to the ACE2 receptor than SARS-CoV, which explains the SARS-CoV-2's higher transmission rate [15].

The host ACE2 receptor is located in abundance on epithelial cells that line the alveoli and bronchioles of the lungs, as well as endothelial cells and myocytes that line the pulmonary blood vessels [16]. The ACE2 gene is also expressed in the small intestine, which could clarify the gastrointestinal symptoms appeared with the viral infection [17].

The spike (S) protein is thought to be the key protein involved in viral entry into target cells [18].

The host transmembrane serine protease 2 (TMPRSS2) "primes" the S protein by cleaving it into two active domains: S1 and S2. The S1 domain can then engage with the ACE2 receptor, while the S2 subunit helps the virus fuse with the target cell, facilitating the viral entry [18]. Blocking the viral entry pathway through ACE2 and TMPRSS2 represents one of the therapeutic strategies that can prevent the virus attachment with the host cell.

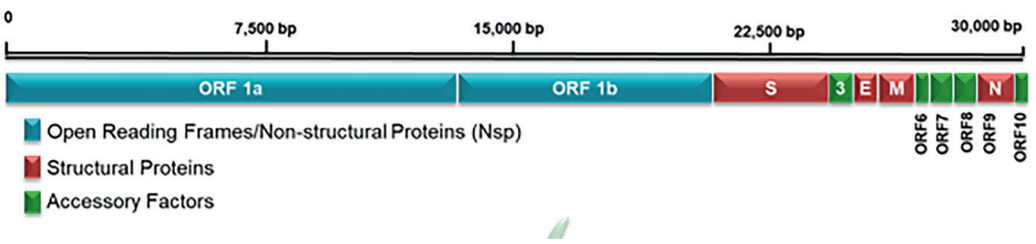

Figure 1.
(a) Illustrative representation of the SARS-CoV-2 genome presenting the location of the structural, nonstructural, and accessory proteins. The figure is created by BioRender program.

3. Mechanism of immune systems in the human body against COVID-19

Both innate and adaptive immunity are required to fight against SARS-CoV-2. The innate immunity includes monocytes, dendritic cells (DCs), granulocytes, and natural killer (NK) cells, while the adaptive immune system includes B and T cells. Severe patients are characterized by the following: Lymphopenia with a drop in CD4+ and CD8+ T cells, lymphocyte activation and dysfunction, an increase in circulating neutrophils with the appearance of circulating neutrophil precursors, and loss of the monocytes function and impaired the function of NK and DCs [19, 20].

Inflammatory cytokine levels are elevated, particularly interleukin-6 and IL-1 [21]. On the other hand, the interferon response is delayed, while the levels of immunoglobulin G (IgG) and total antibodies are increased [22, 23]. Immune disorders, which are characterized by an elevated inflammatory profile, are frequent in severe infections and sepsis and finally ends up with immunosuppression. For severe COVID-19, a similar method has been proposed [24, 25]. Owing to the absence of the effective antiviral therapy, the immunological response of the body is a critical element in disease severity and clinical outcome. Thus, clearer picture regarding the cellular immune response through the disease progression is highly required for establishing diagnostic indicators and potential therapeutic strategies against COVID-19.

During the SARS-CoV-2 infection, the cellular and molecular cascades orchestrate the activation, recruitment, and resolution of the antiviral immune response. These cascades fine-tune the balance between viral eradication and immune injury. Multiple innate immune identification pathways fight viruses during infection [26]. Within the first few hours, The innate immune system inhibits virus replication by releasing type I/III interferon [27], pro-inflammatory cytokines (including: IL-1, IL-6, and IL-18), and chemokines (including: CCL2 and CCL7 and then adaptive immunity is activated.)

Following the SARS-CoV-2 infection, T cells are highly involved in the viral clearance process, whereas humoral immune response is mainly involved in the production of neutralizing antibodies to block the viral entry. T lymphocytes directly attack the infected cells, and they stimulate the cytokines production to boost the immune response of T lymphocytes and other immunocompetent cells such as B lymphocytes and macrophages. To defend the host from nonspecific injury, the body then diminishes innate immunity [28].

Innate immune cells (DCs and macrophages) and adaptive mediated- cell types (regulatory B cells and T cells) establish an inflammation repair status when viruses have been eradicated.

4. Vaccine development

To monitor the global SARS-CoV-2 pandemic, a vaccine development becomes mandatory. The development of a vaccine that provides durable protective immunity will be the most effective therapy for controlling possible epidemics of this virus. The ideal vaccine should be safe, effective, durable, and accessible to a large population. Moreover, the virus genome has the ability to mutate so that it is necessary to develop a safe and pangenotypic vaccine to be effective toward any SARS-CoV-2 variants.

The majority of vaccine approaches have the ability to generate neutralizing antibodies against specific proteins, particularly the spike protein. Some adjuvant components can be added to the vaccine to stimulate the immunity and reduce the amount of antigen required for each vaccine dose. As of August 2022, 222 vaccine candidates

were included in the international clinical phase, and 774 vaccines were included in the preclinical phase [29]. The vaccine platforms include viral vector nonreplicating vaccines, protein subunits, DNA-based vaccines, RNA-based vaccines, viral vector replicating vaccines, virus such as particle, live attenuated virus, and bacterial antigen spore expression vector (**Figure 2**) [31, 32].

