Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Recent advances in passive immunotherapies for COVID-19: The Evidence-Based approaches and clinical trials

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ABSTRACT

In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged, causing a global pandemic called COVID-19. Currently, there is no definitive treatment for this emerging disease. Global efforts resulted in developing multiple platforms of COVID-19 vaccines, but their efficacy in humans should be wholly investigated in the long-term clinical and epidemiological follow-ups. Despite the international efforts, COVID-19 vaccination accompanies challenges, including financial and political obstacles, serious adverse effects (AEs), the impossibility of using vaccines in certain groups of people in the community, and viral evasion due to emerging novel variants of SARS-CoV-2 in many countries. For these reasons, passive immunotherapy has been considered a complementary remedy and a promising way to manage COVID-19. These approaches are based on reduced inflammation due to inhibiting cytokine storm phenomena, immunomodulation, preventing acute respiratory distress syndrome (ARDS), viral neutralization, and decreased viral load. This article highlights passive immunotherapy and immunomodulation approaches in managing and treating COVID-19 patients and discusses relevant clinical trials (CTs).

Abbreviations: ACE-2, Angiotensin-converting enzyme-2; ADE, Antibody-dependent enhancement; $AE_{(s)}$, Adverse effect$_{(s)}$; ARDS, Acute respiratory distress syndrome; CAR, Chimeric antigen receptor; COVID-19, Coronavirus disease 2019; CPT, Convalescent plasma therapy; CRP, C-reactive protein; CRS, Cytokine release syndrome; $CT_{(s)}$, Clinical trial$_{(s)}$; ESR, Erythrocyte sedimentation rate; FCR, Fc receptor; FDA, Food and Drug Administration; GM-CSF, Granulocyte-macrophage colony-stimulating factor; GVHD, Graft-versus-host disease; HBV, Hepatitis B; HCV, Hepatitis C; HIV, Human immunodeficiency virus; HLH, Hemophagocytic lymphohistiocytosis; IBD, Inflammatory bowel disease; IFN, Interferon; IgG, Immunoglobulin G; IVIg, Intravenous immunoglobulin; I.V., Intravenous; LAG-3, Lymphocyte-activation gene 3; LDH, Lactate dehydrogenase; $mAb_{(s)}$, Monoclonal antibody$_{(s)}$; MERS-COV, Middle East respiratory syndrome-corona virus; MV, Mechanical ventilation; PCR, Polymerase chain reaction; PD-1, Programmed cell death protein-1; RA, Rheumatoid arthritis; RBD, Receptor-binding domain; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TIM-3, T cell immunoglobulin domain and mucin domain-3; TNF, Tumor necrosis factor; TRALI, Transfusion-related acute lung injury; VEGF, Vascular endothelial growth factor; 2019-nCoV, 2019 novel coronavirus.

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1. Introduction

The coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus (2019-nCoV) or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in Wuhan, China. COVID-19 is increasingly recognized as a serious, worldwide public health concern [1]. Until January 15, 2022, it had impacted over 324 million individuals, with over 5,532,807 fatal cases (https://coronavirus.jhu.edu/map.html).

Passive immunity is acquired through the adoptive transfer of antibodies or T cells specific for the pathogen, whereas active immunity is conferred by a host response to a microbe or microbial antigen. Both types of immunity lead to resistance against infection and are antigen-specific, but only active immune responses establish immunologic memory.

Active immunization implies vaccination against infection. The COVID-19 outbreak has inspired scientists from all around the globe to develop anti-SARS-CoV-2 vaccinations. The efforts of the scientific community have resulted in the design of more than 300 vaccination programs. Currently, the platforms of SARS-CoV-2 vaccines include encapsulated mRNA, viral vectors, virus-like particles, inactivated viruses, and DNA vaccines are available. However, several challenges regarding the SARS-CoV-2 vaccine have remained unanswered [2]. These challenging questions include: 1-Will the new vaccines contain the COVID-19 pandemic and its novel variants? 2-Will vaccinations be available to safeguard the most vulnerable members of the human population, such as children and the elderly? 3-How much is the long-term efficacy and possible side effects of vaccines? 4-Will financial and political obstacles be overcome, allowing COVID-19 vaccinations to be made accessible to the whole world's population on an equitable basis [2]?

Passive immunotherapy is a method that has been around for a long time. Emil von Behring, an immunologist, pioneered passive immunization in 1890 when he developed diphtheria and tetanus treatments using antibodies extracted from horse blood. In 1901, Von Behring was awarded the Nobel Prize in Physiology or Medicine for his work. Other significant epidemics, such as the Spanish flu in 1918, the measles outbreak in 1934 in the United States, and more recently, the MERS-COV (Middle East respiratory syndrome-corona virus) pandemic in 2012, and Ebola in 2015, have all utilized this method effectively [3]. Passive immunotherapies include convalescent plasma therapy (CPT), intravenous immunoglobulin (IVIg), monoclonal antibody (mAb) therapy, immune checkpoint therapy, and adoptive cell transfer therapy.

At this time, there are no specific treatments for COVID-19, which is especially problematic when cytokine storm and severe acute respiratory distress syndrome (ARDS) develop. The majority of COVID-19 patients with ARDS needed ICU admission and long-term care from a mechanical ventilator. Given the systemic manifestation of COVID-19 on the human body, its complications such as lung fibrosis and secondary bacterial infection, and vaccine-related challenges, it seems that passive immunotherapy and immunomodulation approaches are the merry way for COVID-19 patients in terms of management, prophylaxis, and treatment (Table 1). For this, the effects of immunomodulatory drugs as a treatment for COVID-19 urgently need to be studied. Therefore, this review article will delineate the studies conducted on passive immunization and immunomodulation in COVID-19. Besides, the related clinical trials (CTs) have been included.

2. Method

In this narrative review, we conducted a comprehensive search by using the keywords "COVID-19" OR "SARS-CoV-2" AND "Immunotherapy" OR "Passive Immunotherapy" on PubMed, Web of Science, and Scopus in September 2021. For each section, we used related keywords. For instance, "COVID-19" OR "SARS-CoV-2" AND "Convalescent Plasma Therapy". Articles were included by the following criteria; (1) review studies, (2) randomized controlled trial studies, (3) case reports studies, (4) original articles such as *in vivo* and *in vitro* studies. Additionally, the reference list and citations of all included articles were checked to find potential eligible articles.

Our initial database search revealed a total number of 463 records. We removed 184 duplicate records, and 58 additional records were excluded through title and abstract screening. Finally, a total number of 221 (223 references) articles were entered into our review (Fig. 1).

3. Immunotherapy of COVID-19

There are two type of immunotherapy including active immunotherapy and passive immunotherapy. The process of exposing the body to an antigen or vaccination in order to elicit an adaptive immune response is known as "active immunization" (Fig. 2). This immune response takes days or weeks to develop, but it may last for months or even years. For instance, wild infection with hepatitis A virus (HAV) or the administration of two doses of the HAV vaccine are examples of active immunization [4]. Vaccines are designed to stimulate the adaptive immune response, which includes both cell-mediated and humoral responses, resulting in the production of neutralizing, or virus-blocking antibodies. Vaccines include an antigenic determinant, which when exposed to the host, causes antibodies to be produced, resulting in protective immunity [5].

