REVIEW

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Recent advances in antibody-based immunotherapy strategies for COVID-19

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Abstract

The emergence of a new acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), the cause of the 2019-nCOV disease (COVID-19), has caused a pandemic and a global health crisis. Rapid human-to-human transmission, even from asymptomatic individuals, has led to the quick spread of the virus worldwide, causing a wide range of clinical manifestations from cold-like symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), multiorgan injury, and even death. Therefore, using rapid and accurate diagnostic methods to identify the virus and subsequently select appropriate and effective treatments can help improvement of patients and control the pandemic. So far, various treatment regimens along with prophylactic vaccines have been developed to manage COVID-19-infected patients. Among these, antibody-based therapies, including neutralizing antibodies (against different parts of the virus), polyclonal and monoclonal antibodies, plasma therapy, and high-dose intravenous immunoglobulin (IVIG) have shown promising outcomes in accelerating and improving the treatment process of patients, avoiding the viral spreading widely, and managing the pandemic. In the current review paper, different types and applications of therapeutic antibodies in the COVID-19 treatment are comprehensively discussed.

KEYWORDS
antibody therapy, COVID-19, monoclonal antibody, neutralizing antibody, SARS-CoV-2

1 | INTRODUCTION

The 7th human coronavirus family member was identified in late December 2019 and has become the latest global health threat.[1,2] The recent epidemic of Coronavirus Disease 2019 (COVID-19) resulting from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first appeared in Wuhan, China (Hubei province), and continues to extend universally.[3] According to World Health Organization (WHO), the disease has rapidly spread to more than 221 countries around the world, and by March 31, 2021, more than 128 million individuals were infected, and more than 2.8 million fatalities had been reported.[4] In March 2020, WHO announced COVID-19 as a pandemic. Coronaviruses are enveloped and unsegmented viruses belonging to the subfamily

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Orthocoronavirinae of the Coronaviridae family with a positive-sense single-stranded RNA genome (ssRNA$^+$) and nucleocapsid. Coronaviruses consist of four main subgroups known as alpha, beta, gamma, and delta, causing diseases in animals and humans. SARS-CoV-2 is a new zoonotic betacoronavirus associated with high mortality.[5,6] Structurally, in SARS-CoV-2, gene fragments express two separated groups of proteins. Structural proteins, consisting of nucleocapsid (N) protein, membrane (M) glycoprotein, small envelope (E) glycoprotein, and spike (S) glycoprotein, are encoded by The N, M, E, and S genes, respectively.[7] However, the open reading frame (ORF) encodes nonstructural proteins including papain-like protease, 3-chymotrypsin-like protease, and RNA-dependent RNA polymerase.[8]

Human-to-human transmission is the main reason for the spreading of the SARS-CoV-2 worldwide and the pandemic.[9] The main route of transmission is respiratory droplet transmission; nonetheless, contact, aerial droplets, and fomites are other ways that the virus can spread.[10-12] Besides this, infected and even asymptomatic individuals have an important role in viral transmission as active carriers.[13,14] Based on recent observations on the existence and replication of the virus in the digestive tract, fecal-oral transmission is also possible.[15] SARS-CoV-2 signs of an infection are nonspecific and vary from no symptoms (asymptomatic) to critical lung disorders and mortality. The most commonly reported clinical symptoms in laboratory-confirmed cases are fever, myalgia or fatigue, dry cough, and atypical symptoms such as dyspnea, headache, sputum production, and sore throat.[16,17] Patients are classified to the mild, moderate, severe, or critical stages of COVID-19 disease according to clinical manifestations, with the majority of the cases belonging to a mild-to-moderate stage. Up to 20% of SARS-CoV-2 cases experience acute respiratory distress syndrome (ARDS), a hazardous, possibly lethal respiratory condition in 2019-nCoV-infected patients.[6]

Quick and accurate identification of COVID-19 is vital for the management of social outbreaks. Imaging tests (chest computed tomography [CT] scan) and laboratory diagnostic tests have a great clinical diagnostic value for COVID-19.[18-21] A special therapeutic choice for COVID-19 should be sought with the spread of the epidemic, so far, some clinically approved medications and vaccines have been developed to target SARS-CoV-2.[22,23] Among various treatments for treating infected patients, anti-SARS-CoV-2 neutralizing monoclonal or polyclonal antibodies and passive immunotherapy with transfusion of convalescent plasma (CP) from recovering patients have also been used to improve the patients' condition.[24] The current review is focused on the therapeutic capability of multiple neutralizing antibodies targeting SARS-CoV-2, and also host-directed immunomodulatory monoclonal antibodies to dampen the aberrant proinflammatory responses in the course of infection and help patients' improvement.

2 | SARS-COV-2 IMMUNOPATHOGENESIS

The main cause of death in 2019-nCoV-infected patients is respiratory system injury and severe pneumonia derived from ARDS.[25] SARS-CoV-2 can penetrate any organ expressing the Angiotensin-converting enzyme 2 (ACE2) receptor, eliciting inflammation, and failure in multiple organs. Immunologically, overactivation of the immune system is induced by the entrance of the virus into the lungs, binding to its receptor expressed on lung epithelial cells (Type II pneumocytes), and applying cytotoxic effects.[26] Innate and adaptive immune responses elicit a large number of inflammatory cells and factors, leading to cytokine storm, hyper inflammation, pulmonary tissue destruction, and subsequent ARDS.[27,28] In innate immunity, alveolar macrophages along with neutrophils play a crucial role in increasing inflammation by producing inflammatory mediators (interleukin-1β [IL-1β], IL-6, and tumor necrosis factor-α [TNF-α]) as well as recruiting the other immune cells into the lungs.[7,14] On the other hand, adaptive immune responses are mediated by Cytotoxic CD8$^+$ T cells (CTLs), CD4$^+$ Th (T helper) cells, and B cells against SARS-CoV-2 infection. In this context, CTLs directly kill the virus-infected cells, and B cells fight against the virus by releasing neutralizing antibodies accompanied by Th cell contribution.[29,30] It was found that the decreased frequency of T-regulatory (Treg) cells and their dysfunction, elevated levels of Th1 and Th17 immune cells, as well as the upregulated production of proinflammatory cytokines and chemokines, are considered the main reasons for immunopathogenesis and inflammation in SARS-CoV-2. IFN-γ, TNF-α, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), membrane cofactor protein (MCP-1), Macrophage inflammatory protein-1 alpha (MIP-1α), IL-1β, IL-6, IL-8, and IL-17, are part of the elicited cytokine release syndrome (CRS) and severe inflammation in COVID-19 patients.[6,31] Cytokine storm or CRS is the most common inflammatory phenomenon that occurred in chimeric antigen receptor (CAR)-T-cell therapy of immune disorders, leading to tissue injury.[32-34] Targeting inflammatory immune cells and mediators in the course of COVID-19 infection would considerably mitigate the inflammation and augment the patients' recovery.[35,36] Hence, a better understanding of

SARS-CoV-2 immunopathogenesis and the immune system responses can be beneficial in achieving appropriate treatments.