Several years of research are needed to develop a safe vaccine that can be used in clinical trials. Vaccine evaluation is usually performed in phases after development [33]. Preclinical testing on cell lines and animal models is required in Phase I, followed by testing on a small number of people to affirm immune system stimulation [33]. Phase II involves examining hundreds of people, including children and the elderly, to ensure safety in a new cohort [34]. Finally, thousands of people will be tested in the Phase III trial. During this phases, scientists administer vaccines to volunteers and monitor how many of the placebo and vaccine groups become infected. Typically, these trials are used to monitor if the vaccine provides protection against the virus and detect the absence/presence of adverse effects. Phase III trials are sufficiently large to report efficacy rates, as well as rare side effects.

Of all the vaccines in clinical trials with the SARS-CoV-2 variant, the RNA vaccine appears to be more effective than other vaccines because it requires the development of a large number of vaccines with a limited budget. Although clinical trials are harmless, immune responses elicited by antigens stimulated by RNA vaccines are fewer than those found in animal models [35, 36]. Similar to RNA - based vaccines, DNA-based vaccines are easier and cheaper to provide better safety, efficacy, and long-term immune response. Nevertheless, it has not been approved for human use because it has not elicited a strong enough immune response to be safe. Vaccines based on highly immunogenic vectors, on the other hand, have been shown to induce effective immune responses.

The vaccines that have been registered in phase III clinical trial include vector vaccines (University of Oxford/AstraZeneca, Janssen Pharmaceutical Companies and Gamaleya National Research Centre), mRNA-based vaccines (Pharma/Pfizer and Moderna/National Institute of Allergy and Infectious Diseases), inactivated vaccines (Beijing Institute of Biological Products, Wuhan Institute of Biological Products, and adjuvant recombinant protein nanoparticles (Novavax) [37].

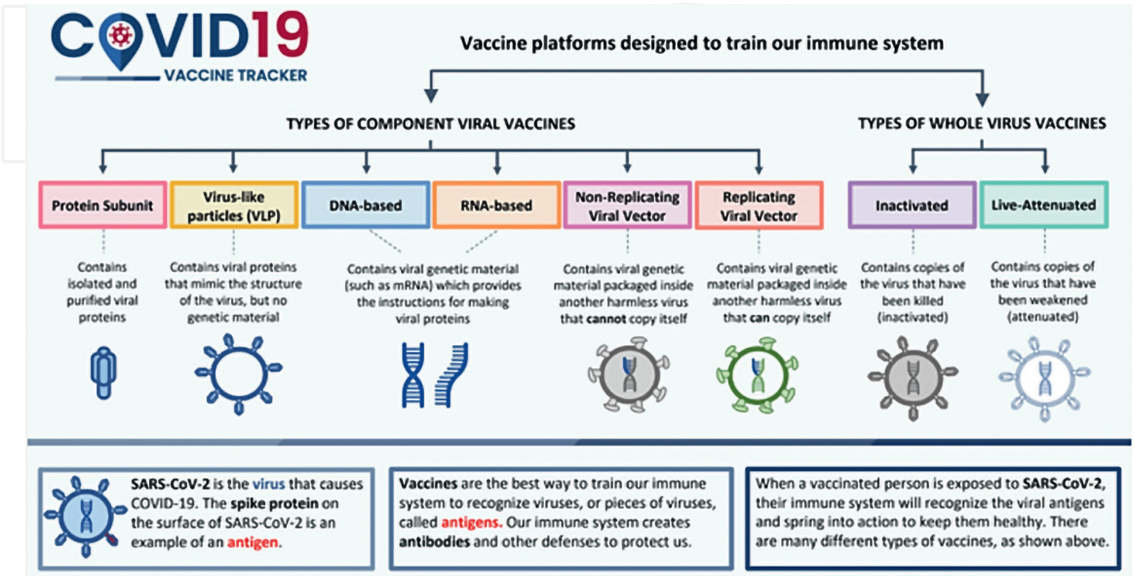

Figure 2.
Illustrates the all the types of approaches for the vaccine development [30].

4.1 Nucleic acid—based vaccine

The nucleic acid vaccine depends on the delivery of the viral genetic codes rather than the viral protein; the transcription and translation processes performed by the host are used to encode the antigen inside the cell before its presentation through the class I of MHC. The technology is relatively new, and no approved nucleic acid vaccines have been used beyond the COVID-19.

4.2 BNT162b2 mRNA COVID-19 vaccine (Pfizer)

BNT162b2 is a lipid nanoparticle–formulated [38], nucleoside-modified RNA expressing the full-length of spike gene, adapted by two proline modifications to keep its structure in the prefusion conformation. Two 30 ug doses of Pfizer vaccine produced significant neutralizing antibody titers directed against SARS-CoV-2, and particular CD8+ and CD4+ T cell responses in healthy individuals in trials done in the United States and Germany [39]. Furthermore, Pfizer vaccine's reactogenicity profile reflected minimal side effects. The development of the BNT162b2 vaccine into phase 3 was encouraged by these findings. The tolerability, safety, immunoreactivity, and efficacy of 30 μg of BNT162b2 in controlling COVID-19 were evaluated in individuals, which are 16 years old or older [40].