In SARS-CoV-2, surface S protein is an antigen. COVID-19 vaccines use a variety of strategies to deliver the S protein into the human immune system. Vector-based vaccines employ a non-pathogenic virus that infects host cells and then expresses the SARS-CoV-2 S protein gene, inducing the SARS-CoV-2-specific immune response. Vector-based vaccines include Oxford AstraZeneca (ChAdOx1) and Johnson & Johnson's (J&J; Ad26.COV2.S). mRNA-based vaccines contain RNA encoding SARS-CoV-2 S protein. After injection, mRNA translate to S protein. Then, host cells present S protein in the context of major histocompatibility complex (MHC) to helper and cytotoxic T lymphocytes (CTLs) to stimulate immune responses. mRNA-based vaccines include Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273). Killed/inactivated vaccines are the forms of killed/inactivated or weakened of SARS-CoV-2. After administration, an immune response is induced without causing COVID-19. These vaccines include Sinopharm and Sinovac. Protein subunit vaccines deliver viral proteins into the body (Here it mean S protein of SARS-CoV-2). As a specific example, Novavax is a full-length S protein on a nanoparticle platform that can stimulate a protective Th1-dominant B and T lymphocyte response in mice and baboons when given intramuscularly with a matrix-M adjuvant [5,6]. Protein subunit vaccines include Novavax (NVX-CoV2373) [5].

Passive immunity is provided by IgG antibodies to defend against infection (Fig. 2). It protects for a few weeks to 3–4 months at most. Passive immunity may be natural or acquired. In the weeks/months after birth, the baby's natural passive immunity is provided by the mother's tetanus antibodies (primarily IgG) via placental transfer. Acquired passive immunity is provided by pooling the serum of immune individuals, concentrate the immunoglobulin fraction, and then transfusing it to protect a vulnerable individual [4]. In the following, we focus on passive immunotherapy approaches in the context of COVID-19, which include humoral immunotherapy and cellular immunotherapy.

4. Humoral immunotherapies approaches

This section will discuss humoral immunotherapy approaches in the management and treatment of patients with COVID-19. These approaches include CPT, IVIg, and mAb administration.

4.1. Convalescent plasma therapy

CPT is among the used antiviral treatments. The convalescent plasma includes neutralizing antibodies against the pathogen (Fig. 3). Many

Table 1
An overview of the paradigms of passive immunotherapies in the treatment of COVID-19.

Paradigm	Agent$_{(s)}$	Current State	Mechanism of Action/Benefits	Viral Variants and Therapeutic Efficacy
Humoral Immunotherapies				
Convalescent Plasma Therapy	SARS-CoV-2-Specific Antibody	CT	Viral neutralization	Alpha (B.1.1.7): NormalBeta (B.1.351) : ResistantGamma (P.1) : ResistantDelta (B.1.617.2): Resistant
Intravenous Immunoglobulin	Pooled IgG	CT	Viral neutralization, Increased phagocytosis, Preventing ADE	Alpha: Retained activity Beta: Retained activity Gamma: Retained activity Delta: Retained activity
Monoclonal Antibodies	Tocilizumab*, Sarilumab/Siltuximab*, Clazakizumab, Sirukumab	NIH treatment guideline*, CT	IL-6 receptor inhibition/IL-6 inhibition	
	Anakinra/Canakinumab,	CT	IL-1 receptor inhibition/IL-1β inhibition	
	Emapalumab	Proposed	IFN-γ inhibition	
	Ravulizumab/Avdoralimab	CT	C5 inhibition/C5a receptor inhibition	
	Infliximab, Adalimumab	CT	TNF inhibition	
	Mavrilimumab/Gimsilumab, Lenzilumab	CT	GM-CSF receptor inhibition/GM-CSF inhibition	
	Lanadelumab	CT	Kallikrein inhibition	
	Itolizumab	CT	CD6 blocking	
	Nivolumab, Pembrolizumab	CT	PD-1 blocking and prevention of T cell exhaustion	
	Monalizumab	CT	NKG2A blocking	
	Secukinumab, Ixekizumab/ Brodalumab	CT	IL-17 inhibition/IL-17 receptor inhibition	
	Bevacizumab	CT	VEGF inhibition	
	IC14	CT	CD14 blocking	
	Leronlimab	CT	CCR5 blocking	
	F5111.2	Proposed	Promotion of Treg differentiation	
	Meplazumab	CT	CD147 blocking and inhibition of virus entry into host cells	
	Bamlanivimab, Etesevimab*	EUA	Binding to spike, viral neutralization, and inhibition of virus entry into host cells	Alpha: Retained activity Beta: Marked reduction Gamma: Marked reduction Delta: Retained activityOmicron (B.1.1.529) : Marked reduction
	Casirivimab, Imdevimab (REGEN-COV)*	NIH treatment guideline, EUA	Binding to spike, viral neutralization, and inhibition of virus entry into host cells	Alpha: Retained activity Beta: Retained activity Gamma: Retained activity Delta: Retained activity Omicron: Marked reduction
	Tixagevimab, Cilgavimab*	CT	Binding to spike, viral neutralization, and inhibition of virus entry into host cells	Alpha: Retained activity Beta: Retained activity Gamma: Retained activity Delta: Retained activity Omicron: Moderate reduction
	Sotrovimab*	NIH treatment guideline, EUA	Binding to spike, viral neutralization, and inhibition of virus entry into host cells	Alpha: Retained activity Beta: Retained activity Gamma: Retained activity Delta: Retained activity Omicron: Retained activity
	Bebtelovimab**	EUA, CT	Binding to spike, viral neutralization, and inhibition of virus entry into host cells	Omicron: Retained activity
Cellular Immunotherapies				
Natural Killer Cell	NKG2D-ACE-2 CAR-NK cell, S309-CAR-NK, CR3022-CAR-NK, CYNK-001	CT	Eradication of infected cells via perforin and granzyme	
Regulatory T Cell	CK0802, RAPA-501-ALLO Cells	CT	Prevention of inflammation-induced tissue damage	
γδ T Cell	TCB008	CT	Releasing of IFN and inducing of an antiviral state	
Mesenchymal Stem Cell	Remestemcel-L, Descartes 30, PLX-PAD, Longeveron MSCs	CT	Anti-inflammatory and immunosuppressive role	
$CD4^+$ /$CD8^+$ T cell	SARS-CoV-2 Specific T Cells	CT	Mitigating uncontrolled inflammation and eradication of infected cells via perforin and granzyme	

Abbreviation: CT: Clinical trial; ADE: Antibody-dependent enhancement; NIH: National Health Institute; EUA: Emergency Use Authorization; TNF: Tumor necrosis factor; IFN: Interferon; ND: Not disclosure.
*Data based on COVID-19 Treatment Guidelines from NIH (https://www.covid19treatmentguidelines.nih.gov/therapies/).
** Data based on https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-new-monoclonal-antibody-treatment-covid-19-retains.

