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REVIEW

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Antibody-based immunotherapeutics and use of convalescent plasma to counter COVID-19: advances and prospects

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) has spread to several countries globally. Currently, there is no specific drug or vaccine available for managing COVID-19. Antibody-based immunotherapeutic strategies using convalescent plasma, monoclonal antibodies (mAbs), neutralizing antibodies (NAbs), and intravenous immunoglobulins have therapeutic potential.

Areas covered: This review provides the current status of the development of various antibody-based immunotherapeutics such as convalescent plasma, mAbs, NAbs, and intravenous immunoglobulins against COVID-19. The review also highlights their advantages, disadvantages, and clinical utility for the treatment of COVID-19 patients.

Expert opinion: In a pandemic situation such as COVID-19, the development of new drugs should focus on and expedite the strategies where safety and efficacy are proven. Antibody-based immunotherapeutic approaches such as convalescent plasma, intravenous immunoglobulins, and mAbs have a proven record of safety and efficacy and are in use for decades. Some of them are already being used to manage COVID-19 patients and found to be useful. However, the mAbs with virus neutralization potential is the need of the hour during this COVID-19 pandemic to be more specific and virus targeted. The research and investment need to be accelerated to bring them into clinical use for prophylactic and therapeutic purposes against COVID-19.

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COVID-19; SARS-CoV-2; coronavirus; immunotherapeutics; immunoglobulin; convalescent plasma; neutralizing antibodies; monoclonal antibodies

1. Introduction

The novel coronavirus, severe acute respiratory syndrome coronavirus – 2 (SARS-CoV-2), which emerged in Wuhan, China, during early December 2019, has affected more than 12.5 million people and killed 0.56 million patients worldwide as of 11 July 2020 [1,2]. This virus is suspected of having an initial zoonotic origin from an animal host, most likely bat, and was further maintained by the human-to-human transmission cycle [3,4]. Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was declared as a pandemic on 11 March 2020, by the World Health Organization [5] and has caused a massive burden to healthcare facilities since [6]. The preliminary findings obtained from genomic analyzes suggested that this pandemic virus has the highest similarity (>88%) with bats coronaviruses (Bat-SL-CoVZC45, and Bat-SL-CoVZXC21) [7,8]. Later the bat coronavirus RaTG13 was found to be 96% identical to SARS CoV-2 [9]. Subsequently, a few more animal species, including pangolins, were proposed as the intermediate host for SARS-CoV-2 [10]. Several pangolin coronaviruses had 91% similar to the SARS CoV-2. Most importantly, the pangolin coronavirus spike protein was highly similar to SARS CoV-2, and the key amino acids at the receptor-binding domain (RBD) were identical [11]. Evidence suggests that SARS-CoV-2 could be a recombinant of bat and pangolin coronaviruses. As of now, seven coronaviruses have been identified causing mild to severe infections in humans, where majorly three, SARS-CoV, MERS-CoV, and the current SARS-CoV-2, are zoonotic with high case fatality rates (CFR) that is still lowest in COVID-19 (2.3%) than SARS (9.5%) and MERS (34.4%) [12]. However, compared to SARS-CoV and MERS-CoV, a higher transmission competence is exhibited by SARS-CoV-2 that has resulted in widespread infections across several countries within a short period of time [3].

The prevention and control measures implemented by countries around the world have bought us some time for developing

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Article highlights

- Vaccines are needed to induce active immunity against SARS-COV-2; however, it may take a long time to get approval and to make it available in the commercial market.
- The gap produced due to the lack of an efficient vaccine against SARS-CoV-2 can be bridged using antibody-based immunotherapeutics for inducing short term immunity.
- Antibody-based immunotherapeutics strategies such as convalescent plasma, monoclonal antibodies (MAbs), neutralizing antibodies (NAbs), and intravenous immunoglobulins (IVIg) have potential therapeutic application against COVID-19.
- Convalescent plasma therapy is already used for managing COVID-19 patients; however, the neutralization potential of plasma needs to be tested to prove its therapeutic utility.
- Approved MAbs against IL-6, IL-6R are used for treating COVID-19 induced pathological conditions such as cytokine storm or cytokine release syndrome.
- Even though SARS-CoV and SARS-CoV-2 share high similarity in their domains, SARS-CoV-2-specific immunotherapeutic approaches are required due to the limited cross-reactivity between these two closely related coronaviruses.
- Monoclonal antibody-based immunotherapeutics are highly specific against the virus and safer compared to plasma therapy. Many monoclonal antibodies against the SARS-COV-2 are under development for the clinical use to treat COVID-19 patients.
- Monoclonal antibodies against the receptor-binding domain of the S1 subunit of spike protein show virus neutralization potential. There is a need for expediting the research to develop new MAbs and bringing the existing SARS-COV-2 specific MAbs into the clinic as quickly as possible.
- This box summarizes key points contained in the article.

vaccines and therapeutics against this novel virus. The race to develop SARS-CoV-2-specific therapeutics and vaccines is already underway [13]. Currently, there are no licensed vaccines or therapeutic drugs against SARS-CoV-2 infection [5]. Moreover, the unavailability of specific drugs targeting SARS-CoV-2 led to a considerable number of new confirmed cases and deaths, leaving the healthcare workers and general global population in a stage of higher socio-economical, physiological, and psychological stress [14]. However, a few therapeutic candidates have exhibited *in vitro* efficacy that requires further validation via a preclinical animal model and randomized controlled trial in humans [15].

The therapies used at first to treat COVID-19 patients included nonspecific and broad-spectrum antivirals and anti-inflammatory drugs, along with supportive therapy and immunotherapy [16,17]. In this context, use of chloroquine or hydroxychloroquine, remdesivir, hyper-immune immunoglobulin, interleukin-6 (IL-6), interleukin-1 (IL-1) inhibitors, mechanical ventilation, corticosteroids, stem cells, and immunotherapy are under investigation in critically ill COVID-19 patients [16,18–21]. The immunotherapies used to treat COVID-19 patients included convalescent plasma and interferons [16,21]. However, the therapy that can be made available immediately is convalescent plasma-based immunotherapy, which uses the plasma collected from patients recovered from COVID-19 [22]. Convalescent plasma contains immunoglobulins, which can help to inhibit virus replication and help patients to recover from symptoms (like cough, pneumonia, and fever). It can also improve oxygen saturation and recovery; hasten resolution of lung infiltration pathology; stabilize inflammatory mediators (by decreasing C-reactive protein and IL-6), leukocytosis, and lymphopenia [23]; improve survival; reduce hospital stay [24]; and reduce mortality without any adverse side effects [24]. Furthermore, they lowered viral loads [24]. However, this immunotherapy is not highly specific and has limitations such as short-term immunity and adverse effects, including anaphylaxis, pulmonary edema, and the chance of disease transmission [22,25,26]. Hence, more specific modalities need to be explored. Monoclonal antibodies could be potential alternatives with higher specificity, but identification of specific targets is imperative for the development of monoclonal antibodies [25,27].