3 | ANTIBODY RESPONSES TO SARS-COV-2

The body will have one of three responses to the SARS-CoV-2 antigens arising from the spike glycoprotein or the nucleocapsid: strong, weak, or difficult to detect the response. Interestingly, weaker antibody responses to the infection have been shown to lead to a higher viral clearance rate and better prognosis in patients, while a strong response is associated with a more severe clinical course.[37,38] Therefore, the level of the patient antibody response to virus exposure can be considered as an independent prognostic factor.[39] In addition to this, antibodies are not completely able to clear virus particles from the body shortly after production, as a patient can still have prolonged virus shedding even after seroconversion.[40]

One interesting study conducted to investigate the acute antibody responses to SARS-CoV-2 in 285 COVID-19 patients found that all patients develop detectable antibody responses to the virus within 19 days of symptom onset, with Day 13 being the median day of seroconversion. Regarding the time of immunoglobulin M (IgM) and immunoglobulin G (IgG) seroconversion, the study demonstrated that IgM seroconversion could occur not only before IgG seroconversion but also concurrently or even later than IgG.[41] This is an interestingly unique result because the usual antibody response to infections consists of IgG seroconversion following IgM. It has been suggested that IgG and IgM assessment is not very useful in identifying the stage and severity of the infection, but it can be used to diagnose polymerase chain reaction-negative patients and perhaps get a grasp of the clinical course and disease severity.[39,41,42,43]

## 4 | APPLICATION AND ADVANTAGES OF ANTIBODY THERAPY

In the current situation of the pandemic that arises from SARS-CoV-2, there are no licensed medications or therapeutic options confirmed by the US Food and Drug Administration (FDA) to treat COVID-19. It is highly desirable to swiftly evolve effective therapeutics against SARS-CoV-2, which not only can be applied against SARS-CoV-2 but also can help to develop therapeutic strategies to resist other coronaviruses. Therefore, the development and manufacture of an effective COVID-19 vaccine is an urgent issue that has recently been addressed by several vaccine manufacturers. Besides that, attempts to apply immune-boosting strategic treatments are recognized as a priority. The recent procedure of coronavirus disease management emphasizes supportive care.[44,45] Scientists started working on coronavirus vaccines during SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) outbreaks, and recently their attempts have been successful. Luckily, passive immunity may provide a substitute therapeutic procedure for COVID-19. It has been experimentally applied in other epidemics, including SARS, Ebola, MERS, and 2009 influenza A (H1N1), to reduce the viral load and disease mortality.[46-48]

Noteworthy is the fact that passive antibody therapy provides a great potential for prophylactic treatment and prevention of SARS-CoV-2 as well as its therapeutic aspect. Antibodies can detect epitopic regions of unique virus particles and directly bind to viral proteins to prevent virus replication and reduce disease severity. Passive antibody therapy can dampen cytotoxicity and phagocytosis and show extra neutralizing effects when applied with other antiviral drugs. Therefore, antibody therapy might be an immediate and potent strategy for emergency prophylaxis and SARS-CoV-2 therapy.[49,50]

Antibody therapy for infections includes plasma and monoclonal antibody therapies. Passive CP immunization requires transfusing the plasma from individuals who have recovered from infection to infected people or at-risk individuals. Immunotherapy by transferring the CP to infected patients can be useful to neutralize the virus and reduce the chance of further infection. The US FDA has currently verified plasma therapy as a treatment alternative for COVID-19 patients.[51,52] Another way is to manufacture and mass-produce specific monoclonal antibodies against the virus via immunized animal models and to re-engineer commonly recognized SARS-CoV antibodies that could supplement the body's immune responses.[24,53]

In the event there is a lack or shortage of CP, the generation of human antibodies by monoclonal antibodies (mAbs) and genetically engineered animal hosts can be viewed as additional sources of antibodies for SARS-CoV-2 (Figure 1 and Table 1). Monoclonal antibodies are specific therapeutic molecules that could be utilized as effective therapeutic or protective candidates in various diseases. The need to treat the novel coronavirus infection has led to the manufacturing of monoclonal antibodies as the passive immunotherapy regimen to create a helpful therapeutic outcome. Approximate treatment of many diseases depends on
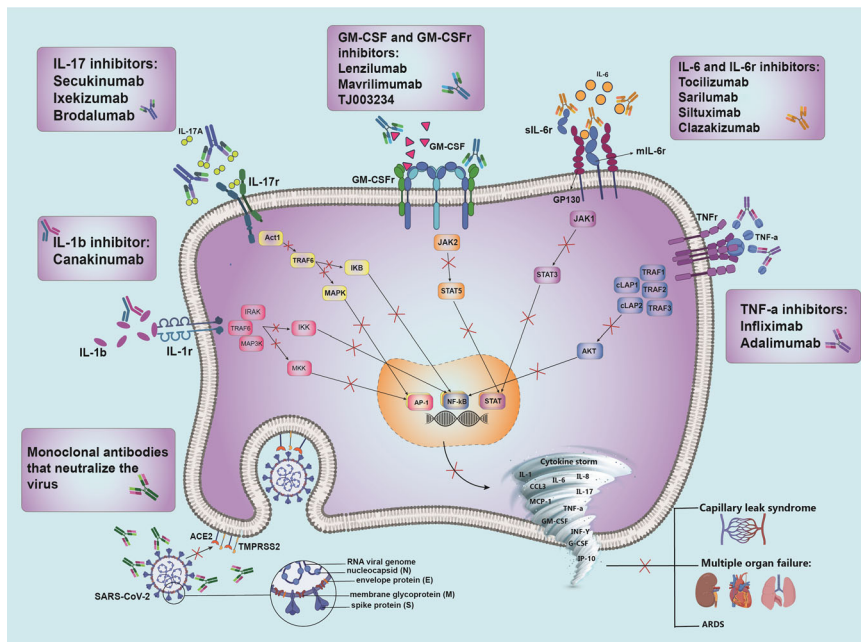
FIGURE 1 The function of monoclonal antibodies in suppressing cytokine storm during COVID-19 infection (Created by Tahmasebi et al.). ACE2, angiotensin converting enzyme-2; ARDS, acute respiratory distress syndrome; AP-1, activator protein 1; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IKK, IκB kinase; IP-10, interferon gamma-induced protein 10; JAK, Janus kinase; MKK, mitogen-activated protein kinase kinases; MCP, membrane cofactor protein; mIL-6R, membrane-bound IL-6 receptor; MAPK, Mitogen-activated protein kinase; NF-κB, nuclear factor kappa B; r, receptor; STAT, signal transducer and activator of transcription; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane Serine Protease 2; TRAF6, tumor necrosis factor receptor (TNFR)-associated factor 6; TNF-α, tumor necrosis factor-alpha

monoclonal antibody therapy, especially viral infections such as HIV-1, influenza A, and Ebola, in addition to cancer and immune disorders. It is also possible to easily scale up monoclonal antibodies for testing during outbreaks.[53-55]

One crucial and noticeable obstacle for therapeutics and antibody-based vaccines is the possibility of aggravating COVID-19 intensity by antibody-dependent enhancement (ADE). ADE can occur when sub-neutralizing or non-neutralizing antibodies attach to viral antigens without clearing or blocking infection.[56,57] It is supposed that antibodies that neutralize the infection caused by the virus can efficiently prevent or treat the first symptoms of COVID-19 even when they are used in small quantities. Also, passive immunity can continue for weeks and months. Although it is possible to accumulate and preserve antibodies for a long time, the appropriate time for their perfect use depends on the probability of mutations that alter the virus features. Preferably, antibodies should be applied within the first days of collection and may show the maximum potency if they are applied at the early phase of the disease.[50,58] Several attempts are being made to use antibody therapy to calm COVID-19 severity until a better medication is found.