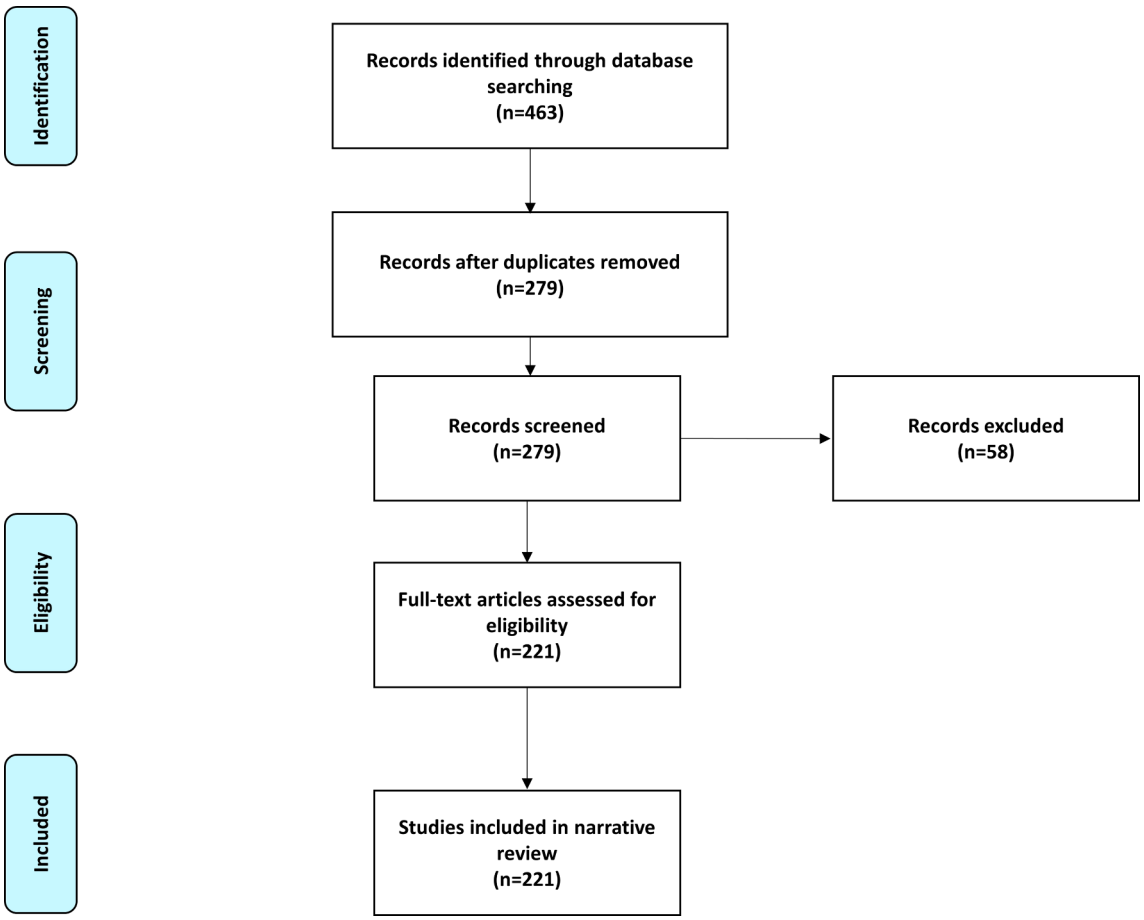

Fig. 1. The diagram of methodology.

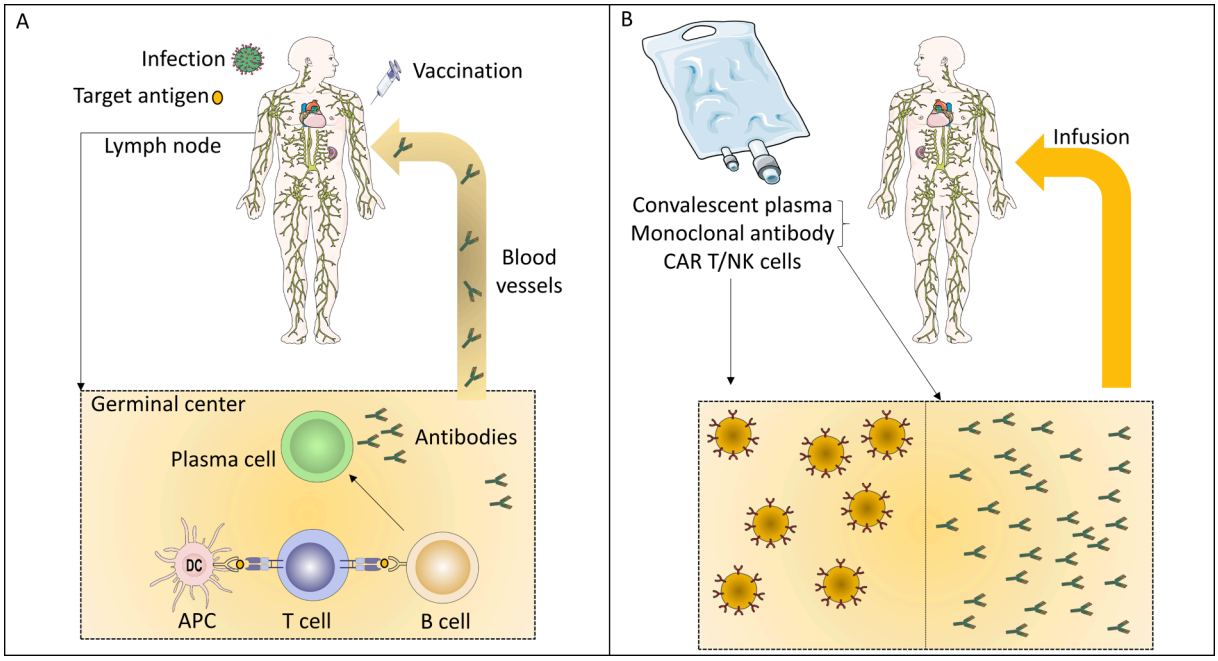

Fig. 2. Active and passive immunization. A) Target antigens are presented by antigen presentation cells (APCs) in the lymph nodes during active immunization. Infection or vaccination triggers active immunization. This causes antigen-specific B lymphocytes to be activated by T cells in the germinal center. As a result, B lymphocytes differentiate into plasma cells, which synthesize and release antigen-specific antibodies. B) Antibodies, convalescent plasma, and engineered cells are the examples of passive immunization, which can be generated recombinantly or collected from donors. These products are infused as a passive vaccination, and enter the bloodstream via blood vessels.

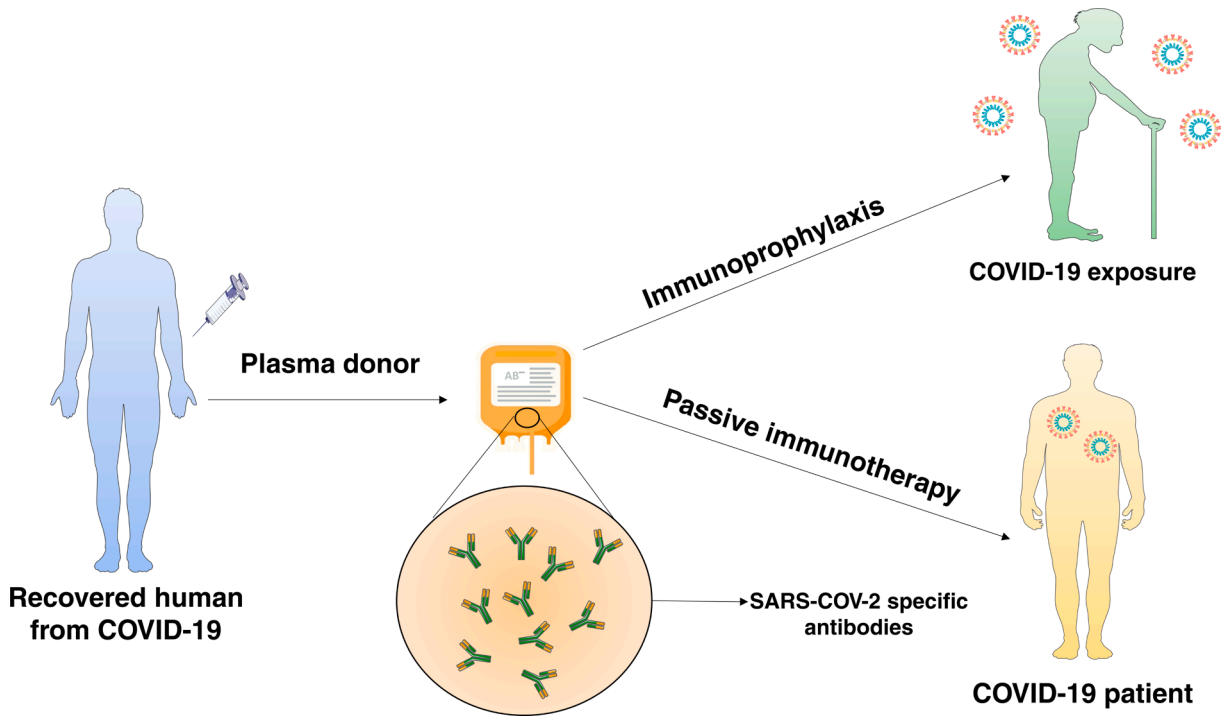

Fig. 3. The effects of convalescent plasma therapy in patients with risk of COVID-19. Convalescent plasma contains anti-SARS-CoV-2 antibodies. The use of plasma in healthy and infected individuals may lead to prevention and recovery, respectively.

studies have demonstrated that this method has been used for the remedy of SARS-CoV [7-10], Ebola [11-15], Influenza A (H5N1) [16], Chikungunya virus [17], H1N1 flu [18,19], H7N9 flu [20], Measles [21], Mumps [22], Human immunodeficiency virus (HIV) [23], MERS-COV [24,25], Pummal virus [26] infections.