The spike glycoprotein or S protein is considered as an important target against which vaccines and drugs are developed [15,28,29]. Targeting the receptor-binding domain (RBD) of S protein that interacts with the angiotensin-converting enzyme 2 (ACE2) receptor in the host cells has the potential to prevent the virus entry and subsequent abrogation of virus replication. This review aims to analyze the potential efficacy of various immunotherapeutic strategies against COVID-19.

2. Convalescent plasma

Convalescent plasma or immune plasma is defined as the plasma that is collected from individuals recovered from the disease. Treatment with convalescent plasma provides passive short-term immunity to susceptible individuals [30]. Therapy using convalescent plasma is ideal for post-exposure prophylaxis against SARS-CoV-2. This strategy has been previously used in SARS-CoV and MERS-CoV outbreaks [26]. The convalescent plasma containing virus-neutralizing antibodies can be used as a prophylaxis in high-risk individuals, health care providers, and vulnerable individuals with any underlying medical conditions [22]. The benefits associated with the use of convalescent plasma are mainly related to the antibody-mediated suppression of viremia [24]. During the initial stages of the outbreak, therapeutic plasma exchange was recommended as a possible treatment option for managing fulminant COVID-19 due to the benefits observed in the infected patients following the transfer of protective antibodies from survivors [31]. Healthcare workers, such as nurses, physicians, and lab technicians, are at high risk of getting exposed to the virus; thus, convalescent plasma therapy provided to these individuals at high risk will prevent the collapse of the health care system [22].

Treatment with convalescent plasma in laboratory-confirmed cases of COVID-19 was found to be associated with the resolution of ground-glass opacities as well as lung consolidations. Transfusion of convalescent plasma was also found to be safe since no adverse effects were observed in the patient under treatment [32]. Following the transfusion of convalescent plasma, a rapid increase in the levels of neutralizing antibodies was also observed [33]. Convalescent plasma could be considered as effective post-exposure prophylaxis until SARS-CoV-2-specific monoclonal antibodies (mAbs) become available (Figure 1).

However, passive antibody administration via convalescent plasma offers only a short-term but rapid immunity to the susceptible individuals. Hence, for long term protection, we

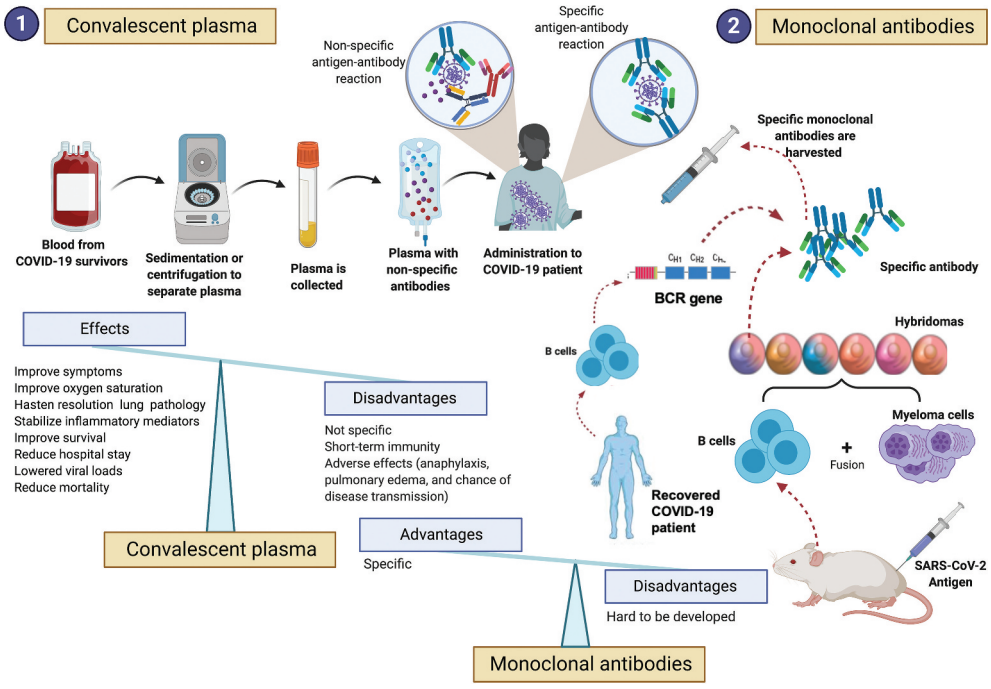

Figure 1. Comparison of production procedures, advantages, and disadvantages between convalescent plasma and monoclonal antibodies for COVID-19. Convalescent plasma is easy to be produced but has some disadvantages such as not specific and also the risk of adverse effects. Contrary, the monoclonal antibody will produce a specific antibody response against SARS-CoV-2, but it is not easy to be produced.

have to rely exclusively on vaccines, hyper-immune globulins, or monoclonal antibodies [30]. Administration of convalescent plasma containing polyclonal neutralizing antibodies at the early stages of infection may inhibit both viral entries as well as replication. Furthermore, it will also blunt the pro-inflammatory pathogenic endogenous antibody response [34]. This is beneficial for the treatment of critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS) [35]. A significant concern associated with the transfusion of convalescent plasma is the possibility of antibody-dependent enhancement (ADE). This is a phenomenon by which antibodies produced during a previous infection exacerbate the disease severity due to infection with a different serotype of the virus [30]. Patients under treatment with convalescent plasma should be closely monitored for any unintended side effects, especially evidence of inflammatory flare-up [34]. Another important concern is disease transmission. Persistence of viral shedding has been observed in the nasopharyngeal secretions of COVID-19 patients even after the resolution of symptoms. This phenomenon was found to be common in older patients. It points out the necessity of testing convalescent plasma for the presence of virus by RT-PCR if the plasma is collected less than 28 days after the resolution of COVID-19 symptoms [36].