4.3 The mRNA-1273 SARS-CoV-2 vaccine (Moderna)

The mRNA1273 vaccine is an mRNA-based lipid nanoparticle encapsulated vaccine expressing the fusion-stabilized full-length spike protein of (SARS-CoV-2) [40]. The moderna vaccine revealed 94.1% efficacy at stopping COVID-19 severity. mRNA-1273's efficacy is comparable to that of the previously disclosed BNT162b2 mRNA vaccination [41].

5. Recombinant vaccines/viral vectors

Viral vector platform involves the insertion of the target gene that encodes for the target protein within an engineered. The viral vector can be able or disabled to replicate there are several viral vectors that are used in the recombinant vaccines such as vesicular stomatitis virus (VSV), adenovirus (Ad), measles virus (MV), alphaviruses, poxviruses, and herpes virus. These types permit the introduction of 5 kb the target gene and have been shown to induce cellular and humoral immunity. The possibility of preexisting immunity to viral vectors, such as Ad5 and MV in vaccine recipients, is one of the major concerns for this platform, which could reduce the vaccine's effectiveness [42]. To avoid this problem, methods such as selecting adenoviral serotypes with low human prevalence (Ad26 or Ad35) have been used.

6. ChAdOx1 nCOVID-19 (AstraZeneca)

A new COVID-19 vaccine is currently in clinical trials; it was developed largely to prevent MERS [43]. This vaccine involves the genetic code of the SARS-CoV-2 spike protein inserted inside an adenovirus vector. The results of the phase 1/2, single-blind, randomized controlled trial revealed that the spike-specific T cell response

was detected on day 14, whereas the anti-spike IgG antibodies peaked on day 28. Neutralizing antibodies were generated in 91% of individuals after receiving the first dose and all individuals generated neutralizing antibodies after the booster dose. The safety and immunogenicity results for the ChAdOx1 nCoV-19 candidate vaccine support the entry of this vaccine into phase 3 clinical trials [44].

7. Ad26.COV2.S

The one-shot Ad26.COV2.S vaccine is a recombinant; replication-deficient viral vector denoted human adenovirus type 26 (Ad26) vector expressing the entire sequence of SARS-CoV-2 spike protein in a prefusion-stabilized shape [45, 46]. Other Ad26-based vaccines, such as an authorized Ebola vaccine, have been found to be safe and generate long-lasting immune responses. In preclinical SARS-CoV-2 challenge studies [47, 48], Ad26.COV2.S caused persistent protection at low doses [49], and preliminary clinical data showed that a single dosage of virus particles was safe and elicited sufficient humoral and cellular immune responses [46]. ENSEMBLE trial showed that the vaccine achieved 52.0 and 64.0% efficacy against moderate to severe–critical COVID-19 with onset at least 2 weeks and at least 3 weeks after vaccination, respectively, and achieved 73.1 and 81.7% efficacy against severe–critical COVID-19, respectively [50]. Ad26.COV2.S could be preserved for up to 2 years in a conventional freezer and 3 months in a fridge, making travel, storage, and use in a pandemic much easier.

8. Sputnik V

Gam-COVID-Vac, developed by the Russia's Gamaleya Research Institute of Epidemiology and Microbiology, is composed of two vector vaccines, based on rAd type 26 (rAd26) and rAd type 5 (rAd5)—both of which express the full-length spike protein (rAd26-S and rAd5-S). Both rAd26-S and rAd5-S are injected intramuscularly separately after 3 weeks interval. The results of the phase 1/2 clinical trials revealed the vaccine safety and immunogenicity in the healthy individuals. Therefore, the vaccine was authorized in Russia in accordance with the national laws. In a randomized, controlled phase 3 trial in Russia, including 21,862 participants, they detected the anti-RBD specific IgG titers, neutralizing antibody titers, and cellular immune response. The proposed regimen of vaccination generates both B cell and T cell responses, with 91·6% efficacy against SARS-CoV-2. The vaccine is preserved and dispersed at −18°C but storage at 2–8°C, an optimum temperature for worldwide supply, has also been licensed by the Ministry of Health of the Russian Federation [51].

9. Sputnik light

It is a new single-dose vaccine based on recombinant replication-deficient adenovirus type 26 (rAd26) vector expressing the spike (S) glycoprotein as an attempt to meet the vaccine demand. The "Sputnik Light" single-dose rAd26 vector-based COVID-19 vaccine has a favorable safety profile and generates significant humoral, and cellular immune responses in both seronegative and seropositive subjects [52].

10. CoviShield - Oxford/AstraZeneca vaccine (AZD1222)

Serum Institute of India's COVID-19 vaccine, called Covishield, is a version of the Oxford-AstraZeneca vaccine that manufacturers in India produce locally. (Covishield) has a favorable benefit-risk profile, with remarkable potential to prevent infections and diminish mortality worldwide [53]. It was proved that might protect people from various SARS-CoV-2 variants. The vaccine efficacy is found to be 95% of recipients and stop the disease progression in those infected after vaccination. In phase 3 clinical trial, they demonstrated that the AZD1222 vaccine was tolerable and successful in suppressing clinical symptoms and severe infection across different ethnic groups that recruited older individuals [54].