5 | CP TRANSFUSION

CP or hyperimmune immunoglobulin therapy is a strategy of artificially inducing passive immunization by transferring blood plasma collected from patients who had recovered from infection to new patients.[59] CP has been administered for the management, prevention of continuous infection, and treatment of many infectious diseases since the late 19th century. CP has been considered a critical method in several pandemics. Over the past two decades, this process has been used in the treatment of influenza viruses H1N1 and H5N1, and MERS, SARS, and Ebola to boost the patients' recovery rates.[60,61]

The plasma collected from recovered COVID-19 patients contains neutralizing and non-neutralizing antibodies, indicating potential benefits in decreasing viral load and increasing viral clearance. In addition to viral clearance, neutralizing antibodies cause accelerated infected cell clearance, and it is better to collect it from donors who have fully recovered from COVID-19 to make sure there is a high titer of neutralizing antibodies.[62,63] This strategy could considerably enhance or keep the neutralizing antibodies at a high level. Also, it is well-tolerated and potentially could recover the medical findings by neutralizing the virus in most COVID-19 cases.[64,65]

TABLE 1 Summary of current clinical trials developing therapeutic antibodies against COVID-19

Target	Stage	Antibody	Reference
IL-6R	Phase 1	Tocilizumab	NCT04560205
	Phase 2	Tocilizumab	NCT04479358, NCT04445272, NCT04331795, NCT04377659, NCT04363736, NCT04332094, NCT04435717, NCT04363853, NCT04339712
		Clazakizumab	NCT04494724, NCT04343989, NCT04363502
		Siltuximab	NCT04329650
		Sirukumab	NCT04380961
	Phase 2/3	Olokizumab	NCT04380519
		Sarilumab	NCT04315298
	Phase 3	Tocilizumab	NCT04412772, NCT04577534, NCT04330638, NCT04320615, NCT04409262
		Sarilumab	NCT04327388
		Siltuximab	NCT04330638
	Phase 4	Tocilizumab	NCT04377750
TNF-α	Phase 2	Infliximab	NCT04425538
GM-CSF	Phase 2	Lenzilumab	NCT04583969
		Mavrilimumab	NCT04447469, NCT04463004, NCT04492514
	Phase 3	lenzilumab	NCT04351152
P-selectin	Phase 2	Crizanlizumab	NCT04435184, NCT03474965
XIIa	Phase 2	Garadacimab	NCT04409509
CD147	Phase 1/2	Meplazumab	NCT04275245
CTGF	Phase 2	Pamrevlumab	NCT04432298
Kallikrein	Phase 1/2	Lanadelumab	NCT04422509
C5aR	Phase 2	Avdoralimab	NCT04371367
VEGF-A	NA	Bevacizumab	NCT04305106
	Phase 2	Bevacizumab	NCT04275414
PD1/PD-L1	Phase 2	Tocilizumab	NCT04335305
		Pembrolizumab	NCT04335305
C5 protein	Phase 2	Eculizumab	NCT04346797
	Phase 3	Ravulizumab	NCT04369469
	Phase 4	Ravulizumab	NCT04390464
CD6	Phase 2	Itolizumab	NCT04475588
IFN-γ	Phase 2	Emapalumab	NCT04324021
CCR5	Phase 2	Leronlimab	NCT04347239
IL-1β	Phase 3	Canakinumab	NCT04510493
Spike Pr	Phase 1	SAB-185	NCT04468958, NCT04469179
		LY-CoV555	NCT04411628
		ABBV-47D11/ABBV-2B04	NCT04644120
		TY027	NCT04429529
		SCTA01	NCT04483375

TABLE 1 (Continued)

Target	Stage	Antibody	Reference
		AZD7442	NCT04507256
	Phase 1/2	REGN-COV2	NCT04426695
		DZIF-10c	NCT04631666, NCT04631705
		COVI-AMG	NCT04584697, NCT04738175
	Phase 2	VIR-7831	NCT04779879
		LY-CoV555/LY-CoV016/ VIR-7831	NCT04634409
		COVI-AMG	NCT04734860, NCT04771351
		REGN-COV2	NCT04666441
	Phase 2/3	AZD7442	NCT04518410
		VIR-7831	NCT04545060
		REGN-COV2	NCT04425629, NCT04381936
		LY-CoV555/LY-CoV016	NCT04427501
		SCTA01	NCT04644185, NCT04683328, NCT04709328
	Phase 3	VIR-7831	NCT04501978
		LY-CoV016	NCT04427501
		LY-CoV555/LY-CoV016	NCT04497987
		REGN-COV2	NCT04452318
		AZD7442	NCT04723394
		AZD7442/AZD1061	NCT04625725, NCT04625972
		TY027	NCT04649515
RBD Pr	Phase 1	B38-CAP	NCT04382950, NCT04375046
		JS016	NCT04441918
		CT-P59	NCT04593641, NCT04525079
		BGB-DXP593	NCT04532294
	Phase 2	BGB DXP593	NCT04551898
	Phase 2/3	CT-P59	NCT04602000

Abbreviations: CD, cluster of differentiation; CCR, C–C chemokine receptor; CTGF, connective tissue growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-6R, interleukin-6 receptor; IFN-γ, interferon gamma; Pr, protein; PD1, programmed cell death protein 1; RBD, receptor-binding domain; TNF-α, tumor necrosis factor alpha; VEGF-A, vascular endothelial growth factor A.

According to recent studies, CP transfusion leads to an increase in lymphocyte levels, respiratory rate, and the improvement of liver function and CRP levels.[61] Theoretically, when CP is administered in the early stage of the disease, it might have more impact in seriously ill COVD-19 patients. Also, it helps to inhibit SARS-CoV-2 shedding and leads to a lower fatality rate in COVID-19 and respiratory failure patients.[61,66] Given that the viremia of the infection peaks in the first few weeks, the administration of plasma therapy in the early stages of the infection can help patients' recovery. The benefits of CP antibodies include restriction of viral replication, suppression of viremia, increased rate of clearance of virus and infected cells, prevention of new infection, and reduced relative risk of mortality. Another advantage of plasma therapy is its ease of access, and it can be prescribed to patients quickly in any medical center and can improve the condition of the disease before the start of the hemorrhagic immune response.[67]

In a pilot study in 10 severe COVID-19 patients, 3 days after CP therapy, there was a significant improvement in clinical symptoms including cough,

shortness of breath, chest pain, and fever. Improved lung and liver function, increased lymphocyte count, and decreased inflammation following plasma therapy were also promising results of this study.[60] Some other related investigations reported the improved clinical manifestations and radiological findings, radiological findings, improved pulmonary and liver function, elevated oxygen level, lower viral load, and reduced mortality rate following the CP therapy.[11,61,68] Encouragingly, several studies documented the well-tolerated capability of CP infusion without any serious adverse effects in COVID-19-treated patients, which would suggest it as a contributed treatment along with other impressive therapeutic approaches.[69-71]

Despite the promising results in improving the condition of patients after receiving plasma, several limitations, as well as no significant effect, have been also reported. As an example, Simonovich et al. investigated CP therapy in 228 severe COVID-19 cases in comparison with 105 placebo receiving severe cases. Results of the study demonstrated no significant difference between plasma therapy and placebo groups in the clinical outcomes and overall mortality rate.[72] Another study showed that the reduction in mortality rate after plasma therapy was limited to patients with severe stage, and also plasma therapy was less effective in patients treated on median day 21.5 during viral shedding. The rate of disease recovery was lower in cases with late CP infusion, as well.[66] Additionally, in this line, Joyner et al reported the increased mortality rate in severe COVID-19 patients treated with CP.[70] Plasma therapy is also associated with several limitations and side effects, including allergic reactions, anaphylactic reactions, fever, bronchospasm, hemolysis, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), ADE, thrombotic events, heart disorders, and the possible risk of infection transmission with the use of plasma therapy.[69,70,73] Consequent to different findings of the study in terms of CP therapy effect against COVID-19, more trials having a larger sample size are required to determine the true clinical efficacy of this intervention.