A study including 80 SARS patients reported that the early administration of convalescent plasma (before day 14) was found more effective in terms of outcome than administration during later stages [37]. Additionally, based on the available literature, convalescent plasma should be administered in the early course of SARS-CoV-2 infection too (before SARS-CoV-2 seroconversion), preferably on day 5, for obtaining maximum efficacy. Researchers also recommend the transfusion of two plasma units (200–250 mL each) in patients weighing 50–80 kg [34]. In some cases, 500 mL is administered in doses over a 12-hour period at an intravenous infusion rate of 250 mL/hour [23]. In a study with 4 critically ill COVID-19 patients, transfusion of convalescent plasma was reported to be a potential therapy with no serious adverse reactions [38]. In addition to the prophylactic use, the convalescent plasma may also be beneficial in suppressing clinical manifestations in SARS-CoV-2-infected patients and may also be able to reduce the mortality rate [22]. The convalescent plasma can be easily collected by apheresis in large volumes without much impact on hemoglobin level of patients. Hence is preferred in severely ill COVID-19 patients for passive immunotherapy. In addition, a study recommended the collection of plasma at least 14 to 28 days post-resolution of clinical symptoms associated with COVID-19 [39]. Moreover, on the basis of previous experiences from SARS-CoV, a neutralizing antibody titer greater than 1:40 is recommended for SARS-CoV-2 [39,40]. Further studies may be required to evaluate the therapeutic potential of the convalescent plasma. Another study on the intravenous administration of humanized immunoglobulins for treating COVID-19 patients with pneumonia showed promising results (ClinicalTrials.gov No. NCT04261426) [41]. For the time being, convalescent plasma therapy is more effective in the prevention of SARS-CoV-2 infection than other treatments. Additionally, the composition of convalescent plasma is highly variable and includes a variety of blood-derived components resulting in its immunomodulatory effects in COVID-19 patients [42]. Moreover, the immunomodulatory effects of plasma from a healthy donor are attributed to the infusion

of antibodies and anti-inflammatory cytokines, which blocks the autoantibodies, complement, and inflammatory cytokines [43].

Of the clinical trials conducted on convalescent plasma, the following parameters are being evaluated: clinical signs, laboratory markers (hematological, biochemical, and inflammatory), lung pathology, radiological data, viral load, virological clearance, antibody levels, cure rate, recovery period, and mortality/fatality [44]. Additionally, to increase the efficacy of many factors like timing of plasma administration, the titer of the specific antibody in administered plasma, and screening for various blood borne pathogens must be considered [22]. As per the FDA guidelines, convalescent sera must be collected only from COVID-19 recovered individuals with complete resolution of associated symptoms at least 14 days before donation. Moreover, convalescent sera with specific SARS-CoV-2 antibody titer greater than 1:320 should only be used [45]. In a study, the convalescent plasma with a neutralizing antibody titer of 1:640 was found to be effective in increasing the level of neutralizing antibody along with oxyhemoglobin saturation level, thereby potentially improved the overall clinical outcome of the disease in severely ill COVID-19 patients [33]. A large-scale study was conducted among 5,000 hospitalized adult patients with severe or life-threatening COVID-19 to analyze the key safety metrics following the transfusion of ABO compatible convalescent plasma. The study reported <1% incidence of serious adverse events during the first four hours period post-transfusion. This included a mortality rate of 0.3% among the patients receiving convalescent plasma [46]. From this finding, we can conclude that the transfusion of convalescent plasma is a safe procedure in COVID-19 patients. In addition, the convalescent plasma not only serves as a crucial treatment approach for the severely ill COVID-19 patients but may also be used as a prophylactic measure for those who are at greater risk for COVID-19 like healthcare workers and individuals with comorbidities. The summary of how convalescent plasma is produced, the effects on COVID-19 and disadvantage is presented in Figure 1. The published evidence of the clinical efficacy of convalescent plasma against COVID-19 is presented in Table 1 [23,32,33,35,38,47–50]. The ongoing clinical studies (clinical trials) with the use of convalescent plasma are presented in Table 2.

The first randomized clinical trial that evaluated the potential of convalescent plasma therapy in patients with severe or life-threatening COVID-19 was conducted in China (Chinese Clinical Trial Registry – ChiCTR2000029757). Even though the early termination of the trial prevented from reaching a definitive conclusion, findings from the study gave an insight on the potential of convalescent plasma therapy in patients with COVID-19 [50]. The addition of convalescent plasma therapy to the standard treatment was found to be associated with clinical improvement in severely ill patients. However, statistically significant improvement was not observed in patients treated with convalescent plasma therapy [50]. The high titer SARS-CoV-2 specific antibody present in the convalescent plasma has antiviral activity in severely ill patients [50,51]. Further trials have to be conducted on

Table 1. The clinical efficacy of convalescent serum used for the management of COVID-19.

S. No.	Number of patients enrolled	Dose	Baseline severity	Outcome	References
1.	06	200 ml of ABO-compatible convalescent plasma for each cycle	Mild to severely infected COVID-19 patients	Favorable; improvement in the viral clearance and clinical condition	[32]
2.	05	400 ml of convalescent plasma	Critically ill	Favorable; improvement in the viral clearance and clinical condition	[35]
3.	10	200 ml of convalescent plasma	Severely ill	Favorable; improvement in the viral clearance and clinical condition	[33]
4.	02	500 ml of convalescent plasma divided into two doses administered in 12 hours interval	Severely ill	Favorable; improvement in the viral clearance and clinical condition	[23]
5.	138	200–1200 ml of ABO-compatible convalescent plasma	severe or critical COVID-19 patients	Favorable; improvement in clinical symptoms and mortality rate	[47]
6.	10	200 ml of ABO-compatible convalescent plasma	Critically ill	Favorable; clinical improvement	[48]
7.	31	Not specified	Severe or life-threatening COVID-19	Favorable; clinical improvement	[49]
8.	103	ABO-compatible convalescent plasma given at the rate of 4 to 13 ml/kg body weight (recipient)	Severe or life-threatening COVID-19	Although convalescent plasma therapy was found to be associated with clinical improvement in severely ill patients, statistically significant improvement was not observed	[50]
9.	04	200–400 ml in one to three consecutive transfusions. A patient received 2,400 ml of B-compatible convalescent plasma divided in eight consecutive transfusions	Severely ill	Favorable; improvement in the viral clearance and clinical condition	[38]

Table 2. Running studies (clinical trials) with the use of convalescent plasma against COVID-19 (www.clinicaltrials.gov).