11. Inactivated vaccine candidate, BBIBP-CorV Sinopharm

Inactivated vaccine development is a well-established platform that is widely adopted for the prevention and control of the virus transmission such as influenza virus and poliovirus. This platform uses the whole organism but inactivated through chemical or physical methods. In this phase 1/2 trial, the BBIBP-CorV inactivated vaccine, given as a two-dose immunization, was safe and well tolerated. The BBIBP-CorV vaccine has the ability to induce humoral immune response in all vaccinated individuals. In preclinical studies, it was observed that the cBBIBP-CorV able to elicit sufficient neutralizing antibody titers in animal model, which have the capacity to protect against SARS-CoV-2 [55]. The generated antibodies against SARS-CoV-2 by the immunization of BBIBP-CorV reached the peak on day 42. The neutralizing antibodies stimulated by BBIBP-CorV have a pangenotypic effect and can prevent multiple SARS-CoV-2 strains infection. These data reveal the BBIBP-CorV has the potential to give cross-protection against different SARS-CoV-2 strains [56].

12. CoronaVac (Sinovac life sciences, Beijing, China)

CoronaVac (Sinovac Life Sciences, Beijing, China) represents one of the inactivated vaccine platform and revealed high immunogenic effects in the preclinical studies in mice, rats, and nonhuman primates. The generated antibodies produced from the immunization of CoronaVac have the ability to neutralize several SARS-CoV-2 variants. Following a SARS-CoV-2 challenge in macaques, the data showed that CoronaVac conferred partial or complete protection and prevent the severe interstitial pneumonia with no detectable antibody-dependent increase of infection, supporting the advance to human clinical trials [57].

The SARS-CoV-2 (CN02 strain) has been transfected into the vero cells and then the virus was collected, treated with β-propiolactone. Then the virus was purified, and absorbed onto aluminum hydroxide. The aluminum hydroxide is used as an adjuvant to induce cellular immunity. The vaccine used in the phase 1 study was prepared using cell factory technology, while the vaccine used in phase2 was prepared by using a highly automated bioreactor. The results showed that the CoronaVac (Sinovac) produced for the phase 2 clinical trial has been enhanced the immunogenic results. Vaccine doses of 3 and 6 μg were injected intramuscularly on either day 0 and day 14 or day 0 and day 28, depending on the cohort. Two doses (days 0 and 28) of 6 μg vaccine

yielded the largest antibody recovery, but 3 μg was selected for phase 3 studies based on production capacity (seroconversion rates of 100 and 97%, respectively) [58].

Concerns have been raised about the level of the generated antibodies. The geometric mean titer (GMT) of neutralizing S-IgG was lower than that of convalescent human serum (HCS) while the antibodies arising from natural infection was (mean GMT23.8-65.4). Meanwhile, the results of other vaccine candidates showed that GMT S IgG was superior to HCS. The low immunogenicity of CoronaVac's is represented as one of the obstacles that face this vaccine. The low immunogenic effect of CoronaVac's is may be due to the alteration of S protein induced by the chemical compounds. These vaccine doses were proven to confer the protection against SARS-CoV-2 infection in macaques. CoronaVac is proved to be tolerated and able to generate humoral responses against COVID-19. These findings are paving the way for its emergency use in China and on phase 3 clinical trials. The therapeutic value of CoronaVac remains to be evaluated.

13. Recombinant protein based vaccine (Novavax)

Novavax vaccine is composed of an engineered baculovirus with a modified spike gene. Then the baculovirus transfects the Sf9 moth cell lines, which produce and display the spike protein on their cell membranes. The spike proteins are then extracted and assembled onto a synthetic lipid nanoparticle [59]. Novavax's unique nanoparticle technology used an adjuvants called Matrix-M, to boost immune system and induce high levels of neutralizing antibodies [60]. In Phase 1–2 clinical trial of a Novavax vaccine, the immunological responses produced by NVX-CoV2373 appeared to be higher than those seen in COVID-19 serum [61]. The Matrix-M1 adjuvant elicited CD4+ T cell responses with a Th1 phenotypic bias.

14. Experimental therapeutic interventions

14.1 Convalescent plasma (CP) therapy

Because an effective vaccine and specific antiviral therapies are no longer available, there is a mandatory demand to develop an alternative approach for COVID-19 treatment, particularly in severe patients. For many centuries, convalescent plasma (CP) therapy, a type of adaptive immunotherapy, has been approved to treat a variety of infectious diseases. CP therapy has been used successfully in the treatment of MERS, SARS, and the H1N1 virus with adequate safety and efficacy [62, 63].

Convalescent plasma received from cured COVID-19 patients with generated humoral response directed toward the virus possesses a high concentration of neutralizing antibodies capable of preventing the viral entry and eliminating the virus from blood stream and lung tissues [64]. The first important determining factor in the success of the CP therapy is the neutralizing antibody titer. It was found in a small sample study of MERS-CoV infection that the titer of the neutralizing antibody should be greater than 1:80% to achieve successful CP therapy [63]. Finding suitable donors with high level of neutralizing antibody represents the cornerstone. Cao et al. [65] revealed that the level of neutralizing antibody to SARS-CoV diminished gradually 4 months after the recovery, eventually reaching undetectable levels in 25.6% (total IgG) and 16.1% t (neutralizing antibodies) of patients 36 months later.