It has been reported that CPT is a safe option [27,28]. However, the findings of another study showed adverse effects (AEs) within hours after transfusion in two patients [29]. A study indicated that CPT may be associated with acute respiratory distress syndrome due to transfusion-related acute lung injury (TRALI) in Ebola-infected patients [30]. This matter should be considered as a potential concern in COVID-19 patients. Another significant concern associated with plasma therapy is antibody-dependent enhancement (ADE). In other words, plasma therapy may cause infection rates to increase in the host. This phenomenon has been observed in SARS-CoV and MERS-CoV. SARS-CoV-2-specific antibodies bind to the virus via Fab and Fc region interactions with the cells bearing the Fc receptor (FCR). Finally, cells are infected with SARS-CoV-2 via endocytosis or phagocytosis. This concern should be considered a significant challenge. It is noteworthy that CPT is a safe and well-tolerated approach. However, the donor's plasma must be screened for blood type and infections like HIV, hepatitis C (HCV), and hepatitis B (HBV). 14 days after recovery from COVID-19, convalescents can donate their plasma [31]. There is still this question of whether the plasma of COVID-19 donors with different severities and grades has various therapeutic effects [32].

Some studies reported that there is no statistically significant difference between CPT and conventional treatment in terms of clinical outcomes [33,34]. In contrast, some studies found that CPT is linked to improved clinical outcomes [29,35,36]. Transfusion of plasma with greater anti-SARS-CoV-2 immunoglobulin G (IgG) antibody levels was linked with a lower risk of mortality than the transfusion of plasma with lower antibody levels in patients hospitalized with COVID-19 who were not undergoing mechanical ventilation (MV) [37].

The issue of plasma administration time is important. In this regard, Briggs et al. [38] have indicated that in patients with moderate to severe COVID-19, early CPT improved clinical outcomes, while late CPT administration had little effect.

4.2. Intravenous immunoglobulin

IVIg comprises pooled antibodies, usually IgG, from blood donors [39]. Previously, IVIg had been used for prophylaxis of the severe 2009 Influenza A (H1N1) infection [40]. MERS-CoV has been inhibited *in vivo* by human polyclonal IgG [41]. IVIG have anti-inflammatory properties by saturating the Fcγ receptor, preventing ADE, anti-idiotypic binding to anti-viral antibodies, and binding of proinflammatory cytokines [42].

IVIg may be an effective treatment and prophylactic approach for COVID-19. This point of view is supported by a study that reported Flebogamma® DIF (Grifols) and Gamunex®-C had been cross-reacted with SARS-CoV-2, SARS-COV, and MERS-COV antigens. Gamunex-C 10% and Flebogamma 5% DIF reacted with the SARS-CoV-2 S1 subunit. These products contain ≥ 98 to 99% IgG [43].

A clinical study has suggested high-dose IVIg might probably be effective during the early COVID-19 infection period [44,45]. Several studies reported that IVIg is associated with improved clinical outcomes [46-50]. In contrast, Tabarsi et al. [51] have indicated that IVIG in combination with hydroxychloroquine and lopinavir/ritonavir has shown no benefit, and IVIg therapy was shown to be ineffective in the management of severe COVID-19 cases. The CTs have been listed in Table 2.

Taken together, it seems that IVIg can be a practical and helpful way to treat and manage COVID-19 in immunocompromised patients. However, IVIg in patients with selective IgA deficiency should be prescribed with caution. Also, the dose of IVIg should be considered. Of note, the disease stage is a significant factor in using this approach.

4.3. Monoclonal antibody therapy

Using mAbs targeting specific sites on viruses has been an effective way for prophylactic and therapeutic purposes [52-54]. The trimeric spike (S) glycoproteins on coronavirus, the prime target for neutralizing antibodies, are crucial for entry into host cells [55,56]. The S

Table 2
Ongoing intravenous immunoglobulin administration-related clinical trials in COVID-19 treatment.

Type of Intervention	Drug/Product	Participants (N)	NCT identifier	Phase
IVIg therapy	IVIg	80	NCT04261426	II/III
CPT and human intravenous anti-COVID-19 immunoglobulin	COVID-19 convalescent plasma and IVIg	75	NCT04395170	II/III
IVIg therapy	IVIG, Bioven	76	NCT04500067	III
IVIg therapy	IVIg	60	NCT04548557	III

Abbreviations: IVIg: Intravenous immunoglobulin; CPT: Convalescent plasma therapy.

glycoprotein consists of two functional subunits: S1 (including A, B, C, and D domains) responsible for binding to host receptors; and S2, which advances the fusion of the viral and cellular membranes [57]. The spike proteins of SARS-CoV-2 bind the human angiotensin-converting enzyme-2 (ACE-2) protein as a host receptor [58]. Interaction between S glycoprotein and ACE-2 triggers conformational changes needed for membrane fusion [59]. Neutralizing antibodies can fulfill their preventive and therapeutic goals by impeding S proteins from binding to their receptors, interfering with conformational changes, which is a prerequisite for membrane fusion, or targeting inflammatory cytokines to temper immune responses [60,61].

The similarity between the S protein of SARS-CoV and SARS-CoV2 gives rise to the possibility that SARS-CoV neutralizing antibodies can display cross-neutralization for SARS-CoV2. Using the memory B cell of a patient infected with SARS-CoV in 2003, Pinto et al. [62] reported that S309 could target the S glycoprotein of SARS-CoV2 by engaging the receptor-binding domain of the S glycoprotein. The cryo-EM structure of S309 bound to S glycoproteins has revealed that S309 recognizes a highly conserved epitope in the S-B domain [62]. Wang et al. [63] have shown that 47D11 also has cross-neutralizing activity for SARS-CoV and SARS-CoV2. 47D11 was found to neutralize infection of VeroE6 cells by SARS-CoV and SARS-CoV-2. It was stated that 47D11 targets the S1B receptor-binding domain (RBD) of SARS-S and SARS2-S [63]. It has been reported that S2E12 and S2M11, which are SARS-CoV-2 human neutralizing antibodies, block ACE-2 and syncytia formation. These antibodies cause the protection of hamsters against the SARS-CoV-2 challenge. Furthermore, FcγRIIIa-dependent ADCC (antibody-dependent cellular cytotoxicity) activity and ADCP (Ab-dependent cell phagocytosis activity) have been associated with S2M11 function [64].

RBD is the most vulnerable site for neutralizing antibodies. Several antibodies can be directed towards specific epitopes. Researchers using antibody depletion assays have shown that antibodies against S14P5 and S21p2 can contribute to the neutralization of SARS-CoV-2 [65].

In vitro, one mAb named 2B04 neutralized wild-type SARS-CoV-2 with exceptional efficacy. 2B04 protected challenged mice from weight loss, decreased viral load in the lung, and prevented systemic dissemination in a mouse model of SARS-CoV-2 infection. As a result, 2B04 seems to be a feasible candidate to prevent SARS-CoV-2 infection [66]. Kreye et al. [67] indicated that CV07-209 was a preventative and therapeutic mAb against hamsters' SARS-CoV-2 infection, weight loss, and lung injury.