S. No.	NCT No.	Title	Status	Phase	Population	Location
1.	NCT04412486	COVID-19 Convalescent Plasma (CCP) Transfusion	Recruiting	Early Phase 1	100 individuals (18 years and older)	Mississippi, United States
2.	NCT04345991	Efficacy of Convalescent Plasma to Treat COVID-19 Patients, a Nested Trial in the CORIMUNO-19 Cohort	Recruiting	Phase 2	120 individuals (18 years and older)	Paris, France
3.	NCT04333355	Safety in Convalescent Plasma Transfusion to COVID-19	Recruiting	Phase 1	20 individuals (18 years and older)	Nuevo Leon, Mexico
4.	NCT04384497	Convalescent Plasma for Treatment of COVID-19: An Exploratory Dose Identifying Study	Recruiting	Phase 1 and Phase 2	50 individuals (18 years and older)	Stockholm, Sweden
5.	NCT04389710	Convalescent Plasma for the Treatment of COVID-19	Recruiting	Phase 2	100 individuals (18 years and older)	Pennsylvania, United States
6.	NCT04415086	Treatment of Patients With COVID-19 With Convalescent Plasma	Recruiting	Phase 2	120 individuals (18 years and older)	São Paulo, SP, Brazil
7.	NCT04353206	Convalescent Plasma in ICU Patients With COVID-19- induced Respiratory Failure	Recruiting	Early Phase 1	60 individuals (18 years and older)	California and Maryland, United States
8.	NCT04343755	Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 Infection	Recruiting	Phase 2	55 individuals (18 years and older)	New Jersey, United States
9.	NCT04397757	COVID-19 Convalescent Plasma for the Treatment of Hospitalized Patients With Pneumonia Caused by SARS-CoV-2.	Recruiting	Phase 1	80 individuals (18 years and older)	Pennsylvania, United States
10.	NCT04348656	Convalescent Plasma for Hospitalized Adults With COVID-19 Respiratory Illness (CONCOR-1)	Recruiting	Phase 3	1600 individuals (16 years and older)	New York, United States; Ontario, Canada; and 21 more
11.	NCT04388527	COVID-19 Convalescent Plasma for Mechanically Ventilated Population	Recruiting	Phase 1	50 individuals (18 years and older)	Pennsylvania, United States
12.	NCT04347681	Potential Efficacy of Convalescent Plasma to Treat Severe COVID-19 and Patients at High Risk of Developing Severe COVID-19	Recruiting	Phase 2	40 individuals (18 years to 85 years)	Jeddah, Dhahran, Dammam, Medina, Qatif, Saudi Arabia and 4 more
13.	NCT04342182	Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study)	Recruiting	Phase 2 and Phase 3	426 individuals (18 years and older)	Zuid-Holland, Alkmaar, Amsterdam, Arnhem, Delft, Den Haag, Eindhoven, Enschede, Gouda, Groningen, Netherlands and 8 more
14.	NCT04390503	Convalescent Plasma for COVID-19 Close Contacts	Recruiting	Phase 2	200 individuals (18 years and older)	New York, United States
15.	NCT04405310	Convalescent Plasma of Covid-19 to Treat SARS-COV-2 a Randomized Double Blind 2 Center Trial	Recruiting	Phase 2	80 individuals (18 years to 70 years)	Mexico City, Mexico
16.	NCT04375098	Efficacy and Safety of Early COVID-19 Convalescent Plasma in Patients Admitted for COVID-19 Infection	Recruiting	Phase 2	58 individuals (More than 18 years of age)	Santiago, Chile
17.	NCT04374526	Early transfusion of Convalescent Plasma in Elderly COVID-19 Patients to Prevent Disease Progression	Recruiting	Phase 2 and Phase 3	182 Older Adults (65 years and older)	RM, Chieti and Rome, Italy
18.	NCT04403477	Convalescent Plasma Therapy in Severe COVID-19 Infection	Recruiting	Phase 2	20 individuals (16 years or older)	Dhaka, Bangladesh
19.	NCT04345523	Convalescent Plasma Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients	Recruiting	Phase 2	278 individuals (18 years and older)	Aragón and Madrid, Spain
20.	NCT04356482	Convalescent plasma for ill patients by COVID-19	Recruiting	Phase 1 and Phase 2	90 individuals (16 years and older)	Jalisco, Sonora and Mexico city, Mexico
21.	NCT04381858	Convalescent Plasma vs Human Immunoglobulin to Treat COVID-19 Pneumonia	Recruiting	Phase 3	500 individuals (16 years to 90 years)	Aguascalientes, Mexico
22.	NCT04384588	COVID19-Convalescent Plasma for Treating Patients With Active Symptomatic COVID 19 Infection (FALP-COVID)	Recruiting	Phase 2 and Phase 3	100 individuals (15 years and older)	Santiago, Chile
23.	NCT04392232	A Study of COVID 19 Convalescent Plasma in High Risk Patients With COVID 19 Infection	Recruiting	Phase 2	100 individuals (16 years and older)	Ohio, United States
24.	NCT04364737	Convalescent Plasma to Limit COVID-19 Complications in Hospitalized Patients	Recruiting	Phase 2	300 individuals (18 years and older)	New York, United States
25.	NCT04362176	Passive Immunity Trial of Nashville II for COVID-19	Recruiting	Phase 3	500 individuals (18 years and older)	Tennessee, United States

(*Continued*)

Table 2. (Continued).

