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REVIEW

Passive antibody therapy in emerging infectious diseases

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Abstract **The epidemic of corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 and its variants of concern (VOCs) has been ongoing for over 3 years. Antibody therapies encompassing convalescent plasma, hyperimmunoglobulin, and neutralizing monoclonal antibodies (mAbs) applied in passive immunotherapy have yielded positive outcomes and played a crucial role in the early COVID-19 treatment. In this review, the development path, action mechanism, clinical research results, challenges, and safety profile associated with the use of COVID-19 convalescent plasma, hyperimmunoglobulin, and mAbs were summarized. In addition, the prospects of applying antibody therapy against VOCs was assessed, offering insights into the coping strategies for facing new infectious disease outbreaks.**

Keywords SARS-CoV-2; COVID-19; convalescent plasma; hyperimmunoglobulin; neutralizing monoclonal antibodies

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded positive-sense RNA virus belonging to the genus *Betacoronavirus*, and it has been responsible for the COVID-19 epidemic since December 2019 [1]. As of March 29, 2023, 761 402 282 confirmed cases of COVID-19, including 6 887 000 deaths, have been reported according to the World Health Organization (WHO) [2]. COVID-19 progression involves two stages: virus replication and immune response. In the host immune response stage, some severe and critical COVID-19 cases progress to the life-threatening condition of multiorgan dysfunction, which includes intractable hypoxemia caused by acute respiratory distress syndrome [3–5]. In accordance with the natural disease progression of COVID-19, before the body's immune response is activated, that is, under high baseline viral load, exogenous immune effectors administered to patients with COVID-19 can passively induce adaptive immune responses, resulting in therapeutic effects [6].

During the COVID-19 outbreak in 2020, obtaining vaccines or antiviral drugs in a short time was difficult [7]. On the basis of the time needed for the development of therapeutic antibody drugs, SARS-CoV-2 passive immunotherapy can be divided into three stages: COVID-19 convalescent plasma (CCP), COVID-19 hyperimmunoglobulin (COVID-HIG), and neutralizing monoclonal antibodies (mAbs). CCP therapy, as a traditional passive immunotherapy, was the easiest and most readily available strategy for COVID-19 treatment prior to the successful development of COVID-19 vaccines. CCP is obtained from the plasma of patients with protective antibodies, who have recovered from COVID-19, and viral inactivation of plasma is mainly performed with psoralen (S-59) in combination with ultraviolet A (UVA) light, riboflavin ultraviolet light, or methylene blue light [8,9]. COVID-HIG is obtained from the plasma of a definite number of patients who recovered from COVID-19 or healthy COVID-19 vaccine recipients with high-titer antibodies. In addition to the viral removal and inactivation techniques, the mixed plasma pool is separated and purified using the industrial low-temperature ethanol method or through caprylic acid precipitation [10,11]. For the development of SARS-CoV-2 neutralizing mAbs, several attractive platforms have been developed. For example, in antigen-specific single B cell sorting technology, single B cells are acquired from patients who recovered from COVID-19 or recipients of vaccines with target specific antigens (receptor binding domain (RBD) or N-terminal domain (NTD) of spike protein, or other sites of spike (S)) (Fig.1), and direct amplification of the genes encoding the VH and VL regions of single B cells and their subsequent

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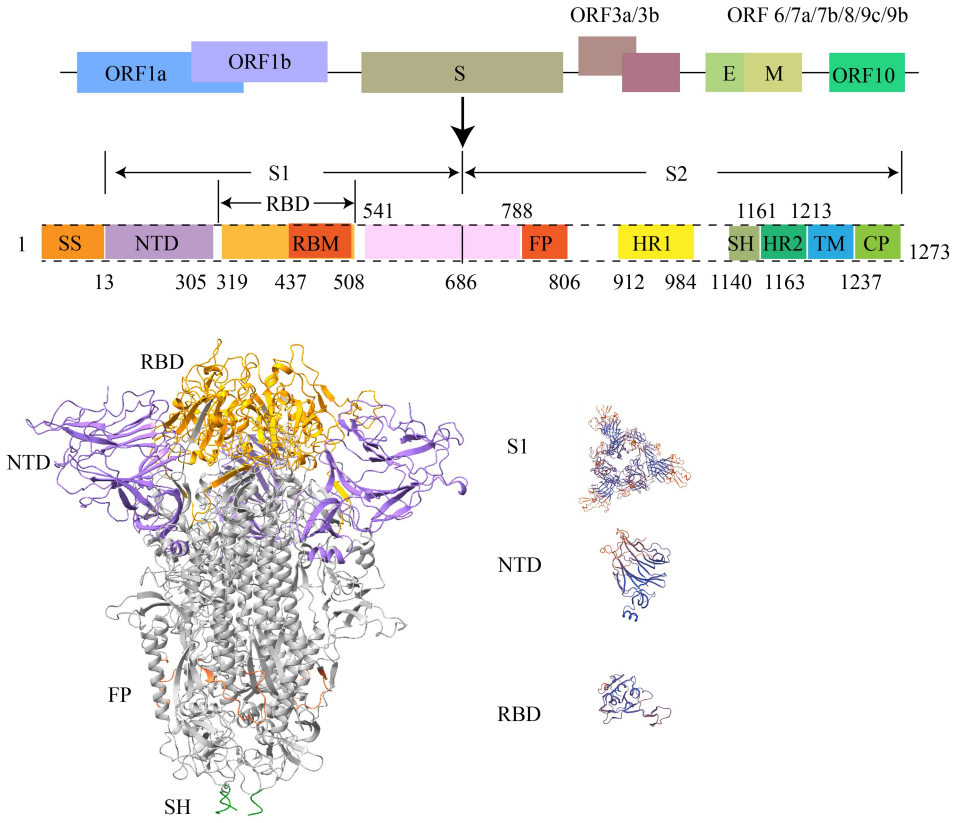