6 | VIRUS NEUTRALIZING ANTIBODY

6.1 | CR3022

CR3022 is a neutralizing antibody that was first isolated from the blood of a convalescent SARS-CoV-1 patient, and it was formerly identified as an effective neutralizing antibody against SARS-CoV-1 and reconstructed into the IgG1 type.[74] The crystal structure of CR3022 consists of heavy and light

chains. The heavy chain is encoded by Immunoglobulin heavy variable 5-51 (IGHV5-51*03) with 8 V gene-encoded residues modified by somatic hypermutation and 12-aa CDR H3. CR3022 light chain is encoded by Immunoglobulin kappa variable 4-1 (IGKV4-1*01) that contains 9-aa CDR L3 with 1 V gene-encoded residue modified by somatic hypermutation.[75] CR3022 is from a different class of neutralizers that connects to a highly conserved epitope; thus, it can play a functional role in neutralizing both SARS-CoV-1 and SARS-CoV-2.[76,77] The CR3022 epitope does not extend over the ACE2 binding site, and it does not have common epitopic regions.[78] The results indicate that CR3022 should be used immediately as SARS-CoV escape mutations, which could easily be created for ACE2 blocking antibodies and are remarkably resistant to virus escape because of the regional isolation of the ACE2 and CR3022 epitopes.[76,77] Conversely, antibodies that bind to the ACE2 binding epitope and compete with ACE2 are likely to be vulnerable to escape.[55]

Based on the study of Yuan et al.,[78] due to conformational changes and improper clashes between CR3022 and irrelevant parts of RBD, CR3022 does not have a neutralizing effect against SARS-CoV-2 in vitro. However, it should be noted that this epitope can provide in vivo protection. Also, according to Rattanapisit et al., mAb CR3022 binds to SARS-CoV-2, but due to the sequence conservation in the epitopic region of the RBD between SARS-CoV-2 and SARS-CoV, it failed to neutralize the virus in vitro.[79]

In contrast, according to the results of the Huo et al. study, CR3022 attaches to the RBD firmly and neutralizes the virus because its presence perturbs the binding of ACE2 and RBD. As such, the escape of ACE2 from the RBD is quickened by the attendance of CR3022. These data indicate an allosteric impact within ACE2 and CR3022.[76]

According to some studies, CR3022 does not have a neutralization effect alone, but when combined with CR3014 it synergistically neutralized the CoV.[74,80]

In summary, CR3022 neutralizes SARS-CoV-2 via an unusual mechanism that is potent, but incomplete (90%). This makes it a feasible therapeutic option, alone or along with other neutralizing antibodies, especially with those that target the ACE2 binding site, to make synergetic interaction for the treatment, management, and prevention of 2019-nCoV infection but further research is needed.[81]

6.2 | CR3022

Extra research and calculations were accomplished to generate a new mAb-based CR3022.[82] Three feasible

mutations were identified, which could enhance the binding affinity of CR3022 to RBD of SARS-CoV-2. The offered mutations are K12E, K170A, and R194A. This new functional molecule has a lower net charge than CR3022 generally, along with reduced repulsion for the close groups. Furthermore, the recommended mutations cannot affect the antigenic regions. The binding affinity was of these computer-designed molecules equivalent to what was measured in CR3022. Therefore, it could increase the ability of this candidate mAb to help block the interaction between virus and host cell.

6.3 | 4A8

A group of researchers at the Academy of Military Medical Sciences, China, discovered a neutralizing human antibody that links to the N-terminal domain (NTD) from the Spike (S) protein of SARS-CoV-2, the so-called 4A8.[83] They investigated the entire SARS-CoV-2 S protein, rather than just the SARS-CoV-2 receptor-binding domain (RBD). According to the researchers, some mAbs have demonstrated neutralization activity toward SARS-CoV-2 (1M-1D2, 4A8, 0304-3H3, 2M-10B11). However, just one of them (4A8) showed promising results against both authentic and pseudotyped SARS-CoV-2 in vitro with high neutralization efficacy but did not attach to the RBD of S protein. Consequently, while they found that 4A8 did not block the interaction between the ACE2 and the S protein used by the virus to access human cells, SARS-CoV-2 could still be neutralized. Among these mAbs, 1M-1D2 and 0304-3H3 showed neutralization just in authentic SARS-CoV-2 and mAb 2M-10B11 provided weak protection against the pseudotyped virus. Based on this study, by limiting S protein's conformational changes, 4A8 can neutralize SARS-CoV-2. Resultantly, because of high neutralization capabilities, 4A8 is a possible candidate for the management of SARS-CoV-2. A mixture of 4A8 with RBD-targeting antibodies may be used to deter viral mutants from escaping and act as a potential therapeutic "cocktail."

6.4 | S309

An S309 antibody has been identified as a neutralizing antibody produced by memory B-cell screenings of a patient who recovered from SARS-CoV-1 infection,[84-86] and which inhibits related coronaviruses, including SARS-CoV-2. Based on a study, several antibodies were isolated, and just some of them (S315, S303, S309, and S304) bound to both SARS-CoV-2 and SARS-CoV RBDs with nano- to sub-picomolar affinity.[87] Specifically, S309 IgG is connected to the immobilized SARS-CoV-2 SB domain and the S glycoprotein ectodomain trimer with sub-picomolar and picomolar affinities. Structural research showed that its epitope is a series of glycopeptides found on the N343 glycoside.

Pinto et al. suggested that S309 would be particularly amenable to not only neutralize SARS-CoV-2 potently but also comparable neutralization abilities were seen against pseudoviruses of both SARS-CoV and SARS-CoV-2, while S303 neutralized pseudo-SARS-CoV but not pseudo-SARS-CoV-2. Besides this, S304 and S315 had a weak neutralizing effect on pseudo-SARS-CoV and pseudo-SARS-CoV-2. As well as being effective in vitro neutralization, S309 can perform extra protective in vivo mechanisms. This can happen because S309 Fc engineering could theoretically improve the stimulation of natural killer cells with the low-affinity FcγRIIIa version. Macrophage- or dendritic cell-mediated antibody-dependent cell phagocytosis (ADCP) may lead to virus management by removing the virus and infected cells as well as inducing the T-cell responses. The best ADCP response closer to the ADCC-mediated responses was seen using the S309 and S306 mAbs; however, FcγRIIa signaling was detected just for S309. These results show that the ADCP of monocytes was associated with the presence of both FcγRIIIa and FcγRIIa receptors. S309 binds to a proteoglycan epitope different from the receptor-binding domain on the SARS-CoV-2 SB and does not interfere with ACE2 because of its binding to the SB protein. In both the open and closed phases of the S glycoprotein, the epitope is available, which clarifies the stoichiometric attachment of Fab to the S glycoprotein trimer.

The identification of S309 glycans indicates the significance of N-glycans in the S protein of SARS-CoV-2. Besides this, S309-containing antibody cocktails further enhanced the neutralization of SARS-CoV-2 and may be beneficial for blocking or minimizing mutants of virus escape. The theory that antibody cocktails could be more powerful than single antibody therapy reinforces this.[88] In brief, S309 has been described as a human mAb with a large neutralization operation against various sarbecoviruses like SARS-CoV-2.

6.5 | 1B07

1B07 is an Fv-human Fc igG1 chimeric monoclonal generated during immunization of C57BL/6 J mice against SARS-CoV-2 S protein, leading to the sorting of individual B cells with refined receptor-binding domain (RBD), direct cloning, and expression.[89] This mentioned antibody identifies the RBD of the virus as well and neutralizes that properly. 1B07 reduces weight loss resulting from SARS-CoV-2 in the first 4 days and considerably reduces the infection. As reported by Hassan et al., this mAb contributes to decreasing

proinflammatory cytokines and chemokines like CCL5, IL-6, CXCL11, CCL2, IFN-β, CXCL10, and IFN-1.