According to a study of MERS-CoV infected patients and high risk group, the prevalence of MERS-CoV IgG seroreactivity was estimated to be very low (2.7%), and the antibodies titer decreased rapidly within 3 months [66]. According to these findings, the neutralizing antibodies were a short-lived humoral immune response, and plasma from recently recovered patients should be more effective.

The second key factor that determined the success of treatment is treatment intervention point. The best treatment outcomes were observed in patients with SARS who received CP infusion by day 14 highlighting the necessity of timely rescue therapy. In recent study, they showed that all the transfused patients with neutralizing antibody titer above 1:640 achieved serum SARS-CoV-2 RNA negativity and accompanied with an elevation in lymphocyte counts and oxygen saturation, as well as an improvement in liver function and CRP. The findings suggest that antibodies found in CP alleviated immune system inflammation and overreaction.

Several approaches have been established to isolate and characterize the neutralizing antibodies generated by the convalescent COVID-19 as an attempt to generate effective antibodies as a therapy for COVID-19 [67, 68]. For example, AbCellera, a private Canadian company has developed a human IgG1 monoclonal Abs-based therapeutics for coronavirus infection in collaboration with Eli Lilly. Clinical studies for such antibodies have already been authorized in China.

14.2 Antiviral drugs

Several antiviral drugs have been adopted as potential candidate to treat SARS-CoV-2. The viral life cycle steps can be used as potential drug targets. The viral entry, nonstructural protein, and immune regulation are the promising drug targets **Figure 3**.

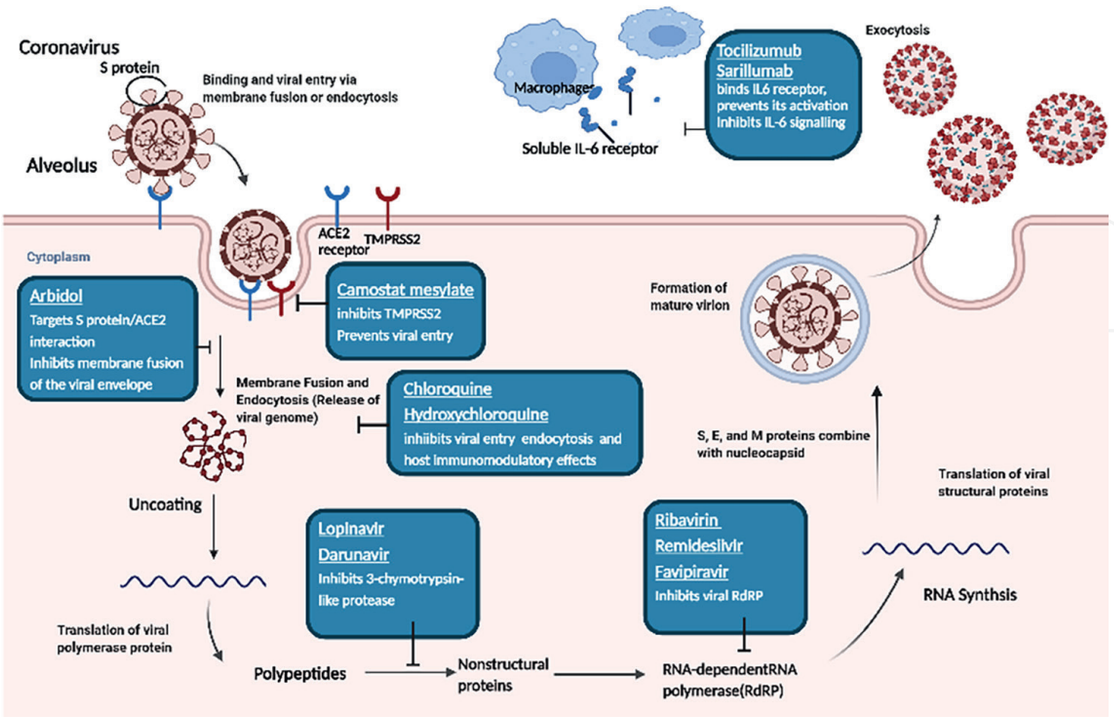

Figure 3.
A diagram represents host immune system stimulated by the virus and viral life cycle within target cells. The figure is created by BioRender program.

14.3 Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine have been permitted for the treatment of malaria and rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) as they have anti-inflammatory activity. These compounds have the ability to inhibit the virus replication through decreasing the endosomal acidification as SARS-CoV-2 needs the acidic media of the endosome for successful replication [69, 70].

Chloroquine has been shown an antiviral activity against SARS-CoV-2 through *in vitro* study [71]. With the use of chloroquine for the treatment of COVID-19, a clinical trial in China reported efficacy with improved pneumonia severity and an acceptable safety profile [72]. Hydroxychloroquine is a chloroquine derivative that is more stable and has a better clinical safety profile than chloroquine. It also has inhibitory activity toward SARS-CoV-2. When taken in conjunction with azithromycin, it has been proven to provide complete cure and virus clearance in COVID-19 patients [73].

Recent study showed that the combination of azithromycin and hydroxychloroquine has discouraging results in the critically ill SARS-CoV-2 infected patients, which may lead to perform more controlled research before final recommendations for chloroquine/hydroxychloroquine in the treatment of COVID-19 are made [74].