Fig. 1 Different neutralizing mAbs target different sites of S protein. Most of the approved COVID-19 monoclonal antibodies target S1 receptor-binding domain (RBD), other target site including: S1 N-terminal domain (NTD), S2 fusion peptide, S2 stem helix (SH).

expression in cell culture systems are performed [12,13]. In phage display technology, the B cells of recovered patients are used to construct a phage library, and high-affinity antibodies are obtained after screening [14]. In transgenic mouse technology, human antibody genes are introduced into mice by using gene editing technology, and fully humanized antibodies are obtained through conventional animal immunization and hybridoma screening technology [15]. The process of obtaining and industrial production of CCP, COVID-HIG, and COVID-19 neutralizing mAbs is illustrated in Fig. 2.

Action mechanism of antibodies in COVID-19 treatment

CCP, COVID-HIG, and mAbs have strong anti-infection and neutralizing activities. The SARS-CoV-2 specific antibodies in CCP, COVID-HIG, or the mAbs targeting S protein, and RBD or NTD of S protein block conformational changes in S protein or bind to it to prevent receptor binding or membrane fusion of SARS-CoV-2, thereby preventing the entry of virus into host cells [16,17]. After antibodies binds to viruses, the antibody–virus aggregates enhance virus clearance [18]. Studies showed in a number of viral infection settings that antibodies eliminate infected cells displaying viral surface antigens through complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, and antibody-dependent cell-mediated cytotoxicity [19]. These same mechanisms have also been shown to be functional in the case of COVID-19 [20, 21]. Antibodies induce endogenous antiviral immune responses, form immune complexes with virus particles and/or infected cells, and enhance antiviral cytotoxic T lymphocyte responses through FcγR-mediated binding to dendritic cells; they also inhibit Treg cell expansion, limit immunosuppressive activity, and induce neutrophil antiviral activity [22]. Moreover, the therapeutic effectors in CCP and COVID-HIG can activate the complement system to dissolve and kill pathogens [23], reduce inflammatory responses to S protein, and enhance nucleocapsid (N) humoral responses [24].

Convalescent plasma as initial COVID-19 treatment

CCP has emerged as a potentially effective drug for the treatment of COVID-19 due to its ability to inhibit viral replication and improve inflammatory responses [25]. Duan *et al.* and Shen *et al.* were the first two groups that independently reported CCP treatment in COVID-19 in the early 2020 [8, 26]. Both groups observed