6.6 | VHH-72

A group of researchers has identified a potential effective COVID-19 treatment developed from antibodies, which is found in a llama immunized by S protein of SARS-CoV and MERS-CoV. It is a camelid antibody with a single domain and is generally referred to as a "nanobody." This nanobody binds to a highly conserved epitope on the RBD, partly like the CR3022 binding area, and shows reactivity against the SARS-CoV-2 S protein. The complex crystal structure between VHH-72 and SARS-CoV RBD revealed that VHH-72 binds to an epitope distinct from that bound by H11-H4.[76,90] Wrapp et al. identified three SARS VHH clones (SARS VHH-72, -6, and -1) that bind SARS-CoV-1 S protein. As determined by surface plasmon resonance (SPR), neutralization of SARS-CoV-2 S VSV pseudotypes by VHH-72 was shown to have a moderately high binding affinity to SARS-CoV-2 RBD at a higher IC50 than SARS-CoV-1 pseudotypes. The practical benefits of using single-domain camelid antibodies have been documented in neutralizing SARS-CoV and MERS-CoV.[90] VHHs can be conveniently formed into multivalent formats, which are more potent than other antibodies in thermal stability and thermostability. It is also recognized that VHHs are less vulnerable to steric hindrances that would inhibit the binding of bigger standard antibodies.[91,92] Camelid VHH domains are extremely conserved with their human peers, and their immunogenicity has been believed to be low,[93] although humanization strategies are well developed.[94] They were able to design a nanobody based on this study to bind to the virus more tenaciously. They achieved this by fusing two copies of the nanobody. The engineered nanobody tightly bound to SARS-CoV-2 and was able to avoid the virus from invading cells. Not only does the bivalent VHH-72-Fc fusion protein resist ACE2 binding but it also has neutralizing action against the pseudovirus SARS-CoV-2. VHH-72 typically indicates the cross-neutralizing ability of closely related coronavirus strains, including SARS-CoV-2, against RBDs.

6.7 | 47D11

47D11 is a neutralizing antibody affecting the S1B receptor binding domain of SARS and SARS-CoV-2.[95,96] Through this effect, the virus cannot bind to the host cell, and thus the viral action is reduced. As a result, this antibody can benefit both infected and uninfected hosts.[97] Although the exact mechanism of this antibody is yet unclear, it is not through

receptor binding interference. Wang et al. hypothesized the alternative mechanism to neutralize the SARS-CoV2 using the anti-RBD antibodies that may mediate it by spike glycoprotein inactivation through antibody-induced destabilization of its prefusion structure.[96]

6.8 | B38 and H4

B38 and H4 are a pair of neutralizing antibodies affecting the SARS-CoV-2 RBD. They exert their function by competing with the ACE2 receptor, which the virus uses to enter the host cell.[26,98-100] Wu et al.[101] reported these antibodies' functions and demonstrated that B38 and H4 have a synergetic neutralizing effect on each other. They also showed, through an "epitope competition assay," that H4 and B38 bind to different epitopes of RBD, with minor overlap, and thus do not inhibit one another's binding abilities.

6.9 | P2C-1F11, P2C-1A3, and P2B-2F6

These two antibodies also neutralize the SARS-CoV-2 RBD through binding competition with ACE2. In a study by Ju et al.,[102] several antibodies were extracted from SARS-CoV-2-infected individuals, coded according to the patient number and collection sequence, and tested for properties such as neutralizing ability, competition with ACE2, neutralizing activities against pseudoviruses that bear the spike protein of SARS-CoV-2 and epitope recognition overlap. P2C-1F11, P2B-2F6, and P2C-1A3 were shown to be the most powerful in terms of competing with ACE2 binding and also neutralizing pseudoviruses. The same results were found regarding neutralizing ability against live SARS-CoV-2. In terms of epitope recognition overlap, P2C-1F11 showed very little competition with other antibodies tested, while P2B-2F6 and P2C-1A3 were found to be somewhat competitive. This indicates that some overlapping exists between the epitopes of RBD recognized by the antibodies tested in this study.

6.10 | CV1/CV35 and CV30

In a study by Seydoux et al.,[103] SARS-CoV-2 spike protein-specific B cells were isolated from an infected patient, which generated several antibodies. Out of the antibodies extracted and tested, CV1/CV35 and CV30 were shown to neutralize the SARS-CoV-2. CV30, the strongest antibody of all, recognizes the RBD and exerts its neutralizing effect directly by inhibiting the binding of the virus to the ACE2 receptor;

while CV1 and CV35 seem to bind to an "unknown epitope region outside the RBD" and have a less ability to neutralize the virus compared with CV30.

6.11 | BD-368-2

In a study conducted by Cao et al., several antibodies were extracted from the B cells of convalescent COVID-19 patients.[104] They identified seven potent neutralizing antibodies, of which one called BD-368-2 was known as the most potent antibody of them all. BD-368-2 showed high potency against pseudovirus and live SARS-CoV-2. It also exhibited high therapeutic and also prophylactic efficacy in infected hACE2 transgenic mice. Epitope binding tests demonstrated that epitope recognition of BD-368-2 does not overlap with other neutralizing mAbs in this study. It can thus be used along with other antibodies to improve efficacy.

6.12 | II62-ScFv

II62-ScFv is another RBD neutralizing antibody identified by Parray et al.[105] This was achieved using a phage display library, which is a beneficial technique that removes the need to use patient samples directly. In this study, the properties of this mAb were evaluated in two formats: II62-ScFv-Fc and full-length II62-IgG1. II62-ScFv demonstrated high potency and specificity as well as a high binding affinity to RBD with a slow binding rate, but also a slow dissociation rate. Additionally, it was able to detect and bind to the SARS-CoV-2 S protein expressed on the surface of HEK293 T cells transfected with a plasmid containing the S protein gene. The epitope that II62-ScFv recognizes was shown to overlap partially with ACE-2.[106] Overall, II62-ScFv seems to be a promising antibody for the development of therapeutic agents and vaccines.

6.13 | Casirivimab and imdevimab

The mixture of Casirivimab and Imdevimab has been approved by the FDA for the treatment of mild-to-moderate infection with SARS-CoV-2 on November 21, 2020.[106] The antibody cocktail developed by Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN), sold under the brand name REGEN-CoV, has been shown to reduce hospitalization rate in high-risk patients, characterized by having a body mass index (BMI) of 35 or more, chronic kidney disease, diabetes, immunosuppressive disease, and other criteria

described by Regeneron®'s fact sheet.[107] The company also stated that the best time of administration for this mixture is "early after diagnosis and in patients who have not yet mounted their immune response or who have a high viral load." Hoffmann et al.[108] conducted a study examining Casirivimab and Imdevimab potency in preventing infection with the UK, South Africa, and Brazil variants of SARS-CoV-2. Entry of all variants of the virus to host cells was inhibited by Imdevimab, but the South Africa and Brazil variants showed partial resistance to Casirivimab. It can be concluded that this cocktail is most efficient in patients who are infected with the wild-type SARS-CoV-2 rather than the new variants.

6.14 | Bamlanivimab and etesevimab

Bamlanivimab (also known as LY3819253 or LY-CoV555) and Etesevimab (also known as JS016, LY3832479, or LY-CoV016) are recombinant IgG1 neutralizing monoclonal antibodies which bind to the receptor-binding domain of the spike protein of SARS-CoV-2. These antibodies can inhibit the binding of the virus to the human angiotensin-converting enzyme-2 receptor and prevent the virus from entering the cell.[109,110] They were first extracted from two different COVID-19 patients in North America and China.[111] The US FDA granted Bamlanivimab an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate COVID-19 patients (in adults and 12 years old and older pediatric patients) who are at risk of hospitalization. According to the FDA, as opposed to a placebo, bamlanivimab has been shown to decrease COVID-19-related hospital admissions or emergency department visits in patients at high risk for disease worsening in the 28 days following therapy, while based on the results of a study by Robert et al. there was no substantial change in viral load reduction when bamlanivimab monotherapy was used, but the cocktail of bamlanivimab and etesevimab can be used in combination for the treatment of COVID-19.[112,113] In the RBD region of the S protein, bamlanivimab and etesevimab bind to separate yet overlapping epitopes. As a result, they can be combined. In clinical trials, combining these two neutralizing monoclonal antibodies has been demonstrated to accelerate the decline in viral load at Day 11 and reduce treatment-emergent resistant variants.[109,114]