As the evidence indicates, antibodies can effectively alleviate inflammation and lung damage [61,68]. Currently, several targets have been reported to use for managing and alleviating COVID-19 patients. These targets include IL-6/IL-6R, IL-1/IL-1R, IFN-γ, complement molecules, TNF, GM-CSF/GM-CSF-R, kallikrein, CD6, PD-1, NKG2A, IL-17/IL-17R, VEGF, CD14, CCR5, IL-2, CD147, and SARS-CoV-2 spike protein. In the following, the clinical evidence related to these targets is highlighted. Additionally, preclinical studies have shown that SARS-CoV-2 entry receptors are candidates for targeted therapy. In this context, Table 4 summarizes SARS-CoV-2 receptors involved in the immunopathogenesis of COVID-19 and potential therapeutic approaches based on their blockade.

IL-6/IL-6R Axis. Tocilizumab and sarilumab are mAbs directed against the IL-6 receptor (IL-6R) that are applied for the treatment of rheumatoid arthritis (RA) [69,70] and cytokine release syndrome (CRS) [71]. Evidence has revealed that tocilizumab treatment has been associated with the reduced mortality rate [72-76], reduced cytokine storm [75,77], and improved clinical outcomes [75,76,78-82]. In contrast to these results, a study stated that tocilizumab had no significant impact on the clinical outcome [83]. Studies showed that sarilumab has been associated with faster recovery of patients with severe SARS-CoV-2 pneumonia [70,84]. However, the overall clinical improvement and mortality rate of treatment group have not been significant compared to the control group [84,85]. Further details of CTs are awaited [86] (NCT04315298 and NCT04324073). In addition to IL-6R, IL-6 is also targeted. Siltuximab is a chimeric human-mouse mAb directed against IL-6 and approved to treat Castleman disease [87]. Considering augmented IL-6 serum concentration in SARS-CoV-2 infected patients (1 2 1), IL-6 antagonist is a treatment approach. Evidence has revealed that siltuximab treatment has been associated with the reduced mortality rate [88], decreased IL-8 and pentraxin 3 levels [89], and improved survival [89]. Clazakizumab and sirukumab are anti-IL-6 mAbs that may assist in suppressing the SARS-CoV-2-related hyper inflammation. Clazakizumab is being studied to treat renal antibody-mediated rejection, although the Food and Drug Administration (FDA) has not yet authorized it [90]. Clazakizumab and sirukumab are being tested in human CTs to treat COVID-19 (NCT04494724, NCT04348500, NCT04659772, and NCT04380961).

IL-1/IL-1R Axis. Anakinra is an FDA-approved recombinant drug for RA treatment with an IL-1 antagonistic characteristic that blocks IL-1 receptor (IL-1R) [91]. Due to increased IL-1 serum levels in COVID-19 patients [92], it seems that using anakinra may be a way to manage and improve clinical outcomes in patients with COVID-19. A study has concluded that using anakinra in four patients has been safe [93]. Evidence has revealed that anakinra treatment has been associated with improved clinical outcomes [94-98]. Contrary to the mentioned findings, anakinra had no effect on clinical outcomes in patients with mild-to-moderate COVID-19 pneumonia [99]. There has been no anakinra related toxicity effect, but it needs to determine optimal treatment dosage in future studies [100,101]. Several CTs have been investigated (NCT04366232, NCT04443881, NCT04364009, NCT04357366, NCT04339712, NCT04362111, NCT04330638, NCT02735707, and IRCT20120703010178N20). In addition to IL-1R, IL-1 is also targeted. Canakinumab is a human anti-IL-1β antibody that acts by inhibiting the function of IL-1β. The effects of canakinumab in patients with COVID-19-related pneumonia were investigated. Canakinumab treatment has been associated with improved clinical outcomes [102-104]. Contrary to the effectiveness of this drug in previous studies, canakinumab therapy had no effect on survival in individuals hospitalized with severe COVID-19 compared to placebo [105]. There is empirical evidence for the role of the inflammasome in the immunopathology of COVID-19. In patients with COVID-19, the NLRP3 inflammasome is activated in response to the SARS-CoV-2 infection. The clinical outcome of the disease is influenced by inflammasome activation, showing a direct association between inflammasome activation, exacerbated inflammatory response, and poor prognosis [106]. In the context of the data presented herein, it has been suggested to use inflammasome inhibitors such as MCC950 and CY-09 in combination with anakinra, canakinumab, and anti-IL-18 agents (Tadekinig alfa or recombinant human interleukin-18 binding protein) to assess their effectiveness in patients with COVID-19. A CT using melatonin for inhibiting inflammasome in COVID-19 is investigating (NCT04409522).

IFN-γ. There is an IFN-γ-related cytokine storm in association with SARS coronavirus infection [107]. The causes of death in 28% of COVID-

19 patients were sepsis and cytokine storm [108]. The plasma concentration of IFN-γ in COVID-19 patients was higher than in healthy adults [1]. Pro-inflammatory cytokines attract neutrophils, monocytes, and T cells to the infection site in the lung. Subsequently, promoted inflammation in this area causes lung injury [109]. Considering the role of IFN-γ in SARS-CoV-2 immunopathogenesis, there is a rational approach regarding IFN-γ targeting. Emapalumab is a fully human IgG1 mAb that targets IFN-γ, and it is used for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) [110]. CTs with a large sample size are needed to scrutinize the efficacy of emapalumab in COVID-19 patients.

Complement Molecules. The complement system can be considered as a target for the improvement and treatment of COVID-19 patients. Complement activation via classic, alternative, and lectin pathways incites accumulation of neutrophils, monocytes, and macrophages, and CRS via anaphylatoxins such as C3a and C5a. These cascades can lead to acute respiratory distress disease (ARDS), NETOsis, and hypercoagulability [111,112]. Ravulizumab (Anti-C5), AMY-101 (C3 inhibitor), avdoralimab (anti-C5aR), and conestat alfa (C1 esterase inhibitor) are promising agents that inhibit the complement system-related maladaptive inflammatory response [111]. The optimal ravulizumab dosage regimen provided rapid and complete terminal complement system suppression, which may be maintained for up to 22 days, according to data from the pharmacokinetic assessment of ravulizumab in 22 patients with severe COVID-19 [113]. C3 targeting-based intervention with AMY-101 in COVID-19 patients has been successful and safe. A significant improvement has been reported following AMY-101 treatment in COVID-19 patients [114]. A phase 2 CT related to the efficacy of AMY-101 in 144 patients with ARDS due to COVID-19 has been designed (NCT04395456). Also, using ravulizumab is being investigated in two CTs [115,116]. Avdoralimab is a mAb directed against C5aR that it-based CTs in patients with COVID-19 are ongoing (NCT04333914 and NCT04371367).

TNF. In patients with COVID-19, symptoms can be observed on the spectrum of respiratory manifestations and dysfunction of several organs. Capillary leakage has also been reported in these patients due to increased inflammatory cytokines such as IL-6, IL-1, and tumor necrosis factor (TNF) [117,118]. Anti-TNF such as infliximab and adalimumab are used to treat a broad spectrum of autoimmune diseases [119]. Evidence has revealed that infliximab and adalimumab alleviate COVID-19 pneumonia [117,120,121]. Infliximab is linked to decreased immunogenicity of the Pfizer/BioNTech and AstraZeneca SARS-CoV-2 vaccines after a single dose administration [122].