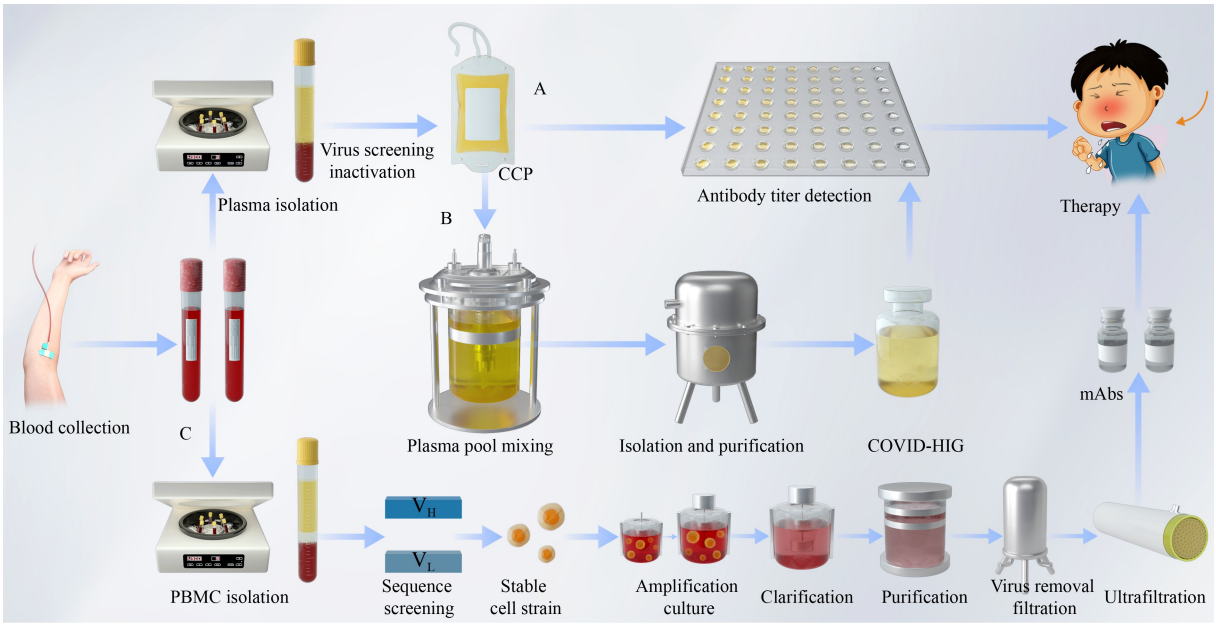

Fig. 2 Schematics of obtaining and industrial production of CCP, COVID-HIG, and mAbs. Blood is collected from a patient who recovered from COVID-19. (A) For CCP preparation, plasma cells are first obtained by centrifugation, and viruses in serum are removed or inactivated. Then, the SARS-CoV-2-specific antibody is detected. Qualified samples can be used for CCP therapy. (B) For COVID-HIG preparation, blood is centrifuged to collect the supernatant plasma, and plasmas from different individuals are mixed, inactivated, separated, and purified. Antibody testing is performed, and qualified samples can be used for COVID-HIG therapy. (C) mAbs are prepared by single B cell sorting technology. First, peripheral blood mononuclear cells (PBMCs) are isolated from the whole blood. Then, target B cells are screened from PBMCs by using flow cytometry. The gene sequence of the SARS-CoV-2 specific antibody secreted from target B cells is analyzed. Plasmid expression of SARS-CoV-2-specific antibody is conducted, and a stable cell line is generated by incorporating the transfection plasmid into the host CHO cell genome. The CHO cells are inoculated with stepwise amplification, and the culture supernatant is clarified by filtration, purified through chromatography, and concentrated through ultrafiltration. After the virus is removed, the mAb formulation is obtained for COVID-19 treatment.

improvements in clinical and biological parameters and rapid decrease in the viral load of critically ill patients with COVID-19 after CCP infusion. Some controlled clinical studies showed that CCP treatment in patients with COVID-19 can help reduce mortality, decrease viral load, and improve their clinical status [27–29].

CCP's therapeutic effect across different clinical trials may be related to the basic characteristics of participants, the specific supportive care, the combination therapy, the risk factors for disease progression, and the time of RCT implementation. Other factors, such as specific antibody titers in CCP, dose and frequency of CCP use, and clinical endpoint determination, may also affect the results of each clinical trial [30–32]. In spite of the controversies on the CCP effectiveness in the literature [30,33–35], many studies showed that in the early stage (within 72 hours after diagnosis) of COVID-19, the application of CCP containing high-titer anti-SARS-CoV-2 antibodies can improve symptoms, decrease incidences of disease progression and hospitalization, and reduce mortality rate, which indicates the importance of timely use of the CCP with high level specific antibodies against SARS-CoV-2 [36–40]. A 2023 systematic review revealed that high-dose CCP treatment within 5 days of symptom onset can offer some protection [41]. This viewpoint is supported by the results of early outpatient treatment for COVID-19 with CCP [42]. Possibly, in the late stage of COVID-19, the body has already produced high titers of antibodies against SARS-CoV-2, so using small doses (1–2 units) of CCP at this stage will not show the therapeutic effect of CCP. High-titer neutralizing antibodies are an effective therapeutic component of CCP; when the SARS-CoV-2-specific IgG titer in CCP was 1:3200 or higher, the risk of severe COVID-19 reduced by 73% in patients with COVID-19 aged ⩾ 75 years. The reason for this phenomenon may rely on the weakened humoral immune function in elderly patients [36]. In a small-sample clinical study, compared with standard-titer (1:160–1:640) CCP, high-titer (> 1:640) CCP demonstrated a crucial role in improving the symptoms of COVID-19 patients [43]. A large-sample clinical study of 3082 hospitalized non-intubated patients with COVID-19 reported 30-day mortality rates of 22.3%, 27.4%, and 29.6% in patients who received high-, medium-, and low-titer CCP treatments, respectively [31]. In high-risk patients (such as pregnant women, immunocompromised children, or solid organ transplant recipients), CCP should be considered early in the course of infection (within 72 h of onset) and administered before or upon admission.

Treatment of convalescent plasma in patients with immunocompromised/ underlying diseases

In the review of four patient groups (patients with cancer, immunosuppressed patients, patients with laboratory-determined risk for disease progression, and elderly patients with COVID-19), no therapeutic effect of CCP was observed when all cases were analyzed together [44]. However, subgroup analysis showed that the patients with cancer, who received CCP treatment, had a shorter recovery time and higher survival rates than the control group. Moreover, the patients with cancer exhibited an increased level of neutralizing antibodies (P = 0.001), indicating that CCP may improve COVID-19 outcomes in these patients who are unable to generate sufficient immune responses. The mortality rate was found to be reduced by 63% in patients with B cell lymphoid malignancies upon CCP treatment, while it is well known that these patients are not capable of generating adequate humoral immune responses to COVID-19 [45]. A 2023 meta-analysis of immunocompromised patients with COVID-19 included three randomized clinical trials (RCTs), five controlled studies, 125 case series or reports, and uncontrolled large case series enrolling 358 participants [46]. According to the stratified and merged model (i.e., RCTs and cohort studies), CCP treatment was associated with a decrease in mortality among immunocompromised patients with COVID-19 (risk ratio (RR), 0.63; 95% CI, 0.50–0.79). Complex interactions involving cytokine storms, inflammation, endothelial dysfunction, and pathological coagulation lead to increased severity of COVID-19 [47,48], and use of CCP exchange therapy may provide some benefits in such cases [49]. A systematic review and meta-analysis including six clinical studies supported that CCP exchange therapy can decrease the mortality rate of critically ill patients with COVID-19 [50].