7 | POLYCLONAL ANTIBODY

Apart from the various attempts in developing the monoclonal antibodies targeting either the hACE2, viral proteins, or the immune response elements, various

polyclonal antibodies (pAbs) are being designed or collected to be a prophylactic treatment for respiratory viral diseases, such as COVID-19.[115,116] Lately, a Japanese drug company called Takeda Pharmaceutical Co. was reported to experimentally acquire an anti-SARS-CoV-2 polyclonal hyperimmune globulin (H-IGs) collected from the plasma of the newly recovered COVID-19 patients.[117]

According to recent data of GigaGen Company, a new class of polyclonal antibody drugs, termed recombinant hyperimmune sera, are derived from donor B cells and are recombinantly produced at a large scale in mammalian cells, comprising thousands to tens of thousands of antibodies. For example, GIGA-2050 is a high-potency product to address the COVID-19 pandemic and has greater IgG purity than plasma-derived antibodies.[118] There are also other pAbs against COVID-19 spike protein and different viral regions, including the S1 and S2 subunits, RBD, nucleocapsid protein, and so on, that are derived from rabbits.[119,120] Besides this, these polyclonal antibodies can be used to make vaccines that may act against the spike protein of SARS-CoV-2 to neutralize viral infection.[121-123] These data suggest that polyclonal antibodies can be effective therapeutic agents and would be useful in COVID-19 patients.

8 | MONOCLONAL ANTIBODIES TARGETING THE INFLAMMATORY MEDIATORS

8.1 | Anti-IL-6

IL-6 is a proinflammatory pleiotropic cytokine expressed in nearly all immune cells, including monocytes and lymphocytes, and plays an important role in human cell proliferation and differentiation. Its receptor, IL-6R, is not only present in the membrane-bound form (mIL-6R) but also in the soluble form (SIL-6).[124] Three IL-6 signaling types are likely to happen: IL-6 binds to mIL-6R (classic) or binds to sIL-6R (trans-signaling), or the connection of IL-6R with gp130 on close cells (trans-presentation).[125]

In cytokine storm and CRS, IL-6 plays an important role. One study found that inflammatory monocytes and pathogenic T cells trigger inflammatory storm with a substantial amount of IL-6; thereby, monoclonal antibodies attacking the IL-6 pathways may theoretically minimize inflammatory storm.[126] COVID-19 patients, those with more severe conditions, have high IL-6 plasma levels.[127] Therefore, blocking IL-6 will theoretically mitigate the SARS-CoV-2-induced noxious immune response. Numerous FDA-approved anti-IL-6 therapeutic agents with different pharmacologic properties have been

developed inhibiting IL-R, like Tocilizumab, Sarilumab, Siltuximab, and Clazakizumab.[128]

8.1.1 | Tocilizumab

Tocilizumab (Actemra®) is a humanized recombinant monoclonal antibody against the IL-6 receptor (IL-6R) that can bind to both membrane-bound and soluble IL-6R and inhibit cis- and trans-signaling mediated by IL-6.[129,130] It is an immunosuppressive medication approved for rheumatoid arthritis treatment and some other diseases.[131] It is also reported that tocilizumab has promising efficacy and safety in suppressing severe CRS in both pediatric and adult patients.[132] According to a recent study by Xu et al., this monoclonal antibody was used to treat 21 hospitalized patients (400 mg single dose), and in addition to a substantial decrease in the CRP level, they had major decreases in their oxygen needs the next day.[130] Based on new studies, the serum levels of ferritin, CRP, and fibrinogen were reduced to the normal range, and the lymphocyte amount was raised after treatment.[133] Hence, it could be an effective treatment to reduce disease severity, ICU admissions, and mortality.[134] Regarding all of these, Tocilizumab may be deemed as a rescue and an effective treatment option in COVID-19 if other treatments have failed or are not available.

8.1.2 | Sarilumab

Sarilumab (Kevzara®) is a human recombinant monoclonal antibody that inhibits IL-6-mediated signaling via attaching to both soluble and membrane-bound IL-6 receptors. This IgG1 monoclonal antibody has been approved for rheumatoid arthritis therapy.[135] According to a study by Della-Torre et al., there was a significant clinical improvement in lung consolidation CT scan of sarilumab-treated patients. It also has a lower mortality rate, a lower rate of severe secondary infections, and a shorter time for clinical improvement; all of these features make it safe and effective.[136]

Based on another study by Montesarchio et al. this mAb caused a reduction in C reactive protein (CRP), D-dimer, white cells including neutrophils, eosinophils and lymphocytes, platelets, neutrophil-to-lymphocyte ratio (NLR), and IL-6 levels are associated with treatment response and quick enhancement in respiratory function in addition to regularization of inflammatory markers.[137] Sarilumab's affinity for human IL-6R is stronger compared with tocilizumab and it has an extended half-life.[135]

8.1.3 | Siltuximab

Siltuximab (Sylvant™) is a glycosylated human-mouse chimeric monoclonal antibody that binds to soluble IL-6 and inhibits IL-6 from binding to membrane IL-6 receptors as well as soluble receptors and forms high affinity.[138,139] Siltuximab directly neutralizes interleukin IL-6, and unlike tocilizumab and sarilumab, it is well-tolerated.[140] The European Medicine Agency (EMA) approved it in 2014 to treat Castleman's disease.[141] A study conducted in Italy analyzed siltuximab in COVID-19 patients and a substantial decrease in CRP levels and clinical development was observed.[142]

8.1.4 | Clazakizumab

Clazakizumab is a humanized IgG1 monoclonal antibody that binds to human IL-6 with high affinity. This antibody was approved for rheumatoid arthritis, and is known as a safe and efficient agent, and it would be beneficial in the late antibody-mediated renal transplant rejection.[143] According to a study, it is more potent (3–120 times) in ex vivo and in vitro assays compared with tocilizumab.[144] Based on a case report, clazakizumab-treated patients had significant improvement in parenchymal infiltrates. As mentioned by Vaidya et al., it is well tolerated and may be a safe and successful choice for controlling the severe COVID-19-related cytokine storm and pneumonia, especially in transplant recipients.[145]

8.2 | Anti-GM-CSF

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a cytokine with immunoregulatory function and produces myelopoietic growth factor that can be released by many diverse cell types. It regulates hematopoietic cell development, proliferation, and differentiation. It also plays a crucial function in tissue inflammation in addition to the initiation and perpetuation of inflammatory diseases.[146,147] This is because myeloid cells activated by GM-CSF can release reactive oxygen species and also increase the expression of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 as well as several chemokines like IL-8, CCL17, and CCL2, which can stimulate neutrophils, lymphocytes, and monocytes, respectively.[148]

In natural conditions, GM-CSF levels are undetectable or very low. However, it can be increased by any immune trigger and has been shown to upregulate CRS.[149] A great safety profile for several patients has been found using mAbs-related to GM-CSF and GM-CSF receptors. Thereby,

GM-CSF has now been proposed as a possible target for COVID-19, and its mAb administration has been demonstrated to cause therapeutic effects in patients.[150,151]

8.2.1 | Lenzilumab

Lenzilumab is a recombinant monoclonal anti-GM-CSF IgG1 antibody with high affinity, which has now obtained FDA permission for therapeutic use in COVID-19 patients.[152] A case study has demonstrated that lenzilumab reduces several inflammatory mediators.[153] It prevents CRS and enhances the effectiveness of CAR T-cell therapy. Furthermore, it has been observed that lenzilumab is secure and well-tolerated.[154] This antibody directly binds to GM-CSF and neutralizes it, and so prevents GM-CSF from binding to its receptor; and therefore, it blocks the intracellular signaling. According to a study, lenzilumab therapy leads to clinical improvement, especially at mean temperatures. The oxygen requirement, IL-6, and CRP levels increased dramatically. Furthermore, a noticeable increase in platelet count was observed. Additionally, there was a significant reduction in multiple inflammatory cytokines derived from CRS, including GM-CSF, G-CSF, IL-1β, IFN-γ, IL-7, and with no reported mortality.[155]

8.2.2 | Mavrilimumab

Mavrilimumab is a monoclonal GM-CSF-Ra IgG4 antibody with high affinity, which inhibits GM-CSF from attaching to its a-chain receptor.[156] Administration of mavrilimumab in rheumatoid arthritis was safe and efficient and associated with a major downregulation of CCL2, IL-6, CRP, and GM-CSF.[157,158] Based on a study by Luca et al., mavrilimumab-treated patients showed oxygenation improvement, shorter hospitalization, and better clinical outcomes compared with patients receiving routine care and intriguingly, no patients in the mavrilimumab group died. Moreover, mavrilimumab was well-tolerated.[159] There are some other anti-GM-CSF monoclonal antibodies, including TJ003234, gimsilumab, otilimab, and namilumab, which are currently under investigation and clinical trials.