Chloroquine and hydroxychloroquine are zinc ionophores, and zinc has been found to block the activity of coronavirus's RNA-dependent RNA polymerase enzyme [75, 76]. As a result, one reason for some of these clinical trials' limited success might well be the lack of zinc supplementation, which may be required to obtain the medicinal value of these drugs on SARS-CoV-2 and other RNA virus infections [77].

14.4 Lopinavir/ritonavir and other antiretroviral

Lopinavir/Ritonavir is a combined approved drug used for the treatment of HIV. Lopinavir is a protease inhibitor that prevents virus particle maturation, whereas ritonavir sustains the lopinavir's plasma level by inhibiting CYP3A enzymes, which delays lopinavir's breakdown in the liver [78]. The data obtained from *in vitro*, and animal studies revealed its potential inhibitory effect against SARS-CoV, MERS, and SARS-CoV-2 [78, 79]. For COVID-19 therapy, lopinavir-ritonavir has been administered alone or in combination with alpha interferon or chloroquine/hydroxychloroquine with modest effectiveness [80, 81]. However, contradictory results have been released from China regarding impact of COVID-19 patients who are very unwell [82]. Recently, a randomized study of 199 hospitalized patients with COVID-19 who were treated with lopinavir/ritonavir reported no significant change in viral load, duration of hospital stay, or mortality rate [82]. The study was too small to conclude the potential role of lopinavir/ritonavir on the COVID-19 treatment and experts suggested that further randomized clinical trial to be conducted to confirm or deny the lack of effect.

As a result, more clinical trials are needed to determine the success of this therapy for COVID-19, which is now being conducted.

Furthermore, it has been observed that patients who received lopinavir/ritonavir regimen have had gastrointestinal adverse side includes diarrhea, nausea, and hepatotoxicity [83]. Elevated level of transaminases was commonly noticed in COVID-19 infected patients as one of the side effects, the case that may be worsened by any viral coinfection and/or combined therapy [84]. Recently RCT found that around half of lopinavir/ritonavir patients suffered a lot of unfavorable side effects, and around sixth of patients stopped medication owing to gastrointestinal complications [82]. Elevated transaminases triggered by drugs have special concern since it has the potential to

worsen COVID-19-induced liver impairment. Notably, the elevation of liver enzyme is an undesired criterion in numerous COVID-19 research study, suggesting that lopinavir/ritonavir triggered liver toxicity may restrict patients' access to those medications [85].

Darunavir/cobicistat (DRV/c) is a protease inhibitor used for the treatment for HIV. *In vitro* study demonstrated an antiviral activity of darunavir against SARS-CoV-2.

In a randomized controlled clinical trial aimed to monitor the efficacy of DRV in treating COVID-19 patients, the obtained results failed to show a significant benefit of using (DRV/c) therapy beyond the standard care in the mild COVID-19 infected patients [86]. In this regard, HIV1 protease inhibitors may not exhibit clinically significant activity against SARS-CoV-2.

14.5 Favipiravir (Favilavir or Avigan)

Favipiravir (FPV) is a safe and effective RNA polymerase inhibitor developed in Japan for different RNA viral infection including influenza [87, 88]. The antiviral activity of the FPV against SARS-CoV-2 has been approved in a controlled study conducted in China [89]. Through the COVID-19 patients' medication, the effects of FPV vs. LPV/RTV were examined in this study. The FPV-treated individuals showed a considerably superior therapeutic response, with rapid viral clearance and a higher amelioration in chest radiography. Upon these hopeful data, the FPV therapy has been authorized as first anti-COVID-19 medication by the Chinese National Medical Products Administration [68].

14.6 Remdesivir (GS-5734)

Remdesivir is a nucleotide analog compound that inhibits the viral RNA-dependent RNA polymerase; its inhibitory effect against MERS CoV, SARS-CoV, and SARS-CoV-2 replication has been confirmed in *in vitro* studies and in animal models [90, 91]. The development company (Gilead Sciences, USA) declared a clinical improvement in more than half of patients (36 of 53) [92]. However, recent study in China did not exhibit significant clinical benefit, with the exception of the diminishment in the time required for recovery [93]. Additionally, in some patients, treatment with remdesivir had to be stopped prematurely due to unfavorable complications in 12% of patients compared to 5% of patients receiving placebo. Similar results were also reported in the first clinical trial in the United States. Repeated clinical trials of remdesivir in multiple countries must be performed to obtain more convincing recommendations for use in COVID-19 patients. Moreover, the efficacy of remdesivir against the novel COVID-19 variants are not well evaluated and the acquired drug resistance to the mutant strains should be monitored.

15. Immunomodulatory agents

Several data pointed out the role of immunosuppressive treatments (e.g., corticosteroids, inhibitors, IL-6 inhibitors, interleukin (IL)-1 inhibitors, and kinase inhibitors) and immunomodulators (e.g., interferon alpha and beta (IFNα), (IFNβ), in COVID-19. The rationale for using these immunomodulatory/immunosuppressive agents for the treatment of COVID-19 is the involvement of the pro-inflammatory mediator with pieces of evidence of cytokine release storm (i.e., critical hyper inflammation and immune imbalance), which is required to induce multi-organ dysfunction and failure, worsening COVID-19 prognosis [94].