Guide support for convalescent plasma use

Joyner *et al*. provided four viewpoints to support CCP treatment [51]. The Chinese guideline "Diagnosis and Treatment Protocol for COVID-19 (Trial Version 9)" emphasizes that CCP and COVID-HIG can be used in patients in the early stages of COVID-19 with high-risk factors, high viral loads, and rapid disease progression [52]. In August 2020, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for CCP treatment of hospitalized patients with COVID-19 [53]. Based on pooled data from 16 RCTs involving 16 236 mild, severe, and critically ill patients with COVID-19, the WHO recommends that CCP therapy can be used only for severe and critically ill groups [54]. The current EUA stipulates that CCP products with high-titer anti-SARS-CoV-2 antibodies can be used for the treatment of outpatients or inpatients with COVID-19 having immunosuppressive diseases or those receiving immunosuppressive therapy, and it has also revised the standards for high-antibody titer CCP products [55]. On the basis of two systematic reviews of RCTs evaluating the efficacy of CCP treatment from January 1, 2019, to January 26, 2022, the Clinical Practice Guidelines from the Association for the Advancement of Blood and Biotherapies provided the guidelines for CCP use and stated that high-titer CCP treatment is highly effective in the early stage of COVID-19 infection [56]. Overall, CCP treatment should be used in the early stages for patients with COVID-19 having high-risk factors or serious underlying diseases.

Role of COVID-hyperimmunoglobulin (HIG) in COVID-19 treatment

HIG products are commonly used to treat diseases, such as varicella-zoster virus, hepatitis B, anthrax, and cowpox [57–59]. The process of preparing COVID-HIG, a polyclonal antibody product from CCP, is highly complicated. Therefore, its clinical use was not as common as that of CCP during the COVID-19. However, many systematic reviews, meta-analyses, and clinical studies suggested the potential use of COVID-HIG for COVID-19 treatment [60,61].

Similar to CCP, conflicting results have been reported in clinical studies on the efficacy of COVID-HIG in COVID-19 treatment. A multicenter proof-of-concept interventional study revealed that COVID-HIG reduced the mortality rate of patients with COVID-19 compared with the expected mortality rate according to the national statistics. However, because of the lack of a control group and limited control of patients' basic characteristics, further clinical trials were required to validate the findings [62]. A single-center, single-blind, phase I/II RCT in Pakistan reported that administering COVID-HIG to severe and critically ill patients with COVID-19 was safe and associated with high survival rate and reduced disease progression risk [63]. Meanwhile, a randomized, double-blind, placebo-controlled phase III trial reported that COVID-HIG did not provide any benefit, possibly because antibody therapy might be ineffective in patients who had already developed an immune response; other factors associated with progressive COVID-19 could also affect the efficacy of COVID-HIG [64]. In several clinical studies, early administration of a high dose of COVID-HIG was reported to improve the prognosis of patients with COVID-19, such as a decrease in 28-day mortality rate; this finding might be related to the

COVID-HIG functions of anti-cytokine effects, the decrease in pro-inflammatory responses, the inhibition of complement activation, and the suppression of B- and T-cell functions, which could prevent organ failure and subsequent death [65–69]. Compared with CCP, COVID-HIG meets the high-titer requirements of neutralizing antibody in COVID-19 treatment. Though the number of COVID-HIG clinical studies is less in number than that of CCP clinical studies, based on the existing clinical studies and the component of the two plasma products, the use of COVID-HIG should also be recommended for patients with COVID-19 with high-risk factors or serious underlying diseases in early stages.

Use of mAbs for COVID-19 treatment

The use of mAbs was proven to be highly effective in treating infectious diseases, with numerous successful cases worth emulating. In 1998, the FDA approved the use of the short-acting palivizumab for the treatment of respiratory syncytial virus (RSV) [70]. In 2018, the FDA approved the mAb drug Trogarzo (ibalizumab) for HIV treatment [71]. Given the well-established manufacturing method for mAbs and the well-characterized preclinical and clinical studies, the effectiveness of multiple mAbs was extensively evaluated in COVID-19 treatment [72].

In a 2020 phase I–III clinical trial, Regeneron Pharmaceuticals reported a high efficacy of REGEN-COV cocktail therapy consisting of two mAbs (casirivimab and imdevimab) in reducing the SARS-CoV-2 viral load in non-hospitalized patients, especially those with a high baseline viral load or lacking an immune response [73]. Based on the results of a phase II/III clinical trial in 2020, Eli Lilly and Company reported that cocktail therapy comprising bamlanivimab and etesevimab, both targeting the critical RBD of the virus S protein, could yield better results in terms of the viral load reduction and clinical symptom alleviation in non-hospitalized patients with mild-to-moderate COVID-19, as compared to bamlanivimab monotherapy [74]. A phase III clinical trial conducted by VIR/GSK in 2021 reported that sotrovimab could reduce the risk of disease progression leading to hospitalization or death in non-hospitalized patients with mild-to-moderate COVID-19 but also high-risk factors, with a relative risk reduction (RRR) of 85% [75]. In a 2021 phase III clinical trial, based on 6-month follow-up data, AstraZeneca reported that a single dose of intramuscularly injected tixagevimab/cilgavimab could effectively prevent COVID-19 infection, with an RRR of 83% [76]. In a phase II/III clinical trial conducted by Brii Biosciences in 2021, the combination therapy of amubarvimab and romlusevimab could significantly reduce hospitalization or all-cause death risks in non-hospitalized COVID-19 patients, with an RRR of 81% [77]. Ample clinical evidence indicated that mAb therapies were effective in non-hospitalized patients with mild-to-moderate COVID-19 but not in hospitalized patients with severe COVID-19. This finding might be attributed to most severely ill patients who did not lack neutralizing antibodies but developed multiple-organ failure and life-threatening conditions in the later stages of the disease complicated by overactivation of the immune system and subsequent cytokine storm [78].