8.3 | Anti-TNF-α

8.3.1 | Infliximab

Infliximab is a chimeric monoclonal antibody that acts against TNF-α. In a study by Stallmach et al., some COVID-

19 patients were treated with infliximab, which resulted in quick promotion in lymphocyte count in addition to the reduction of proinflammatory cytokines like IL-6 and other inflammatory markers [c-reactive protein (CRP) and Lactate dehydrogenase (LDH)] and mortality rate reported together with medical development.[160] Based on other investigations, infliximab therapy can effectively treat both multisystem inflammatory syndrome in children (MIS-C) and pediatric Crohn's disease, which is temporally associated with COVID-19 infection. According to these recent studies, recovery from fever, tachycardia, hypotension, and a reduction in IL-8, TNF-α, IL-6, and CRP were observed in patients after receiving Infliximab.[161,162]

8.3.2 | Adalimumab

Adalimumab is an anti-TNF-α mAb approved for use in gastroenterology, dermatology, rheumatology, and many immunological disorders. Recently, a 30-year-old man's case study with Crohn's disease with a mild course of COVID-19 treated with adalimumab has shown rapid clinical improvement and fast hospital discharge along with the disappearance of fever and chest pain.[163] Another study reports that an adalimumab-administered patient suffering from metabolic syndrome and hypertension did not experience any symptoms associated with COVID-19 after many near interactions to COVID-19 confirmed cases.[164] In other cases, there was no respiratory disturbance or complicated development of COVID-19 infection with concomitant adalimumab treatment.[165]

8.4 | Anti-IFN-γ

Emapalumab (Gamifant®) is a completely human IgG1 monoclonal antibody against IFN-γ, which binds to free and receptor-bound IFN-γ. It inhibits the binding of IFN-γ to surface receptors of the cell and inflammatory signals activation. It is used to treat pediatric (newborn and older) and adult primary hemophagocytic lymphohistiocytosis (HLH), which leads to severe inflammatory conditions.[166,167] A clinical trial for COVID-19 investigating the effectiveness of concomitant IL-1 (Anakinra) and IFN-γ (emapalumab) inhibition in severe patients with COVID-19 has just begun (NCT04324021).

8.5 | Anti-IL-1β

Canakinumab (Ilaris®) is an anti-IL-1beta humanized monoclonal antibody that does not obstruct IL-1a and is approved for COVID-19 pneumonia by the Italian drug agency (AIFA). Due to canakinumab's anti-inflammatory effects, it is used in atherosclerotic diseases, familial Mediterranean fever, and rheumatologic disorders.[168,169] According to recent studies, COVID-19 patients who were treated with canakinumab had a reduced treatment period, and improved indications were also seen in patients with SARS-CoV-2 induced myocardial damage.[170] It may be an efficient therapy for the regulation of COVID-19-related hyperinflammation.[171]

8.6 | Anti-IL-33

IL-33 is another antibody produced in the course of SARS-CoV-2 infection. MEDI3506 is used clinically as an anti-IL-33 monoclonal antibody designed to treat skin disorders and chronic obstructive pulmonary diseases.[172] Based on Wilkinson et al., MEDI3506 has shown potent ability to treat respiratory failure caused by COVID-19. This works to dampen the cytokine storm that allows the immune system to overdrive and cause fever, inflammation, and tiredness.[173]

8.7 | Anti-FcγRII

The endosomal/lysosomal signaling pathway of FcγRII in macrophages has been known as a large infection pathway that contributes to neutralize and digest infectious agents through antibody-mediated opsonization. This mechanism goes through the ADE-FcγRII pathway.[42] As mentioned by Sedokani et al., ACE2 is not the only cell-entering target of the virus. Therefore, in addition to anti-ACE2 monoclonal antibodies in treating the severe phase of COVID-19 patients, anti-FcγRII monoclonal antibodies can be beneficial.[174]

8.8 | Anti- IL-17

Secukinumab (COSENTYX) is a fully human IgG1κ monoclonal antibody, which binds to the IL-17A. It is very effective in the treatment of severe ankylosing spondylitis and plaque psoriasis.[175] It also has a rapid onset of action, tolerability, high potency, and a well-established protection profile that does not reduce the count of lymphocytes.[176] One of the proinflammatory mediators in coronavirus infection is IL-17, which induces the activation of cytokines and other inflammatory mediators that may lead to the cytokine storm.[177] Therefore, in suppressing the abnormal inflammation and acute respiratory failure in COVID-19, agents blocking this pathway play an important role and have

strong therapeutic effects on Th17-associated CRS.[178,179] According to a study, secukinumab therapy causes the lowest infection rate for COVID-19.[180] In addition to patients without any respiratory problems, studies on older patients treated with secukinumab showed promising findings for SARS-CoV-2 infections.[181,182] Other IL-17 blocking agents, such as ixekizumab and brodalumab, may be useful for COVID-19 therapy.[183]

8.9 | Anti-connective tissue growth factor (CTGF)

Pamrevlumab is a first-in-class monoclonal antibody that regulates CTGF activity and can reduce or reverse pulmonary edema caused by CTGF and thus enhance oxygenation in individuals with pneumonia resulting from COVID-19. This antibody is used to treat unresectable pancreatic cancer and is currently in phase II of the COVID-19 clinical trial.[184,185]

8.10 | Anti-CD6

Itolizumab is a first-in-class humanized recombinant monoclonal anti-CD6 IgG1 antibody that binds to human domain 1 of CD6 (an area in the distal membrane domain), essential for T-cell differentiation, activation, and priming.[186] This mAb exclusively attacks the CD6-ALCAM pathway, inhibits T-cell differentiation, proliferation, and activation, and decreases the development of proinflammatory cytokines like IFN-γ, IL-2, and TNF-α.[187] Since 2013, itolizumab has been used to treat mild to severe chronic plaque psoriasis, its injection has not contributed to an improvement in the risk of infection.[188] Based on a study, itolizumab decreased the circulating level of IL-6 in serious and critical COVID-19 patients and maintained the circulating level of IL-6 in patients with moderate conditions.[189] According to a study by Diaz et al., the use of itolizumab along with other antiviral and anticoagulant drugs is accompanied by a decrease in the worsening of COVID-19 disease and the need for mechanical ventilation and oxygen therapy, as well as a decrease in fatality in older patients with mild COVID-19.[190]

8.11 | Anti-VLA4

Natalizumab is an α4β1-integrin (VLA4) humanized monoclonal antibody used in Crohn's disease and multiple sclerosis (MS). Some recent findings show that in addition to ACE2, SARS-CoV-2 can use integrins as cell receptors to enter cells. Therefore, integrin-blocking medications such as tirofiban or natalizumab may be an alternative choice for the therapy of COVID-19.[191,192] This antibody is preferable to some other mAbs as there is a reduced chance of systemic immunosuppression, and excessive loss of lymphocytes may not happen.[193]

8.12 | Anti-C5a

Complement-mediated thrombotic microangiopathies (TMA) seem to be the likely phenotype of severe COVID-19 infection leading to ARDS.[194,195] Eculizumab is an anti-C5a mAb that is efficiently and safely used for paroxysmal nocturnal hemoglobinuria (PNH) and TMAs.[196,197] Eculizumab exerts its functions through binding to C5 and preventing the generation of C5a and MAC formation.[197] This mAb has been used by Diurno et al. to treat COVID-19 patients identifying with ARDS or severe pneumonia.[198] They observed that Eculizumab reduced the level of inflammatory factors, CRP levels, and hospitalization duration. In another study executed by Laurence et al., Eculizumab also dropped the level of D-dimers and neutrophil counts and normalized liver functions and creatinine levels in COVID-19 patients who had acute kidney injury simultaneously.[199] Currently, Eculizumab is used in clinical studies to treat severe COVID-19 cases and is a promising drug in combating severe COVID-19 infection.