S. No.	NCT No.	Title	Status	Phase	Population	Location
26.	NCT04392414	Hyperimmune Convalescent Plasma in Moderate and Severe COVID-19 Disease	Recruiting	Phase 2	60 individuals (18 Years to 75 Years)	Moscow, Russian Federation
27.	NCT04385199	Convalescent Plasma for Patients With COVID-19	Recruiting	Phase 2	30 individuals (18 years and older)	Michigan, United States
28.	NCT04393727	Transfusion of Convalescent Plasma for the Early Treatment of Patients With COVID-19	Recruiting	Phase 2	126 individuals (18 years and older)	Pisa, Italy
29.	NCT04354831	A Study Evaluating the Efficacy and Safety of High-Titer Anti- SARS-CoV -2 Plasma in Hospitalized Patients With COVID-19 Infection	Recruiting	Phase 2	131 individuals (18 years and older)	Wisconsin, United States
30.	NCT04374565	Convalescent Plasma for Treatment of COVID-19 Patients With Pneumonia	Recruiting	Phase 2	29 individuals (18 years and older)	Virginia, United States
31.	NCT04425915	Efficacy of Convalescent Plasma Therapy in Patients With COVID-19	Recruiting	Phase 3	400 individuals (18 years and older)	New Delhi, Delhi, India
32.	NCT04438694	Use of Convalescent Plasma for Treatment of Patients With COVID-19 Infection (CP IN COVID19)	Recruiting	Phase 1 and Phase 2	60 individuals (21 years to 70 years)	Cairo, Egypt
33.	NCT04397523	Efficacy and Safety of COVID-19 Convalescent Plasma	Recruiting	Not Applicable	20 individuals (18 years and older)	Skopje, North Macedonia
34.	NCT04433910	A Clinical Trial of Convalescent Plasma Compared to Best Supportive Care for Treatment of Patients With Severe COVID-19 (CAPSID)	Recruiting	Phase 2	100 individuals (18 years and older)	Germany
35.	NCT04352751	Experimental Use of Convalescent Plasma for Passive Immunization in Current COVID-19 Pandemic in Pakistan in 2020	Recruiting	Not Applicable	2000 individuals (18 years to 55 years)	Karachi, Sindh, Pakistan
36.	NCT04356534	Convalescent Plasma Trial in COVID −19 Patients	Recruiting	Not Applicable	40 individuals (21 years and older)	Manama, Bahrain
37.	NCT04442191	Convalescent Plasma as a Possible Treatment for COVID-19	Recruiting	Phase 2	50 individuals (40 years and older)	Chicago, Illinois, United States
38.	NCT04408209	Convalescent Plasma for the Treatment of Patients With Severe COVID-19 Infection	Recruiting	Not Applicable	60 individuals (18 years and older)	Athens, Attiki, Greece
39.	NCT04434131	Treatment With Investigational Convalescent Plasma and Measure Antibody Levels in Patients Hospitalized With COVID-19	Recruiting	Phase 2	30 individuals (18 years and older)	New Mexico, United States
40.	NCT04421404	Effects of COVID-19 Convalescent Plasma (CCP) on Coronavirus-associated Complications in Hospitalized Patients (CAPRI)	Recruiting	Phase 2	30 individuals (18 years and older)	San Francisco, California, United States
41.	NCT04359810	Plasma Therapy of COVID-19 in Critically Ill Patients	Recruiting	Phase 2	105 individuals (18 years and older)	New York, United States
42.	NCT04361253	Evaluation of SARS-CoV-2 (COVID-19) Antibody-containing plasma therapy (ESCAPE)	Recruiting	Phase 3	220 individuals (12 months and older)	Massachusetts, United States
43.	NCT04357106	Treatment of Severe Forms of C0ronavirus Infection With Convalescent Plasma (COPLA)	Recruiting	Phase 2	10 individuals (18 years and older)	Puebla, Mexico
44.	NCT04383535	Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia (PLASM-AR)	Recruiting	Not Applicable	333 individuals (18 years and older)	Argentina
45.	NCT04373460	Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004)	Recruiting	Phase 2	1344 individuals (18 years and older)	United States

determining the efficacy and to establish the optimal conditions for convalescent plasma therapy in less severely ill COVID-19 patients.

3. Monoclonal antibodies (mAbs) and neutralizing antibodies (NAbs)

Even though plasma derived from convalescent patients are a good source of polyclonal NAbs, their outcome is unpredictable due to the variability of sera obtained from different patients [52]. Many studies reported that within the first 7 days after the onset of clinical symptoms COVID-19, patients rarely develop specific antibodies. Moreover, after 10–11 days of symptom development more than 90% of the COVID-19 patients have been reported to develop virus-specific IgG and IgM antibodies [53–56]. The mAbs can be specific and can minimize the adverse effects of convalescent plasma [27] (Figure 1). They can also reduce the course of infection or protect uninfected cells exposed to SARS-CoV-2 [25]. However, there is an urgent need to develop mAbs and identify their ideal target. Monoclonal antibodies against the specific viral targets can be identified through conventional immunization of mice approach or isolation of the antigen-specific memory B cells from the recovered patients. By these approaches, the B-cell receptor gene can be identified, and therapeutic monoclonal antibody can be synthesized on a large scale by expressing the gene in cell lines. Antibodies are recognized as therapeutic biological molecules, and it has been widely used for the treatment of different cancers since the approval of first monoclonal antibody in 1986 by United States Food and Drug Administration (US FDA) [57–60].

The presence of NAb following SARS-CoV-2 infection is critical for the virus clearance and protection following convalescent plasma therapy. A recent study showed that all the 26 patients recovered from COVID-19 had IgG antibodies against the SARS-CoV-2 S1 protein in serum. Of these 26 patients, all the patients except three had high titers of SARS-CoV-2 S1 RBD specific IgG antibodies. However, most importantly, only 3 out of 26 patients had antibodies that were able to block SARS-CoV-2 binding to the hACE2 receptor. It showed that most COVID-19 recovered patients were able to generate antibodies against SARS-CoV-2 spike protein, and only a small fraction of them actually block the virus binding to the hACE2 receptor and have virus-neutralizing activity [61].

The spike protein, or S protein, of SARS-CoV-2, has a significant role in viral attachment, fusion, and entry. Therefore, the S protein is considered as the major target for developing antibodies and vaccines [62]. Antibodies against the RBD of the S protein have enormous potential to neutralize the infection, thereby acting as an important target for antibody development [63]. Even though there is high similarity between the RBD of SARS-CoV-2 and SARS-CoV, it is necessary to develop SARS-CoV-2-specific mAbs, since the degree of similarity is not high enough to produce cross-reactivity among these closely related viruses [64]. Studies have also found that the RBD-specific antibodies produced against SARS-CoV cross-reacted with the SARS-CoV-2 RBD protein [62]. Therefore, a cocktail of neutralizing antibodies targeting different epitopes of SARS-CoV-2 should be provided to offer a comprehensive coverage against SARS-CoV-2 [52]. Though the antibody against RBD of S1 protein is the most critical target for virus neutralization, some NAbs binding to epitopes on the S2 unit have also shown a neutralization effect against SARS CoV [65,66].