Owing to the efficacy of SARS-CoV-2 mAbs confirmed in clinical trials, the FDA issued emergency use authorizations (EUAs) for multiple mAb drugs. In November 2020, Eli Lilly and Company's bamlanivimab was granted the first EUA in the world, followed by Regeneron Pharmaceuticals' casirivimab/imdevimab combination, Eli Lilly and Company's bamlanivimab/etesevimab combination, GSK and Vir Biotechnology's sotrovimab, AstraZeneca's tixagevimab/cilgavimab combination, and Eli Lilly and Company's bebtelovimab. In December 2022, Brii Biosciences' amubarvimab/romlusevimab combination received conditional approval for marketing from the National Medical Product Administration, China. Almost all mAbs approved for marketing are indicated for use in individuals aged $\geqslant$ 12 years with mild-to-moderate symptoms, who are at a high risk of progressing to severe disease, including hospitalization or death. The FDA authorized six mAbs targeting specific SARS-CoV-2 proteins for emergency use in COVID-19 treatment, and numerous mAbs targeting cytokines associated with severe disease progression, such as IL-6, CCR5, and granulocyte macrophage colony-stimulating factor (GM-CSF), also were under clinical stage [79–81] (Table 1).

Currently, most mAbs used to treat COVID-19 are administered intravenously. However, this mode of administration decreases the local antibody levels in the lungs and respiratory tract of patients by 200–500 times compared with those in serum, thereby limiting their effectiveness [89]. A high intravenous dosage is generally required to achieve therapeutic neutralizing antibody concentrations in the respiratory tract, whereas nasal spray or inhalation delivers mAbs locally to the upper respiratory tract and lungs, thereby providing benefits in terms of dose saving, strengthened targeting, and increased safety. Hence, research on COVID-19 treatment and prevention focuses on delivering mAbs through nasal spray or inhalation. For instance, the mAbs (F61 and H121) developed by Lu *et al*., administered through the nasal route at a low dose, offered significant prophylactic protection against lethal challenges of the Delta and Omicron variants in mice [90]. In addition, a nasal immunization protection trial of F61 mAb in susceptible populations exhibited a prophylactic protective effect (ChiCTR2200066391). Researchers at

Table 1 Research progress of mAbs

Antibody name	Target site	Company	Suitable for the crowd/ ClinicalTrials.gov Identifier	Relevant progress
Bamlanivimab	mAbs to RBD	Eli Lilly and Company	Individuals aged 12 years or older weighing at least 40 kg, mild-to-moderate COVID-19	Granted EUA by the FDA in November 2020/withdrawn [82]
Casirivimab/ imdevimab	mAbs to RBD	Regeneron Pharmaceuticals/Roche	Individuals aged ⩾ 12 years and older who have recently tested positive for coronavirus, mild-to-moderate COVID-19	Granted EUA by the FDA in November 2020/withdrawn; approved for marketing in Japan, UK, EU, and Australia [83]
Bamlanivimab/ etesevimab	mAbs to different epitopes of RBD	Eli Lilly/Junshi Biosciences	Individuals aged ⩾ 12 and older weighing at least 40 kg, mild-to-moderate COVID-19	Granted EUA by the FDA in February 2021/withdrawn [84]
Sotrovimab	mAbs to RBD	GSK/Vir Biotechnology	Individuals aged ⩾ 12 years and older who have recently tested positive for coronavirus, mild-to-moderate COVID-19	Granted EUA by the FDA in May 2021/withdrawn [85]
Tixagevimab/ cilgavimab	IgG1 mAbs to RBD	AstraZeneca	Individuals aged ⩾ 12 years and older who have recently tested positive for coronavirus, mild-to-moderate COVID-19	Granted EUA by the FDA in December 2021/withdrawn; approved for marketing in EU in March 2022 [86]
Bebtelovimab	IgG1 mAbs to RBD	Eli Lilly	Individuals aged 12 years or older weighing at least 40 kg, mild-to-moderate COVID-19	Granted EUA by FDA in February 2022/withdrawn [87]
Amubarvimab/ romlusevimab	mAb to RBD	Brii Biosciences	Mild COVID-19 in patients aged ⩾ 18 years, and those aged 12–17 years with a body weight of ⩾ 40 kg (conditional approval) who are at high risk of progressing to severe disease	Approved for marketing in China in December 2021/withdrawn [77]
Regdanvimab	mAb to RBD	Celltrion	Individuals aged > 50 years with at least one underlying medical condition (obesity, cardiovascular disease, chronic lung disease, diabetes, chronic kidney disease, chronic liver disease, and patients on immunosuppressive agents) and mild symptoms of COVID-19 and in adult patients with moderate symptoms of COVID-19	Approved for marketing in Korea and EU/withdrawn [88]
TY027	mAb to SARS-COV-2	Tychan Pte. Ltd.	NCT04649515	Phase III clinical trial/active
ADM03820	1:1 mixture of two human IgG1 targeting different epitopes of RBD	Ology Bioservices	NCT05142527	Phase II/III clinical trial/withdrawn
ADG20	mAb to RBD	Adagio Therapeutics	NCT04805671	Phase II/III clinical trial/terminated

(*Continued*)