GM-CSF/GM-CSF-R Axis. Mavrilimumab (also known as CAM-3001 or KPL-301) is a human monoclonal IgG4 antibody that targets granulocyte–macrophage colony-stimulating factor (GM-CSF) receptor-α subunit [123]. Given the cytokine storm and inflammatory myeloid cell infiltration into the lung, such as monocyte-derived macrophages in severe COVID-19 patients [124], and serum increased GM-CSF in patients with COVID-19 [1], it seems that GM-CSF blockade-based immunomodulatory therapies would benefit patients [125]. Furthermore, the percentage of GM-CSF-expressing $CD4^+$ T cells in patients with COVID-19 was higher than in the control group [126]. A study has shown that mavrilimumab treatment associated with improved clinical outcomes [127]. Gimsilumab is a fully human mAb directed against GM-CSF. Inflammatory responses and ARDS are triggered by GM-CSF which in turn triggers the production of myeloid precursors such as granulocytes and monocytes from bone marrow (BM) [128]. During the SARS-CoV-2 infection, pathogenic Th1 cells release GM-CSF. Consequently, $CD14^+CD16^+$ monocytes with high expression of IL-6 are triggered by GM-CSF, and it causes severe lung pathology [126]. Table 3 summarizes the findings of GM-CSF-based therapy in patients with COVID-19.

Kallikrein. Lanadelumab (also known as DX-2930) is a fully human mAb directed against kallikrein used to treat hereditary angioedema with C1 inhibitor deficiency [129]. A hypothesis suggests that dysregulation of bradykinin (BK) signaling has been associated with respiratory complications in COVID-19 patients. Based on this hypothesis, SARS-CoV-2 probably downregulates ACE-2 expression at the plasma membrane of infected cells. Then, the levels of des-Arg (9) bradykinin (DABK) increase. This metabolite is related to acute lung injury and inflammation. Plasma leakage results in an amplification loop of BK and DABK, which bind to the bradykinin2 receptor (B2R) and the bradykinin1 receptor (B1R), respectively. Subsequently, vascular permeability and angioedema increase [130,131]. Given the hypothesis, targeting the

Table 3
GM-CSF-based therapy in patients with COVID-19.

Type of intervention	Drug	Participants (N)	NCT identifier/ Number	Phase	Results/Interpretations	References
	Otilimab (GSK3196165)	1157	NCT04376684	II	In individuals over the age of 70, otilimab showed a significant improvement.	[200]
GM-CSF inhibition (anti-GM-CSF antibody)	Namilumab	146	ISRCTN40580903	II	Namilumab reduced inflammation in hospitalized COVID-19 pneumonia patients, which was compatible with secondary clinical outcomes.	Fisher et al. [201]
	Gimsilumab	227	NCT04351243	II	NR	
	Lenzilumab	520	NCT04351152	III	1- Compared to a matched control cohort of patients hospitalized with severe COVID-19 pneumonia, GM-CSF neutralization with lenzilumab was safe and associated with faster improvement in clinical outcomes, including oxygenation, and more significant reductions in inflammatory markers. 2- Over and beyond remdesivir and corticosteroids, lenzilumab substantially improved SWOV in hospitalized, hypoxic COVID-19 pneumonia patients.	Temesgen et al. [202] Temesgen et al. [203]
	TJ003234 (Anti-GM-CSF mAb)	384	NCT04341116	II/III	NR	
		32	NCT03794180	I	NR	
	Mavrilimumab (KPL-301 or CAM-3001)	40	NCT04399980	II	On day14, 12 (57%) of the mavrilimumab patients were alive and no longer required supplementary oxygen, compared to nine (47%) of the placebo patients. No treatment-related death was reported.	Cremer et al. [204]
		588	NCT04447469	II/III	NR	
		50	NCT04397497	II	NR	

Abbreviations: GM-CSF: Granulocyte-Macrophage colony-stimulating factor; rhuGM-CSF: Recombinant human GM-CSF; NR: Not released; SWOV: Survival without ventilation; mAb: Monoclonal antibody.

Table 4
SARS-CoV-2 receptors involving in the immunopathogenesis of COVID-19 and their targeting-based therapies.

Receptor	Expression	Antibody/Drug	Ligand	Results	References
CD147	Brain, Lung. Intestine, Liver, Pancreas, Kidney	Meplazumab	SARS-CoV-2 spike protein	1- Inhibition of SARS-CoV-2 amplification in Vero E6 and BEAS-2B cell lines 2- CRP↓, Lymphocyte count↑, time to virus clearance↓	Wang et al. [148], Bian et al. [149]
TMPRSS2	Endocrine tissues, Proximal digestive tract, Gastrointestinal tract, Pancreas, Kidney & urinary bladder, Male tissues, Bone marrow & lymphoid tissues	Camostat mesilate, Enzalutamide	SARS-CoV-2 spike protein	1- In the case of Covid-19, camostat mesilate therapy was not linked to an increase in adverse events during hospitalization and did not affect time to clinical improvement, progression to ICU admission, or death. 2- In human and mouse lung cells, therapy with the antiandrogen enzalutamide diminishes TMPRSS2 levels. In lung cells, enzalutamide substantially decreased SARS-CoV-2 entrance and infection. 3- A TMPRSS2 inhibitor that has been licensed for clinical usage prevented SARS-CoV-2 entrance and may be used as a therapy.	Gunst et al. [205], Leach et al. [206], Hoffmann et al. [58]
ACE-2	Lung, Kidney, Intestine	311mab-31B5 and 311mab-32D4	SARS-CoV-2 spike protein	These two mAbs can bind to SARS-CoV-2 RBD, inhibit the interaction between SARS-CoV-2 RBD and the ACE2 receptor, and neutralize SARS-CoV-2 S protein pseudotyped viral infection effectively.	Hoffmann et al. [58], Chen et al. [207]
TTYH2	Myeloid cells	–	RBD	Although TTYH2 does not promote active replication of SARS-CoV-2, its interaction with the virus produced strong proinflammatory responses in myeloid cells that were associated with COVID-19 severity	Lu et al. [208]
Neuropilin-1	Respiratory and olfactory epithelium, endothelial cells	Anti-NRP1 antibody	Furin-cleaved S1 fragment of the spike protein	SARS-CoV-2 entry and infectivity in cell culture↓	Castelvetri et al. [209], Daly et al. [210]
DC-SIGN (CD209)	Lung and blood DCs,	–	Spike receptor binding domain	DC-SIGN aids virus transmission to permissive ACE2 + Vero E6 cells.	Thépaut et al. [211]
L-SIGN (CD209L)	Human lung and kidney epithelial and endothelial cells, Liver sinusoidal endothelial cells	–	Spike receptor binding domain	1- L-SIGN aids virus transmission to ACE2 + Vero E6 cells. 2- ACE-2 interacts withCD209L. 3- SARS-CoV-2 infection is permissive in human endothelium cells, and blocking CD209L activity using a knockdown approach or soluble CD209L prevents viral entrance.	Thépaut et al. [211], Amraei et al. [212], Kondo et al. [213]
CLEC10A, ASGR1, and LSECtin	Myeloid cells	–	Regions outside of the RBD	Strong proinflammatory responses in myeloid cells following engagement of these receptors with the spike.	Lu et al. [208]

Abbreviation: CRP: C-reactive protein; RBD: Receptor-binding domain; DC: Dendritic cell; ACE2: Angiotensin-converting enzyme; ↑: Increased; ↓: Decreased.

kallikrein pathway can prevent ARDS in patients with COVID-19.

CD6. CD6 is a glycoprotein found on mature T cells that plays a vital role in T-cell activation. Itolizumab is a CD6-targeting humanized antibody that has decreased numerous cytokines, particularly those involved in the Th1/Th17 pathway [132,133]. Itolizumab treatment could decrease mortality [133] and IL-6 serum levels in COVID-19 patients, improving respiratory conditions [134].