NAbs can be in the form of mAb, antigen-binding fragment (Fab), single-chain variable region fragment (scFv), or single-domain antibody which can bind to the S1 subunit or S2 of the viral S protein and inhibit the viral entry into the host cells. There were several NAbs that have been developed for the SARS CoV-2 ancestors, such as SARS-CoV and MERS-CoV [63]. Some of the most potent NAbs, such as m396 and CR3014 that are specific to the SARS-CoV ACE2 binding site, failed to bind to the S protein of SARS-CoV-2. However, another SARS-CoV-specific human mAb, CR3022, was found to bind to the RBD of SARS-CoV-2, indicating potential cross-reactivity [64]. In another study, polyclonal anti-SARS-CoV S1 antibodies T62 that have the potential to inhibit the entry of SARS-CoV S pseudo-virions failed to produce a similar effect on SARS-CoV-2 [67]. Wang et al. [68] reported that the 47D11 (human) mAb neutralize SARS-CoV-2; this antibody targets a conserved epitope on the S protein of SARS-CoV-2, especially the core structure of the S1B RBD of the S protein.

Using the enzyme-linked immunosorbent assay, researchers confirmed that patients who recovered from COVID-19 had high titers of anti-SARS-CoV-2 S1 spike protein specific IgG antibodies in their sera, which is capable of obstructing the binding of SARS-CoV-2 RBD to human ACE2 receptor (hACE2) [61,69,70]. It was observed that specific memory B cells containing anti-SARS-CoV-2 RBD-specific IgG antibodies were prevalent only in the patients who had recovered from COVID-19. The variable heavy chain and variable light chain of IgG-antibodies obtained from these specialized memory B-cells were used for cloning, and three human origin mAbs (311mab–31B5, 311mab–32D4, and 311mab–31B9) were produced. Among these three antibodies, 311mab-31B5 and 311mab-32D4 could firmly and specifically bind to SARS-CoV -2 RBD protein to neutralize SARS-CoV-2. Likewise, humanized anti-SARS-CoV-2 RBD-hACE2 blocking mAbs are promising prophylactic and therapeutic anti-SARS-CoV-2 agents [61]. Apart from SARS-CoV-2 specific monoclonal antibodies, several others approved for different indications have been found useful for treating COVID-19 patients. A clinical trial performed at Qilu Hospital, Shandong University, China, in over 20 critically ill COVID-19 patients has shown positive results after application of another humanized mAb, bevacizumab, which binds to vascular endothelial-derived growth factor (VEGF), for improving symptoms of respiratory distress in COVID-19 patients (ClinicalTrials.gov No. NCT04275414) [71]. The cytokine storm and increase in the level of IL-6 is considered as a reliable indicator of poor outcome in a severe form of COVID-19 [72,73]. In this context, a humanized mAb tocilizumab, which binds competitively with IL-6 receptors, was found effective in a clinical trial (ChiCTR2000029765) against the severe form of COVID-19 [72,74]. Siltuximab is a humanized

mAb that binds to IL-6 can also be used for treating for IL-6 mediated hyper inflammation in COVID-19 patients [75]. The use of tocilizumab and siltuximab for IL-6 antagonism prevent the cytokine storm and associated clinical symptoms in patients with severe COVID-19 [76]. However, the antagonism of IL-6 may weaken the immune system of affected individuals making them more vulnerable to secondary infections. Blocking IL-6 also helps to reduce the excessive immune mediated inflammation and tissue damage in various organs of COVID-19 patients. The overall benefit is higher than the risk involved in blocking the IL-6. A study suggested that a single dose of tocilizumab is not effective in critically ill COVID-19 patients. However, repeated doses of tocilizumab, even when repeated with lower doses, might prove effective in critically ill patients [77]. A multicentre, prospective, randomized double blind, placebo-controlled trial has been initiated on 27 April 2020, to evaluate the efficacy as well as safety of single-dose Tocilizumab therapy in patients with severe COVID-19 [78]. The trial is anticipated to be completed by December 2020 and is expected to give an insight into the clinical utility of Tocilizumab therapy in COVID-19 patients. As per the report, ocrelizumab, a B-cell depleting humanized anti-CD20 mAb, has been proven effective as a treatment option for dealing with the progressive multiple sclerosis disease complicated with SARS-CoV-2 infection. This therapy is reported to cause the absence of new COVID-19 symptoms after 14 days of treatment [79]. Data on the use of eculizumab with anti-complement C5 activity for treating severe cases of COVID-19 indicates the successful recovery of the patients and the reduction of inflammatory markers along with mean C-reactive protein [80].

In an *in vitro* study, several mAbs were identified from a panel of mAbs isolated from the B cells of infected subjects that target spike or S glycoprotein of SARS-CoV-2. Among these mAbs, the most potent ones, COV2-2196 and COV2-2130, were found to block the receptor-binding domain (RBD) of S protein from interacting with the ACE2 receptor [81]. The passive transfer of these two mAbs in the murine model of SARS-CoV-2 as monotherapy or in combination protected the mice from severe weight loss as well as reduced the viral burden and inflammatory changes in the lungs [81]. Scientists are currently attempting to develop SARS-CoV-2-specific mAbs and/or their functional fragments as prophylactic or therapeutic agents. Once developed, such mAbs would have to undergo *in vitro* evaluation for neutralizing potential, *in vivo* protective efficacy studies in SARS-CoV-2 animal models, preclinical studies, and clinical trials [63]. Although the conventional approach of developing therapeutic monoclonal antibody is a time-consuming process, the great effort made by the researchers worldwide during this pandemic has accelerated the development of such neutralizing mAbs or their fragments at a fast pace due to the urgent need to save COVID-19 patients.