Antibody name	Target site	Company	Suitable for the crowd/ ClinicalTrials.gov Identifier	Relevant progress
SCTA01	mAb to S protein	SinoCellTech	NCT04683328/ NCT04709328	Phase II/III clinical trial/unknown
MAD0004J08	IgG1 mAbs to S protein	Toscana Life Sciences Sviluppo s.r.l.	NCT04952805	Phase II/III clinical trial/active, not recruiting
Lenzilumab	Antihuman GM-CSF mAb	Humanigen, Inc.	NCT04351152	Phase III clinical trial/unknown
Bevacizumab	Anti-VEGF humanized mAb	Qilu Hospital of Shandong University	NCT04305106	Phase III clinical trial/recruiting
Leronlimab	IgG4, kappa mAb that recognizes CCR5	Hospital Israelita Albert Einstein	NCT04901676/ NCT04901689	Phase III clinical trial/suspended
Ravulizumab	mAbs targeting terminal complement products	Brigham and Women's Hospital	NCT04570397	Phase III clinical trial/active, not recruiting
Meplazumab	Anti-CD147 IgG2 mAb	Jiangsu Pacific Meinuoke Bio Pharmaceutical Co., Ltd.	NCT05679479	Phase III clinical trial/recruiting
Tocilizumab	IgG1 mAbs to human IL-6 receptor	Asociacion Instituto Biodonostia	NCT05002517	Phase III clinical trial/active, not recruiting
LY3819253	mAb to RBD	NIAID	NCT05780268	Phase III/completed
VIR-7831	IgG1 kappa mAb	NIAID	NCT05780281	Phase III/completed
AZD8895 and AZD1061	IgG1 kappa mAb	NIAID	NCT05780437	Phase III/completed
BRII-196	IgG1 mAb	NIAID	NCT05780424	Phase III/completed
Mavrilimumab	GM-CSF-Rα mAb	Kiniksa Pharmaceuticals, Ltd.	NCT04447469	Phase III/completed
Sarilumab	IgG1 mAb	Assistance Publique-Hôpitaux de Paris	NCT04324073	Phase III clinical trial/unknown

Note: mAbs that have been approved for use and progressed to phase III clinical trials are sourced from ClinicalTrials.gov; NIAID, National Institute of Allergy and Infectious Diseases.

the University of Texas modified the constant region of existing IgG mAbs to obtain the corresponding IgM subtype of mAbs, which was more potent than the parental IgG. Further, nasal administration of IgM-type mAbs in mice showed good preventive and therapeutic effects [91]. Researchers at Fudan University (Shanghai, China) constructed a bispecific single-domain antibody targeting two conserved epitopes on S protein. This antibody could efficiently neutralize various variants, including Omicron, when delivered to the lungs through nebulization, and demonstrated promising therapeutic effects in a mouse infection model [92]. Overall, mAbs therapies were proven to be highly effective in treating infectious diseases, including COVID-19, and thus represent a promising avenue.

Difference among three antibody therapies

As CCP and COVID-19-HIG are from plasma, they share several common features, such as relatively rapid manufacturing process and quick adaptation to the new VOCs, and a variety of antibody species against many different viral antigens [93]. For example, different isotype antibodies have been identified in CCP and COVID-HIG, including IgG, IgM, and IgA [94,95]. CCP and COVID-HIG contain polyclonal antibodies, with high binding affinities to the S, RBD, NTD, and nucleocapsid proteins of SARS-CoV-2, thus providing certain broad-spectrum antiviral effects against SARS-CoV-2 VOCs [10,96]. Meanwhile, some differences exist between CCP and COVID-HIG. COVID-HIG is produced by pooling numerous units of the donor plasma in a limited volume for purified high titers of SARS-CoV-2 neutralizing antibody, and the average IgG concentration of COVID-HIG may be 5.5-fold higher than that of the pooled plasma [10,97,98]. COVID-HIG is significantly superior to CCP in terms of high purity, low risk of blood-related viruses and potentially harmful clotting factors, uniform accurate antibody titer and dose, and ease of storage and transport [99,100]. However, CCP may be physiologically more effective because of the presence of other plasma factors with positive clinical effects such as procoagulants and anti-fibrinolytic factors [99]. CCP may carry autoantibodies, including those against immunoreactive components. Therefore, selecting donors on the basis of individual characteristics is of importance [101].

CCP and COVID-HIG therapies also pose challenges, including the heavy donor selection process, and large amounts of donated plasma from convalescent individuals with COVID-19 or COVID-19 vaccine recipients, and the strict procedures to eliminate the risk of blood-related pathogens. Compared with CCP and COVID-HIG, mAbs have the advantages of good specificity, high safety, and identified antibody titer [75,102,103]. In addition, mAbs can be used for the prevention and treatment of patients infected with SARS-CoV-2 VOCs via intranasal administration, which quickly inhibits viral invasion and replication [90,104].