Immune Checkpoint Molecules. Immune checkpoint inhibition has the potential to be utilized as a treatment strategy in COVID-19. Immune checkpoint inhibition such as programmed cell death protein-1 (PD-1) can augment T cell responses against SARS-CoV-2 in patients with lymphopenia. It can also revive SARS-CoV-2-specific exhausted T cells [135]. NCT04413838, NCT04356508, NCT04343144, and NCT04335305 are some of the CTs that use nivolumab and pembrolizumab to target PD-1. A study has shown the expression of PD-1, lymphocyte-activation gene 3 (LAG-3 or CD223), and T cell immunoglobulin domain and mucin domain-3 (TIM-3) on NK cells from most patients with COVID-19 [136]. A hypothesis suggests that anti-NKG2A mAb such as monalizumab is a promising avenue for patients with COVID-19 [137]. Monalizumab is a humanized antibody with specificity against the NKG2A immune checkpoint [138]. A CT of using monalizumab in patients with advanced or metastatic cancer and SARS-CoV-2 infection is ongoing (NCT04333914). It can be concluded that immune checkpoint combination therapy, including anti-NKG2A, anti-PD-1, anti-CD39, anti-TIM-3, and anti-LAG-3 mAbs, may be more effective than each of them alone (Fig. 4). Overall, further research will be needed to investigate the expression of other immune checkpoints on immune cells regarding COVID-19.

IL-17/IL-17R Axis. IL-17/IL-17R axis leads to a cytokine storm by promoting excessive and unregulated synthesis of proinflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α. IL-17 inhibition is immunologically feasible as an ARDS prevention approach in COVID-19 and is readily accessible. Secukinumab (human mAb against IL-17), ixekizumab (humanized mAb against IL-17), and brodalumab (human mAb against the IL-17 receptor) are available [139]. Resende et al. [140] have reported that secukinumab had no effect on clinical outcomes. In the setting of ARDS, COVID-19 mortality is linked to myocarditis. Severe viral myocarditis has been related to a TH17-dominant immunophenotype. This matter indicates that anti-IL-17 treatment may help reduce the morbidity and mortality associated with COVID-19-induced myocarditis [139]. A phase 2 CT with secukinumab intervention is ongoing (NCT04403243).

VEGF. Bevacizumab targets VEGF-A. A hypothesis based on COVID-19-induced respiratory pathological and vascular alterations stated that bevacizumab may help relieve COVID-19 patients. Bevacizumab treatment is linked to improved clinical outcomes [141]. Compared to COVID-19 patients receiving tocilizumab, patients receiving bevacizumab would benefit from a significant survival benefit [142].

CD14. The IC14 is a mAb directed against a human protein called CD14, which is present on the surface of immune cells circulating in

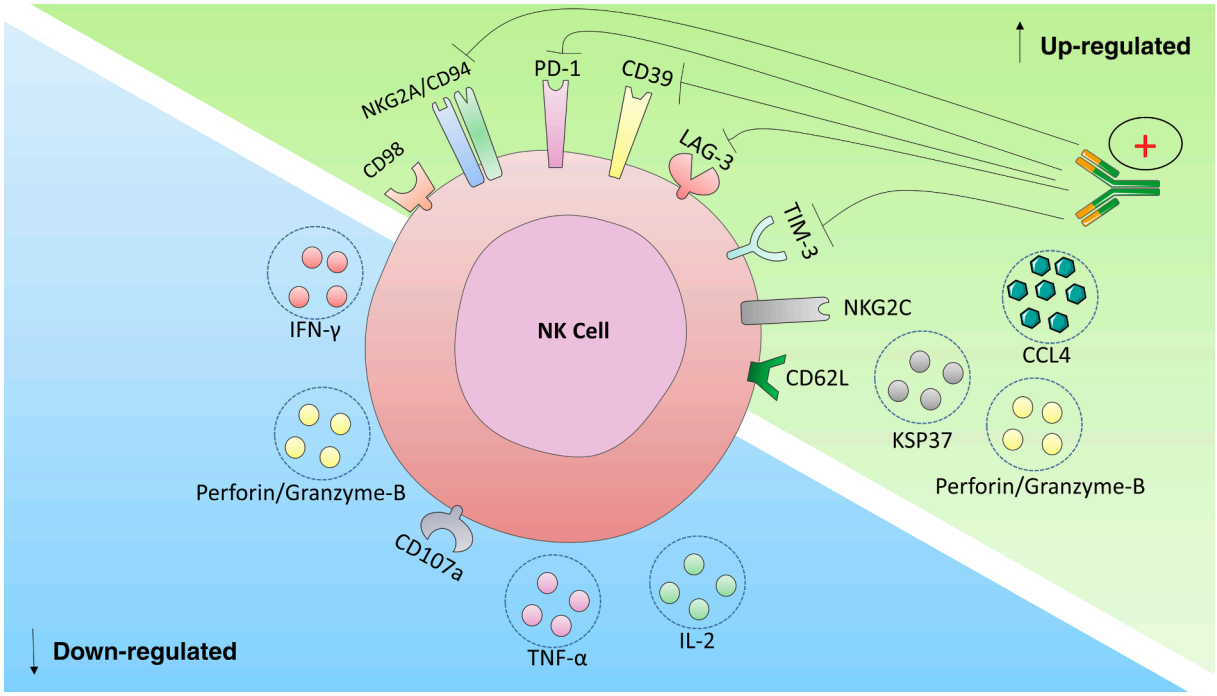

Fig. 4. Phenotype and markers alterations in NK cells in SARS-CoV-2 infection. During SARS-CoV-2 infection, the immune checkpoint molecules increase, and the NK cell becomes exhausted. Inhibition of these molecules by specific monoclonal antibodies leads to an increase in the ability of NK cell's cytotoxicity and more effective eradication of the virus.

blood and airway fluid and also circulates as a stand-alone protein. CD14 aids immune cells in recognizing infections as well as damaged or dying cells, alerting the immune system and triggering a response [143]. CD14 overamplifies the later stages of the immune response to SARS-CoV-2 infection in the lungs, potentially leading to a hyperactive inflammatory response and cytokine storm. A cytokine storm in COVID-19 patients may cause severe inflammation and tissue damage in the lungs, leading to respiratory failure and ARDS [143]. The mAb IC14 has the ability to attenuate the damaging inflammatory responses of immune system to SARS-CoV-2, thus reducing related tissue damage and improving clinical outcomes [143].

CCR5. Leronlimab (also known as PRO 140) is a humanized IgG4 mAb that binds the C-C chemokine receptor type 5 (CCR5). In COVID-19, disrupting the C-C chemokine ligand 5 (CCL5)-CCR5 axis with leronlimab may limit the pulmonary trafficking of pro-inflammatory leukocytes and decrease pathogenic immune activation. Two CTs are assessing the efficacy of leronlimab in patients with COVID-19 (NCT04901689 and NCT04347239).

IL-2. In COVID-19 patients, the number of Treg cells is reduced, which helps to explain why certain COVID-19 patients have significant inflammation and lung injury [144]. F5111.2, a human anti-IL-2 antibody, was recently developed to potentiate Treg cells through STAT5 phosphorylation and provides immunotherapy to treat autoimmune diseases and graft-versus-host disease (GVHD) [145]. From this point of view, using F5111.2 could alleviate COVID-19-induced hyper-inflammation and ARDS in the lungs. Further human clinical studies are needed to validate the efficacy of F5111.2. Webster et al. [146] used IL-2 combined with a specific IL-2 mAb to induce robust proliferation of Treg cells *in vivo*. In animal models of autoimmune and inflammatory disorders, this approach yielded encouraging outcomes. The therapeutic application of this approach in COVID-19 is still unidentified.

SARS-CoV-2 Spike Protein. Recently, CD147 has been introduced as a receptor for the SARS-CoV-2 entry into the host cells [147,148]. Therefore, inhibition of this receptor can interrupt the viral load in human cells. Meplazumab is a mAb directed against CD147. Significantly, the meplazumab improved clinical outcomes in COVID-19 patients [149]. *In vitro*, meplazumab inhibited virus invasion [148].

Bamlanivimab (LY-CoV555 or LY3819253) and etesevimab (LY-CoV016 or LY3832479), two neutralizing mAbs directed against spike protein of SARS-CoV-2, were identified from convalescent plasma collected from COVID-19 patients in the United States and China, respectively. Bamlanivimab and etesevimab improved clinical outcomes [150-154]. A study reported that bamlanivimab decreased SARS-CoV-2 viral proliferation in the upper and lower respiratory tract in a rhesus macaque model [155].