Recently, the Regeneron Pharmaceuticals, Inc. has announced the initiation of the first clinical trial of REGN-COV2, which is a dual antibody cocktail of REGN10933 + REGN10987 for the prevention and treatment of SARS-CoV-2. Moreover, the REGN-COV2 clinical program will include four separate study populations, i.e. hospitalized COVID-19 patients, non-hospitalized symptomatic COVID-19 patients, uninfected high-risk individuals like healthcare workers or first responders, and uninfected people in close exposure with a COVID-19 patient like a housemate. The placebo-controlled trials of REGN-COV2 will be initiated soon at multiple locations [82]. The LY-CoV555 is a mAb specifically binds with different epitopes on the spike protein of SARS-CoV-2 and is the first neutralizing antibody developed by Eli Lilly and Co. to enter Phase 1 of a clinical trial. Moreover, the LY-CoV555 is currently being evaluated in hospitalized COVID-19 patients for safety and tolerability [83]. In addition, Eli Lilly is planning a clinical development program with antibody cocktails of JS016, LY-CoV555, and additional antibodies to understand the tolerability and efficacy in COVID-19 patients in a better way [83]. The Tychan, a Singapore-based biotechnology company, has already completed recruiting healthy volunteers for Phase 1 clinical trials of TY027, a specific mAb against SARS-CoV-2, and will start dosing the individuals soon [84]. Another antibody named S309 was reported to neutralize the SARS-CoV-2 by binding with the RBD of S protein. Moreover, the S309 along with S309 containing antibody cocktails, may prove crucial for prophylaxis against COVID-19 in high-risk individuals [85]. Researchers also proposed an ACE2 immunoadhesin developed by fusing the receptor of SARS-CoV-2, ACE2, and the Fc domain of an immunoglobulin. Such an approach is expected to provide long term protection [86,87]. Rather than using monotherapy, the combined use of several potent NAbs could decrease the possibility of certain viral isolates escaping antibody-dependent neutralization [52]. Although mAb-based passive immunotherapy has been widely studied for coronavirus infections, none of them have been marketed till now. The primary reason that limits the use of mAbs is the expensive, laborious, and time-consuming production process [27,86]. The advancement in therapeutic protein production platforms may be useful for low-cost mAb production. The sequences of SARS-CoV-2 specific mAbs can be expressed in suitable mammalian, yeast, or plant expression systems, which facilitate their evaluation as well as large scale production [27]. Even though MAbs are an excellent therapeutic option for SARS-CoV-2 infection, the current lack of commercially available MAbs either for SARS-CoV or MERS-CoV indicates the limitations of this therapeutic strategy [52]. Nevertheless, mAbs have several advantages over the other forms of immunotherapies, such as convalescent plasma and intravenous immunoglobulin preparations. They are superior in terms of safety, purity, and specificity; they are associated with a no risk of blood-borne pathogen transmission and also provide immediate protection against infectious diseases [27]. Ongoing clinical trials for MAbs against COVID-19 are presented in Table 3.

4. Intravenous Immunoglobulin (IVIg)

IVIg is a blood-derived product that has been used for several decades. It contains polyclonal IgG isolated from healthy donors [88]. IVIg therapy is another immunotherapeutic

Table 3. Ongoing clinical trials for monoclonal antibodies against COVID-19 (www.clinicaltrials.gov).

S. No.	NCT No.	Title	Status	Phase	Population	Location
1.	NCT04425629	Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for the Treatment of Ambulatory Adult Patients With COVID-19	Not yet recruiting	Phase 1 and Phase 2	1054 individuals (18 years and older)	Regeneron Pharmaceuticals
2.	NCT04426695	Safety, Tolerability, and Efficacy of Anti-Spike (S) SARS-CoV-2 Monoclonal Antibodies for Hospitalized Adult Patients With COVID-19	Not yet recruiting	Phase 1 and Phase 2	1860 individuals (18 years and older)	Regeneron Pharmaceuticals
3.	NCT04391309	IC14 (Anti-CD14) Treatment in Patients With SARS-CoV-2 (COVID-19)	Not yet recruiting	Phase 2	300 individuals (18 years and older)	Washington, United States
4.	NCT04351152	Phase 3 Study to Evaluate Efficacy and Safety of Lenzilumab in Hospitalized Patients With COVID-19 Pneumonia	Recruiting	Phase 3	238 individuals (18 years to 85 years)	Arizona, Florida, Georgia, Minnesota, New Hampshire, North Carolina, and Texas, United States
5.	NCT04354766	COVID-19: Neutralizing Human Monoclonal Antibodies Against SARS-Cov-2	Recruiting	Not applicable	10 individuals (18 years and older)	Lyon, France
6.	NCT04341116	Study of TJ003234 (Anti-GMCSF Monoclonal Antibody) in Subjects With Severe Coronavirus Disease 2019 (COVID-19)	Recruiting	Phase 1 and Phase 2	144 individuals (18 years and older)	Columbia, Illinois, Indiana, Louisiana, Mississippi, Oregon, Pennsylvania, and Texas, United States
7.	NCT04429529	Safety of TY027, a Treatment for COVID-19, in Humans	Recruiting	Phase 1	25 individuals (21 Years to 50 Years)	Singapore
8.	NCT04324021	Efficacy and Safety of Emapalumab and Anakinra in Reducing Hyper-inflammation and Respiratory Distress in Patients With COVID-19 Infection.	Recruiting	Phase 2 and Phase 3	54 individuals (30 Years to 79 Years)	Brescia, Milano, Parma and Roma, Italy
9.	NCT04351243	A Study to Assess the Efficacy and Safety of Gimsilumab in Subjects With Lung Injury or Acute Respiratory Distress Syndrome Secondary to COVID-19 (BREATHE).	Recruiting	Phase 2	270 individuals (18 years and older)	California, Georgia, Illinois, Louisiana, Michigan, New York, United States and five more
10.	NCT04343651	Study to Evaluate the Efficacy and Safety of Leronlimab for Mild to Moderate COVID-19	Recruiting	Phase 2	75 individuals (18 Years to 99 Years)	California, Connecticut, Georgia, Massachusetts, New Jersey, New York, North Carolina, Ohio and Oregon, United States
11.	NCT04305106	Bevacizumab in Severe or Critically Severe Patients With COVID-19 Pneumonia-RCT	Recruiting	Not applicable	140 individuals (18 Years to 80 Years)	Shandong, China
12.	NCT04357808	Efficacy of Subcutaneous Sarilumab in Hospitalized Patients With Moderate to severe COVID-19 Infection (SARCOVID)	Recruiting	Phase 2	30 individuals (18 years and older)	Madrid, Spain
13.	NCT04377750	The Use of Tocilizumab in the Management of Patients Who Have Severe COVID-19 With Suspected Pulmonary Hyper-inflammation	Recruiting	Phase 4	500 individuals (18 years and older)	Ramat Gan, Ashkelon, Israel and two more
14.	NCT04347239	Study to Evaluate the Efficacy and Safety of Leronlimab for Patients With Severe or Critical Coronavirus Disease 2019 (COVID-19)	Recruiting	Phase 2	390 individuals (18 years and older)	California, Connecticut, Massachusetts, New Jersey, New York, North Carolina, Ohio Oregon, and Texas, United States
15.	NCT04365153	Canakinumab to Reduce Deterioration of Cardiac and Respiratory Function Due to COVID-19	Recruiting	Phase 2	45 individuals (18 years and older)	Ohio, United States
16.	NCT04322773	Anti-IL6 Treatment of Serious COVID-19 Disease With Threatening Respiratory Failure	Recruiting	Phase 2	200 individuals (18 years and older)	Copenhagen and Hillerød, Denmark
17.	NCT04390464	Multi-Arm Therapeutic Study in Pre-ICU Patients Admitted With Covid-19 – Repurposed Drugs (TACTIC-R)	Recruiting	Phase 4	1167 individuals (18 years and older)	Cambridgeshire, United Kingdom