The humanized monoclonal antibody (tocilizumab) has been developed to bind with the receptor of IL-6 (IL-6R) that has been licensed by the FDA for the treatment of RA, giant cell arteritis, and systemic juvenile idiopathic arthritis [95]. IL-6 was involved in the production of cytokine storm (CS) found in ICU-admitted COVID-19 patients [95]. As a result, it has been offered as a possible treatment for such individuals [96]. Tocilizumab, for example, has been approved to be used as an immunosuppressive agent in severely ill COVID-19 patients in China and Italy, with promising findings [97, 98]. In a Chinese cohort, the administration of tocilizumab showed an improvement in patients with severe symptoms. While in the Italian cohort, the administration of tocilizumab in a COVID-19 patient with pneumonia revealed good alterations in CT findings within 14 days of therapy [99]. It is proving to be a viable treatment for treating. Several randomized controlled trials (NCT04310228, ChiCTR200002976) of tocilizumab alone or in combination in COVID-19 patients with severe pneumonia are ongoing in China and are included in the current Chinese protocol for the treatment of COVID-19 patients [100].

Sarilumab, another IL6 receptor antagonist approved for the treatment of R, is being investigated in a phase 2/3 clinical trial in hospitalized patients with severe COVID-19 (NCT04315298) [101].

Bevacizumab is monoclonal antibodies directed against vascular endothelial growth factor that are undergoing clinical trials in China and the United States NCT04275414).

Interferon alpha and beta have been studied against nCoV, and interferon beta is active against MERS [102, 103]. The use of interferon for the treatment of SARS-CoV-2 cannot be recommended at this time because of contradictory *in vitro* and animal results and the lack of clinical trials [104]. Current Chinese regulations recommend interferon as an alternative to combination therapy.

16. Soluble human (ACE2)

For successful COVID-19 treatment, it has been proposed that blocking the interaction between the viral spike protein and ACE2, which is the host receptor for SARS-CoV-2 infection, might be a viable treatment [105].

This finding has opened debate about whether ACE inhibitors and/or angiotensin receptor blockers could be used to treat COVID-19 or, conversely, aggravate the disease [106]. ACE inhibitors can cause a decrease in angiotensin I levels, triggering a possible negative feedback loop, which in turn activates more ACE2 receptors to interact with available angiotensin I substrates. On the contrary, angiotensin receptor blockers may theoretically provide clinical benefit by blocking the ACE2 receptor. There are inconsistent *in vitro* results to verify if these drugs are harmful or protective in patients with COVID-19. There is insufficient data to conclude that patients on long-term ACE inhibitors, or ARB medication are at a higher risk of poor COVID-19 outcomes [107].

A recent *in vitro* investigation found that humanized recombinant soluble ACE2 (hrsACE2) may inhibit SARS-CoV-2 replication, resulting in significantly lower virus load in vero cell lines in a dose-dependent manner [108]. These findings are encouraging because they offer up a new avenue for using hrsACE2 to prevent SARS-CoV-2 infection at an early stage by inhibiting the virus's entrance into target cells, potentially saving patients from lung damage.

17. Umifenovir (also known as arbidol)

Umifenovir (also known as arbidol) is a potent antiviral drug with a novel mechanism that inhibits viral envelope fusion by targeting the S protein/ACE2 interaction [109]. Based on *in vitro* studies demonstrating action against SARS, the medication is now authorized in Russia and China for the treatment and prevention of influenza. It is also gaining interest in treating COVID-19 [110]. The current influenza treatment dosage of 200 mg orally every 8 hours is being investigated for COVID-19 therapy (NCT04260594). In China, only limited clinical experience with umifenovir for COVID-19 has been reported. In a non-randomized analysis of 67 COVID-19 patients, therapy with umifenovir for 9 days was related with reduced fatality rates and higher discharge rates than patients who did not get the drug [111]. This finding cannot approve the success of umifenovir for COVID-19 treatment, but several RCTs are required for further investigation of this agent.

18. Corticosteroids

Corticosteroids are used to reduce the host's inflammatory process in the lungs, which can contribute to acute lung damage and acute respiratory distress syndrome (ARDS). COVID-19 induces severe endothelial and alveolar damage as a result of host-mediated excessive inflammation and cytokine storm [7]. Excessive inflammation and an unregulated immunological response are the major causes of COVID-19-related death [112]. Corticosteroids are extensively used and well tolerated over the world. They have the potential to minimize the risk of cytokine storms and inflammation in COVID-19 [113]. They may also be able to control the course of respiratory failure and mortality by regulating inflammation-mediated lung damage [113, 114]. Previous research regarding the efficacy of corticosteroid therapy in severe pneumonia [115] revealed a link between corticosteroid usage and a lower risk of ARDS, as well as shorter hospital stay duration [116]. However, corticosteroids have the potential to greatly reduce the use of mechanical ventilation required in COVID-19 patients while also limiting major side effects. Additionally, for individuals with COVID-19, a pulse dosage of methylprednisolone for fewer than 7 days may be a useful therapy strategy [117].