8.13 | Anti-C5aR1

Avdoralimab is a human Fc mAb, which is an antagonist for the receptor C5aR1, or cluster differentiation 88 (CD88).[200] It prevents C5a binding to C5aR1 and thus impairs the recruitment and activation of C5a-mediated myeloid cells. Avdoralimab also inhibits the increase in the production of IL-6 and TNF-α induced by C5a.[201] As a result, Avdoralimab can be a potential candidate for controlling the CRS and inflammation in COVID-19 patients.

8.14 | Anti-CD147

Meplazumab is a humanized mAb against CD147. CD147 is a type I transmembrane glycoprotein presented on the surface of epithelial cells.[202] It has been observed that CD147 plays a role in the SARS-CoV-2 entry into the cells through the spike protein. The spike protein binds to CD147 on the human cells and thereby enters the cells.[96,203] These data show that Meplazumab can prevent the cellular invasion of the virus and thus slow the disease's progression by blocking CD147.

8.15 | Anti-CCR5

CCR5 is a trans-membrane G-protein coupled receptor present on macrophages and T cells, especially Th1.[204,205] One of the ligands it binds to is CCL5 (RANTES) and mediates the inflammatory responses by increasing inflammatory cytokines such as IL-6 and causes CRS. Leronlimab is a CCR5-blocking antibody, initially developed as an HIV therapy. It binds to the extracellular loop 2 domain and N-terminus and prevents the receptor from binding to its ligands. In a study by Patterson et al., 10 severely COVID-19-infected patients were treated with Leronlimab. The treatment resulted in Leronlimab occupying CCR5 receptors on T cells and macrophages, rapid reduction of plasma IL-6, and a decrease in SARS-CoV-2 viremia.[206] These data suggest that using Leronlimab in critically infected individuals helps suppress CRS and improve prognosis.

8.16 | Anti-VEGFA

Bevacizumab is an anti-vascular endothelial growth factor (VEGF) agent usually used to treat neoplasms such as glioblastoma and ovarian cancer.[207,208] It binds to the VEGF-A protein and inhibits angiogenesis.[209] A study by Pang et al.[121] showed that treating severely ill COVID-19 patients with bevacizumab can help improve oxygenation and shorten the oxygen-support duration. The hypoxia-induced in COVID-19 patients by the ARDS syndrome and dyspnea stimulates the VEGF production and release. VEGF can contribute to plasma extravasation and pulmonary edema by increasing vascular permeability. Therefore, using monoclonal antibodies such as bevacizumab to inhibit the function of VEGF can prevent further development of pulmonary edema and improve the healing process of patients.

9 | HIGH-DOSE INTRAVENOUS IMMUNOGLOBULIN (IVIG) THERAPY

Intravenous immunoglobulin (IVIG) consists of normal IgG immunoglobulins obtained from healthy donors. The main component of IVIG preparations is IgG monomers (>96%), but they can also contain a small percentage of IgG dimers, IgM, and IgA.[210] IVIG therapy is used for inflammatory diseases as well as neuromuscular disorders, immunodeficiencies, and severe infections.[210,211] This therapy has also been used in previous coronavirus outbreaks, SARS, and MERS, with satisfying results.[212,213] IVIG therapy has also been investigated in COVID-19 patients. Treating COVID-19 patients with IVIG has been shown to improve oxygenation, reduce the length of hospital stay, and decrease respiratory morbidity.[104,214-216] It is an appropriate method of treating patients severely infected with the SARS-CoV-2 virus and speed up their recovery. IVIG therapy plays a therapeutic role by targeting inflammatory immune responses mediated by neutralizing and degrading autoantibodies, complement scavenging, suppressing the production of inflammatory factors, preventing the activity of innate and adaptive immune cells, including neutrophils, macrophages, dendritic cells, monocytes, Th1 and Th17 cells, and augmenting the Treg cells.[210] Accordingly, Shao et al. reported the improved prognosis of critical COVID-19 patients after early prescription (≤ 7 days post-admission) of IVIG (> 15 g Day 1).[217] In COVID-19 patients, it has been suggested that IVIG therapy might suppress the activity of super antigen-activated T cells, decrease cytokine storm and inflammation in severe and critically infected patients by suppressing the inflammatory immune cells and expanding Treg cells.[218] In the case of COVID-19 infection, IVIG with immunomodulatory function might inhibit immune system hyperactivity and mitigate lung injury derived from hyperinflammation.[219] Also, according to investigations, it seems that IVIG possessing the SARS-CoV2 reacting antibodies may prevent the inflammatory cytokine release and lung injury.[220] Some supportive studies suggested the safety and efficacy of IVIG against COVID-19 infection leading to reduced viral load and clinical condition improvement in infected patients.[221-223]

Despite the IVIG benefits, some adverse events can occur such as headache, lethargy, fever, flushing, malaise, fatigue, arrhythmia, thrombosis, renal impairment, hemolytic anemia, and TRALI that should be paid attention to in the use of this therapeutic approach.[224] Nevertheless, the exact and documented results of this treatment have not been clear in the course of COVID-19 infection and for the majority of patients, so much effort is necessary to evaluate the efficacy and safety of this therapy in infected patients.

10 | CONCLUDING REMARKS

Considering the rapid and pervasive spread of new viruses, pandemics, and irreparable human and financial damage to global communities, there is a critical need to expand and improve effective treatments. Neutralization of the virus, reduction of inflammation, and enhancement of antiviral immune responses are the main goals of various therapies to control infection, prevent disease progression to severe conditions, and accelerate the

recovery of patients. The use of antibody-based therapies, as a supportive therapeutic regimen, will likely continue to play a key role in patient management along with the use of currently developed vaccines. During the SARS-CoV-2 infection, antibody-producing and memory B cells play a critical role in employing the humoral immunity and specific B-cell responses against SARS-CoV-2 proteins.

Accordingly, monoclonal antibodies with a specific function and neutralizing antibodies with the mechanism of targeting virus antigens have shown promising steps toward treating the COVID-19 patients and managing the inflammation. Consistently, monoclonal and neutralizing antibodies have been documented as key components in eliciting protective immunity against most viral infections. Interestingly, neutralizing monoclonal antibodies pave the way for designing vaccines due to the therapeutic and prophylactic capabilities against SARS-CoV-2. In conclusion, the profound comprehension of efficient therapeutic aspects of the antibody-based therapies, particularly neutralizing monoclonal antibodies and establishing their therapeutic or prophylactic applications against SARS-CoV-2, revives hopes to help the better treatment of COVID-19 patients.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Abdolreza Esmaeilzadeh contributed to the hypothesis, data gathering, and writing the primary draft of the manuscript, and Samaneh Rostami and Pegah M. Yeganeh writing the primary draft, and designing figures and tables. Safa Tahmasebi and Majid Ahmadi contributed to the hypothesis, corresponding, and editing the manuscript.

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