Immune escape of SARS-CoV-2 VOCs against antibody

As for CCP and COVID-19-HIG, along with most mAbs targeting the RBDs developed during the early waves of prototype COVID-19, their neutralizing activity against Omicron has been observed to decrease *in vitro* [105-107]. With the continuous mutation of SARS-CoV-2, the Omicron variants were reported to contain over 15 mutation sites on RBD [108], with more mutants in the strains XBB and BQ.1.1 that are currently globally prevalent [109, 110] and possess strong immune escape ability. Yi *et al*. isolated and identified 93 RBD-specific antibodies from the memory B cells of convalescent patients with COVID-19 by using single B cell cloning technology. They found that K417N, E484K, L452R, F486L, N450K, F490S, and R346S mutations might lead to the occurrence of immune escape [111]. According to the cryo-electron microscopy structure of ACE2-bound SARS-CoV-2 Omicron S protein, mutation sites on the Omicron RBD are concentrated in the epitope region of most neutralizing antibodies, decreasing the binding affinity of the Fab antibody to S protein, where some mutation sites could form new interactions with ACE2 [112–114]. Owing to the immune escape of VOCs from mAbs [115], the FDA has withdrawn EUAs for all the COVID-19 mAb drugs.

Regarding the immune escape of VOCs, researchers have found that although CCP and COVID-HIG against the prototype virus cannot effectively neutralize the Omicron variants BA.1–BA.5, CCP obtained from BA.1 infection and 2020 hyperimmune anti-SARS-CoV-2 intravenous immunoglobulin (hCoV-2IG) can effectively neutralize Omicron subtypes [116,117]. However, the speed of the development of mAbs against SARS-CoV-2 VOCs seems unable to catch up with the mutation rate of SARS-CoV-2 that the existing mAbs cannot compete with the VOCs. Many researchers have thus turned their attention to developing more broad-spectrum anti-SARS-CoV-2 VOC mAbs. Peking University researchers identified mAbs from convalescents individuals who received COVID-19 inactivated vaccine previously; these mAbs can effectively recognize conserved sites in the RBD region of various SARS-CoV-2 VOCs, including all Omicron subvariants. The conserved sites are related to the core functions of the virus (ACE2 binding and glycosylation), making it difficult for the new VOCs to escape from the antibody [118]. On the basis of the S protein extracellular region, the neutralizing mAbs

targeting the highly conserved S2′ cleavage site and fusion peptide region have been isolated from the PBMCs of convalescent patients. These antibodies can inhibit S2′ cleavage, block virus–host cell membrane fusion, and inhibit virus entry, thus exerting a neutralizing effect on the virus. Owing to the presence of a novel neutralizing mechanism, these antibodies exhibit extensive neutralizing activities against various VOCs [119]. Furthermore, computer-stimulated algorithm has been used in antibody design, and on the basis of the protein structure prediction and target antibody screening, new broad-spectrum antibodies are rapidly being designed. By using a large amount of data on the structure and affinity of antibody–antigen complexes, Tsinghua University team has induced mutations on the antibody complementarity-determining regions, obtained broad-spectrum high-affinity antibodies and validated them using pseudovirus-based neutralizing activity assay [120]. Computer-stimulated algorithms such as XBCR-net and high-throughput artificial intelligence have been used to identify target antibodies that can effectively neutralize different variants of the virus by predicting broad-spectrum mAbs against SARS-CoV-2 and its VOCs directly from single-cell B cell receptor sequences to rapidly design new broad-spectrum mAbs against SARS-CoV-2 [121]. Though only few approved antibody drugs can maintain neutralizing activity against the latest circulating strain XBB, they bring hope for the development of broad-spectrum mAbs.

Study on the possible antibody-dependent enhancement with anti-COVID-19 antibody therapies

Antibody-dependent enhancement (ADE) has been clinically or epidemiologically proven to occur in various viruses, including dengue virus (DENV), RSV, and measles virus. Studies have shown that infection with one DENV serotype increases the likelihood of infection with another serotype, and vaccinations against RSV and measles can intensify disease symptoms after infection [122–125]. In SARS and Middle East respiratory syndrome (MERS), although laboratory studies have suggested that the pre-existing antibodies to SARS-CoV and MERS-CoV may induce ADE, clinical evidence is lacking [126,127]. Studies have documented several mechanisms for ADE-mediated viral infection. Binding of SARS-CoV-2 with virus-specific antibodies (generally non-nAbs) can enhance viral infection and replication by facilitating virus entry into the macrophages expressing Fcγ receptor IIa (FcγRIIa), subsequently leading to increased inflammation and immunopathology. In addition, ADE can be induced by excessive Fc-mediated effector functions or immune complex formation, further exacerbating disease progression [128–131]. ADE may also be enhanced through the mediation of the complement component C1q [132]. The potential risk of ADE induced by CCP, COVID-HIG, and mAbs in SARS-CoV-2 infection is a major concern among researchers, primarily due to its ability to enhance infection and worsen disease caused by new SARS-CoV-2 variants. *In-vitro* assays have shown that 1Ba-3H can enhance the Gamma variant infection of Vero E6 cells in a dose-dependent manner [133], whereas the higher the neutralizing activity of certain mAbs against the S protein, the lower is the potential risk of ADE. A comparison of ADE potential induced by three mAbs (Cas, Imd, and Sot) has suggested that the FcR binding function of these antibodies are not necessarily the reason for ADE [134]. More interestingly, *in-vitro* assays have demonstrated that two types of FcγRs (FcγRIIA and FcγRIIIA) can eventually enhance the infection of SARS-CoV-2 and its VOCs in monocyte-derived macrophages, although the two FcγRs are unable to cause excess cytokine production from macrophages [135]. Besides, mAbs (S1D2-hIgG1 and STI-1499-LALA) and CCP may display a weak ability to induce ADE in human blood monocyte-derived macrophages [136].