However, side effects such as delayed virus clearance and an increased risk of subsequent infection may balance this advantage. In an observational study, no link has been found between corticosteroids and high survival rate in patients with SARS and MERS but reported a link between delayed virus clearance and high incidence of comorbidities such as hyperglycemia, psychosis, and avascular necrosis [102, 118]. Moreover, a meta-analysis of 10 observational studies of 6548 patients with influenza pneumonia in 2019 found that corticosteroids were linked to an increased risk of death and twice the risk of secondary infection [119]. While the effectiveness of corticosteroids in ARDS and septic shock is generally controversial, Russell and colleagues [120] claimed that individuals with bacterial infection are more likely to benefit from corticosteroids than those with viral infections. The data currently supports the use of corticosteroids in COVID-19 patients; however, additional study is needed on the type, dose, start time, and duration.

19. The situation in Egypt and the governmental efforts to control the COVID-19 transmission

Here in the next few lines, we summarize the situation of COVID-19 statistics in Egypt and focus on the efforts and actions of the Egyptian government to regulate and halt the COVID-19 transmission.

To date (August 2022), over 515,198 confirmed laboratory cases have been detected with more than ~24,786 deaths in Egypt, according to the official website of the Egyptian MOH (https://www.care.Gov.eg/Egypt Care/index.aspx accessed August, 2022).

The decreased incidence of COVID-19 in Egypt does not match the reality. The recorded number of the infected cases depended only on the laboratory-confirmed cases; however, many Egyptians have been infected with SARS-CoV-2 and have been homelily isolated till recovery without performing the COVID-19 test. The decreased incidence in Egypt may be related to the large population, minimal screening testing, warmth and humidity, and use of the bacille Calmette-Guerin (BCG) vaccination. Host genetic alteration has also been shown to influence indigenous Africans' resistance to a range of infectious diseases [121]. The appearance of SARS-CoV-2 strains are raising high public health problem owing to their high transmission rate, higher pathogenicity, and in some cases, ability to infect vaccinated people (vaccine breakthrough). The risk of death is increased significantly with age [122, 123] and

Antipyretic	Paracetamol
Cough suppressants	Acelylcysteine
Anticoagulants	Enoxaparine
Fluid therapy	According to the condition of the patient
Multivitamins	Vitamin C or Zinc
Antiviral drugs and Antibiotics	Hydroxychloroquine - Ivermectin – Favipiravir - Remdesivir - Lopinavir/Ritonavir - Monoclonal antibodies - Convalescent plasma - Azithromycin - Nitazoxanide- Oseltamivir - Ribavirin - Interferon beta 1b - Doxycycline
Anti-inflammatory	Hydrocortisone – Dexamethasone - Methylprednisolone
Supplement	Lactoferrin
Immunosuppressive	Tocilizumab
Oxygen therapy	
Mechanical ventilation	

For patients with COVID-19, the Egyptian Ministry of Health approved a standard of a care treatment strategy that included
By the end of May 2020, the Egyptian MOH guideline recommended that mild and some moderate cases will be managed by home isolation

Figure 4.
The protocol for the treatment of COVID-19 patients approved by the MOH [126].

comorbidities (cardiovascular disease, cancer, diabetes, and chronic lung disease) [6, 124]. Patients with one or more comorbidities had low survival rates [125].

The Egyptian Ministry of Health and Population (MOH) has built a hotline service to help persons in need of medical advice. The Egyptian government has launched a huge disinfection program using chlorine-containing disinfectants as lipid solvents that targeted all squares, workplaces, and touristic spots. The standard of care treatment strategy for COVID-19 patients has been approved by the Egyptian Ministry of Health (**Figure 4**) [127]. The Egyptian Ministry of Health has advised that mild and possibly moderate cases can be handled at home.

Egypt has been receiving nine approved anti-COVID-19 vaccines since December 2020 including Moderna (mRNA-1273), Pfizer/BioNTech(BNT162b2), Gamaleya (Sputnik Light), Janssen (Johnson & Johnson): (Ad26.COV2.S), Sinovac(CoronaVac), Sinopharm (BBIBP-CorV), AstraZeneca vaccine, and Sputnik V. Priority categories for vaccination include (A) health care workers in quarantine, fever, and chest hospitals, (B) immunocompromised patients, and the elderly, and (C) eventually all people over the age of 18. Egypt has begun the distribution of COVID-19 vaccines as of March 2021. It was estimated that the percentage of fully vaccinated individual is 19.8% while the percentage with at least one dose is 31.8% [128]. In developing countries, the application of strict regulations to halt the viral transmission is difficult due to human overpopulation, so it is mandatory to highlight the importance of boosting the host immunity.

20. Conclusion

COVID-19 patients are characterized by lymphopenia and elevated cytokine levels, which could be used as indicators for disease progression. COVID-19 has immunological profiles that can lead to microbial infection and various organ failures. As a result, improving lymphopenia and decreasing inflammation may be helpful therapeutic methods for COVID-19 patients. Currently, antiviral drugs and immunotherapies are two principal therapeutic approaches for COVID-19, whereas vaccines are still considered the most effective strategy to get rid of this virus. COVID-19 vaccine advancements are encouraging because this is the first time vaccine development has moved so quickly. Vaccinology-based research advances have assured that the most crucial public health intervention is created in a timely manner. Researchers and clinicians still need to perform better planned controlled clinical trials and collect more biological samples to better understand host immune responses to pathogens and their implications for the treatment of patients.

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