option for managing COVID-19 patients besides other options [89,90]. The efficacy of IVIg therapy can be further enhanced by using IgG antibodies that are collected from recovered COVID-19 patients in the same city or locality. This will improve the chances of neutralizing this novel virus [91]. High-dose IVIg therapy is considered to enhance passive immunity and has a role in modulating immune inflammation. Therefore, IVIg can be considered as a therapeutic option in the early stages of SARS-CoV-2 infection [88]. Shi et al. [92] reported a severe case of SARS-CoV-2 that was successfully treated without mechanical ventilation or intensive supportive care by using intensive plasma exchange along with IVIg. As per the report, the application IVIg was observed to be effective in a patient suffering from COVID-19 associated with mucous membrane pemphigoid, hypertension, and diabetes [93]. Additionally, a high dose of IVIg is reported to interfere with the inflammatory factors without compromising the immunological status of COVID-19 patients [94,95]. However, the efficacy of the concurrent drugs used along with IVIg in the course of the disease needs further clinical trials.

The early use of IVIg as adjuvant therapy in patients with COVID-19 pneumonia was found to be effective in reducing the use of mechanical ventilation and promotes early recovery, thereby reducing the hospitalization period [96]. Similarly, in another study, high-dose IVIg at a dose of 0.3–0.5 g/kg continuously for five days was found to improve clinical condition as well as O_2 saturation in COVID-19 patients, thereby preventing the progression of pulmonary lesions [97]. Inclusion of IVIg as adjuvant therapy in the treatment protocol within 48 hours of intensive care unit (ICU) admission was found to reduce the need for mechanical ventilation in COVID-19 patients with pneumonia [98]. In another study, a high dose of IVIg therapy in laboratory-confirmed SARS-CoV-2 infected patients resulted in the improvement of outcome as well as blocked disease progression. Administration of IVIg was not found to be associated with any adverse events [88]. Moreover, the use of SARS-CoV-2-specific immune IgG antibodies will boost immune responses in newly infected patients [91]. However, further randomized clinical controlled trials are required to evaluate the efficacy of IVIg therapy in managing COVID-19 outbreaks. At present, a randomized controlled trial has been initiated to evaluate the efficiency of high-dose IVIg therapy in managing severe cases of COVID-19 (NCT 04261426) [88]. The findings from this trial are expected to give an insight into the usefulness of IVIg therapy in SARS-CoV-2 infection. Infusion of SARS-CoV-2 specific IgG with a binding titer > 1:1000 and a neutralization titer > 40 in 5 critically ill COVID-19 patients after 10–22 days of admission has demonstrated considerable efficacy [35]. Flebogamma® DIF (Grifols) and Gamunex®-C are two commercially available IVIg products that were evaluated for the presence of antibodies that may cross-react with SARS-CoV-2 virus. Both of these products were found to contain antibodies that bind to SARS-CoV-2 antigens and, therefore, might have clinical utility in managing COVID-19 [99]. However, further studies are required to validate their utility.

During the collection of immunoglobulins, steps must be taken to eliminate or inactivate any possible pathogens that are present in the plasma of recovered COVID-19 patients. Some of these methods include the use of solvents/detergents, nanofiltration, and heat-treatment (60°C) [91]. Combination therapy using IVIg and antiviral drugs might be an efficient therapeutic option for managing SARS-CoV-2 infection. The major factor that determines the outcome of IVIg therapy is the timing of administration; it has to be administered before the initiation of systemic damage; otherwise, IVIg therapy would not be beneficial [88].

5. Expert opinion

Researchers around the globe are exploring many therapeutic strategies to develop an effective treatment regimen for COVID-19. Immunotherapeutic strategies, such as convalescent plasma and IVIg, are potential therapeutic options for managing COVID-19 patients. The benefits of using convalescent plasma in SARS-CoV-2-infected patients outweigh the risks by a considerable margin. With the lack of specific antivirals or vaccines against COVID-19, convalescent plasma is potentially an immediately available therapeutic approach, helping to minimize disease severity, prevent mortality, facilitate early recovery, and reduce viral load and lung pathology. However, limitations such as the transmission of other diseases, complications of anaphylaxis, ADE, pulmonary edema, difficulty in procurement, and non-specificity needs to be addressed through the development of specific entities like mAbs. Specific mAb-based immunotherapeutics can target a specific antigenic epitope on SARS-CoV-2, thus acting efficiently against the virus. mAbs against the RBD of the S1 subunit of Spike protein show virus neutralization activity and have the potential to become a targeted therapy against the virus. Researchers have already identified a few such neutralizing antibodies, and they are under preclinical development stage. It will take several months or even years to develop SARS-CoV-2-specific mAbs if the conventional drug development approach is taken. Considering the pandemic situation, expedited approval of the promising mAbs is possible if the safety and efficacy are proven even in a small number of patients. There is also a need for identifying new neutralizing antibodies with therapeutic potential against COVID-19. The advances made in the development of immunotherapeutics against SARS-CoV and MERS-CoV is expected to fuel the development of suitable therapeutics against SARS-CoV-2. Even though SARS-CoV and SARS-CoV-2 share some similarities in their domains, SARS-CoV-2-specific immunotherapeutic approaches are required due to the limited cross-reactivity between these two closely related coronaviruses. Some governments are considering the use of immunity passports, a document that certifies an individual has recovered from COVID-19 infection and immune to SARS-CoV-2 to allow them to work in places where the risk of acquiring infection is high [100,101]. However, this approach needs scientific evidence based on the presence of lasting neutralizing antibodies. At present, we have to rely

exclusively on convalescent plasma therapy, and it also needs to be based on the virus neutralization activity of the donor plasma to ensure the therapeutic benefit. Cell based immunotherapeutic approaches using Natural Killer cells, virus specific T cells, genetically engineered T cells also need to be explored for treating COVID-19 patients. At present, there is an urgent need for effective and safe mAb-based immunotherapeutics suitable for all physiological categories of humankind, which can be used to treat critically ill COVID-19 patients and prophylactically used to protect healthcare professionals, frontline workers, and naïve population at higher risk of acquiring the disease.

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