Although the existence of ADE has been elucidated at the laboratory level, whether ADE occurs as the molecular and host immunological responses to SARS-CoV-2 and its VOC infections has not been fully clarified. Among numerous clinical trials, only two clinical studies reported higher cumulative deaths in the CCP treatment group than in the standard-of-care group, though the CCP treatment group showed more serious adverse events; however, no direct evidence pointed ADE as the cause [137,138]. No significant immune damage or ADE was observed after reinfection with SARS-CoV-2 in animal models immunized with inactivated vaccine, providing an insight into the protective effect of pre-existing antibodies in the body against SARS-CoV-2 [139–141]. The safety of CCP was investigated in a large cohort study of 5000 people, followed by a large cohort study of 20 000 people. The results indicated that no ADE effect was present in the antibody treatment strategy and supported the viewpoint that early antibody therapy in the clinical course of COVID-19 was more likely to reduce mortality [36,142]. mAbs (sotrovimab) provided real-world evidence for the effectiveness in reducing hospitalizations among outpatients with COVID-19 during the Delta variant epidemic that sotrovimab reduced hospitalizations and death instead of aggravating the disease [143]. Based on the available clinical data, *in-vivo* imported antibodies (CCP, COVID-HIG, and mAbs) do not produce ADE in humans.

Study on plasma-borne pathogens with CCP and COVID-HIG

Since 1987, no transmission of blood-borne pathogens has been reported in commercial plasma products received by hemophiliacs with multiple transfusions [144]. ABO and Rh compatibility in CCP contributor and recipients is essential because CCP and COVID-HIG present no viral transmission risk through strict development and production processes including donor screening, virus screening, virus inactivation, and virus removal [98]. Although CCP exhibits moderately increased levels of the inflammatory markers IL-6 and TNF-α, no discernible difference in *ex-vivo* bioactivity has been noted in comparison with control plasma [145]. Large-sample data from the US Expanded Access Program of CCP have provided evidence supporting the safety of CCP treatment in hospitalized patients with COVID-19 [146]. Only low rates of serious adverse events were observed, such as transfusion reactions and thromboembolic or thrombotic events. Moreover, most thromboembolic or thrombotic events and cardiac events were judged to be unrelated to plasma transfusion, thereby proving the safety of CCP use in hospitalized patients with COVID-19 [41,147]. Hyperimmunoglobulin has been indicated for use in various diseases, including immunodeficiency or autoimmune diseases, and it is associated with mild and temporary adverse reactions, such as headache, flushing, fever, chills, fatigue, nausea, diarrhea, changes in blood pressure and tachycardia [148,149], as confirmed in numerous clinical studies [150,151]. mAbs demonstrate good safety in clinical trials owing to their relatively pure components. Sufficient clinical evidence suggests that mAbs can be used as the first-line therapeutic option for patients with COVID-19 [147,152]. In conclusion, the benefits of antibody intervention therapy outweigh its risks.

Conclusions

During the initial phase of SARS-CoV-2 pandemic in 2020–2021, CCP and COVID-HIG emerged as the preferred options for COVID-19 treatment, especially in the early disease stage, and they could bring benefits to many patients with COVID-19. CCP and COVID-HIG are still required for treating patients with COVID-19 and immunosuppressive diseases as well as those receiving immunosuppressive therapy. CCP treatment strategy has been retained in the COVID-19 Treatment Guidelines of NIH and the Chinese guideline “Diagnosis and Treatment Protocol for COVID-19 (Trial Version 9)” [153]. With the emergence of new SARS-CoV-2 mutant strains and the availability of many types of antiviral drugs, the healthcare providers almost no longer provide CCP and COVID-HIG as a routine, but their clinical values against COVID-19 cannot be negated within selected settings.

The immune escape mechanism of SARS-CoV-2 VOCs is associated with great risks and challenges to approved or in-development mAbs. The origin of the convergent evolution, escape mutation profiles, and neutralization activity of mAbs isolated and screened from individuals with SARS-CoV-2 and its VOC infections should be thoroughly analyzed based on deep mutational scanning profiles. Meanwhile, convergent RBD mutations should be accurately inferred. The prediction of future mutations and possible monoclonal antibody structures relying on existing biological procedures should be explored in depth, combined with humoral immune spectrum and antibody response mechanism, to design versatile mAbs. Nasal spraying or inhalation provides a preventive effect, facilitating direct targeting of viruses in the respiratory tract and offering the convenience of self-administration. Broad-spectrum mAbs can also be injected as a post-exposure treatment.

Studies on ADE should focus on two key aspects. First is the composition of serum antibodies (the antibody spectrum) and the biological effects of the antibody spectrum in viral infection. The composition ratio distribution of antibodies against different antigens of SARS-CoV-2, such as the structural proteins S, N, E, and M and nonstructural antigens, and the antibody function during the process of SARS-CoV-2 and its VOC invasion, release, and cell-to-cell transmission should be emphasized and subject to further studies [134]. Second, the circulating immune cells and the immune molecule response to SARS-CoV-2 and its VOCs should be addressed [154]. Changes in the balance of pro-inflammatory cytokines/chemokines ultimately leading to the pathogenesis of COVID-19 after antibody-mediated invasion must be investigated.

Overall, the components, structure, and immune mechanisms of antibody drugs including CCP, COVID-HIG and neutralizing mAbs should be comprehensively studied, and their therapeutic potential should be further explored against new or mutant infectious disease viral strains.

Compliance with ethics guidelines

Conflicts of interest Xiaoming Yang declares no conflicts of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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