REGEN-COV (previously known as REGN-COV2) is an antibody cocktail consisting of casirivimab (REGN10933) and imdevimab (REGN10987), which binds to specific, non-overlapping epitopes on the SARS-CoV-2 spike protein RBD and prevents viral entrance [156,157]. REGEN-COV treatment is associated with improved clinical outcomes [158-160]. In humans and model animals, treatment with REGEN-COV reduces the development of SARS-CoV-2 escape variants and protects against current variants [161].

AZD7442 is a combination of two long-acting antibodies generated from B cells donated by convalescent patients following SARS-CoV-2 virus infection: tixagevimab (AZD8895) and cilgavimab (AZD1061). These antibodies bind to distinct sites on the SARS-CoV-2 spike protein. SARS-CoV-2 viral variants, particularly the Delta variant, are neutralized by AZD7442. AZD7442 reduced the risk of catching symptomatic COVID-19 by 77% [162].

Sotrovimab, also known as VIR-7831, is a mAb specific to the spike protein of SARS-CoV-2 and is used to prevent the virus from attaching to human cells and infecting them. Sotrovimab significantly decreased the progression of COVID-19 in individuals with mild to moderate disease [163].

Bebtelovimab (LY-CoV1404) is a recombinant human mAb that binds to the spike protein and neutralizes SARS-CoV-2. Bebtelovimab is likely to be active against a wide variety of SARS-CoV-2 variations, including the Omicron [164,165].

5. Cellular immunotherapies approaches

This section will delineate cellular immunotherapy-based approaches using NK cells, Treg cells, γδ T cells, mesenchymal stem cells (MSCs), and $CD4^+$ /$CD8^+$ T cells to treat COVID-19. Table 5 presents comprehensive data from cell therapy-related CTs and findings in COVID-19 treatment.

5.1. Natural killer Cell-Based therapy

Natural killer (NK) cells are a type of lymphocyte that is involved in innate immunity. These cells cooperate with the parts of the immune system to eradicate viruses and tumors. NK cells are the first cells that respond to virus-infected cells. These cells produce memory cells following exposure to the antigen [166]. Given the importance of NK cells in anti-virus defense, revival, amplification, NK cells may be effective in COVID-19 treatment. Table 5 provides NK cell-based immunotherapy-related CTs.

A growing body of scientific literature exists about the potential of NK cell therapy in COVID-19 [167]. It has been reported that NK cells have undergone functional exhaustion and reduction in COVID-19 patients. In addition, killer cell lectin-like receptor subfamily C member 1 (NKG2A) has been increased on NK cells [168,169] (Fig. 4). This heterodimeric receptor is a type of inhibitory receptor for MHC class I molecules. NKG2A recognizes the non-classical MHC class I molecule HLA-E in humans [170]. Another study has revealed an augment in the expression of the NKG2A, PD-1, and CD39 receptors on NK cells in COVID-19 patients [171]. Notably, the expression of molecules such as CD107a, IFN-γ, IL-2, granzyme-B, and TNF-α in transcription levels has decreased in COVID-19 patients (Fig. 4). Following CPT in COVID-19 patients, the numbers of NK cells and $NKG2A^+$ NK cells increased and decreased, respectively [168].

Another NK cell-based treatment approach is chimeric antigen receptor (CAR) NK cell therapy. First, this approach was used in cancer immunotherapy. Recently, evidence suggests the use of a CAR NK cell-based product in the treatment of COVID-19 (Fig. 5). GVHD and alloimmune/autoimmune toxicities do not occur when using NK cells. Therefore, this approach is a safe type of cellular therapy [172]. Recently, an ongoing CT is investigating the effect of NKG2D-ACE-2 CAR-NK cells secreting IL-15 superagonist and GM-CSF-neutralizing single-chain variable fragment (scFv) for therapy of COVID-19 (Table 5). NKG2D is an activating receptor expressed on NK cells, $CD8^+$ T cells, subclasses of $CD4^+$ T cells, and γδ T cells. NKG2D binding to its ligand on tumors or infected cells causes triggering an immune response [173]. IL-15 activates human NK cells [174]. Using an IL-15 superagonist is more valuable than natural IL-15 in circulating concentrations due to its prolonged half-life and more strongly triggering NK cells [175]. With this rationale, an IL-15 superagonist named sIL-15/IL-15Rα chimeric protein has been prepared in these CAR NK cells. Also, all CAR NK cells have been armored with the GM-CSF-neutralizing scFv transgene to prevent CRS and neurotoxicity. Sterner et al. [176] have indicated that GM-CSF inhibition gave rise to reduced CRS and neuroinflammation and promoted CAR T cell function.

Ma et al. [177,178] have developed S309-CAR-NK cells and CR3022-CAR-NK cells, which are CAR NK cells that express the S309 scFv domain and the scFv domain of CR3022, respectively. S309 is a neutralizing antibody for SARS-CoV and SARS-CoV-2 that targets a highly conserved area of the SARS-CoV-2 spike glycoprotein, while CR3022 can specifically bind to the RBD of SARS-CoV-2 and pseudotyped SARS-CoV-2 spike protein. *In vitro*, S309-CAR-NK cells and CR3022-CAR-NK cells could kill SARS-CoV-2 spike protein-expressing target cells and pseudo-SARS-CoV-2 infected target cells, respectively [177,178]. It seems that the effectiveness of using these CAR NK cells should be evaluated in CTs with a large sample size.

NK cells have reduced significantly in terms of number and count in COVID-19 patients [136,168,179,180]. However, the number of NK cells has increased in the severe and progressive form of COVID-19 [180]. Given this issue, a product named CYNK-001 will be infused in adults with COVID-19. CYNK-001 is an allogeneic off-the-shelf NK cell therapy enriched for $CD56^+/CD3^-$NK cells expanded from human placental $CD34^+$ cells (Table 5). Earlier, this approach was used in adults with acute myeloid leukemia (AML) (NCT04310592).

5.2. Regulatory T cell-based therapy

Treg cells can prevent inflammation-induced tissue damage correlated with acute infection [181]. The usefulness of Treg cells in the improvement of acute lung injury has been proved [182].

Treg cells have been reduced in patients with severe COVID-19 [144], which is partly the reason for delayed lung repair and ARDS [183]. The first treatment report with Treg cells in two COVID-19 patients suggests a relationship between recovery and Treg cell infusion [184]. Table 5 provides Treg cell-based immunotherapy-related CTs.

Considering what was mentioned, there is a rational consensus on adoptive cell therapy with Treg cell-based products in COVID-19-associated ARDS management. It has been suggested that a combination of Treg cell-based therapies and mAbs would benefit COVID-19 patients.

5.3. γδ T cell-Based therapy

Higher anti–SARS–CoV-1 IgG titers were connected to the development of the $V\gamma9V\delta2^+$ T cell population. *In vitro* studies further revealed that activated $V\gamma9V\delta2^+$ T cells have an anti-SARS-CoV-1 activity reliant on IFN and may directly kill SARS-CoV-1–infected target cells. These results support the theory that $V\gamma9V\delta2^+$ T cells protect people against SARS infection [185,186].

Lei et al. [187] analyzed the phenotype of γδ T cells from the blood samples of 18 healthy donors and 38 COVID-19 patients. Findings showed that after SARS-CoV-2 infection, the proportion of γδ T cells was reduced compared to control, while CD25 expression increased in response to the infection. Also, CD4 expression was increased in γδ T cells, while CD69 and PD-1 were not expressed at a higher level.

The frequency and activation status of Vγ9Vδ2 T cells in 24 hospitalized patients with PCR-proven SARS-CoV-2 infection were investigated in research [188]. This study demonstrated that ten days after the onset of clinical symptoms, the proportion of Vγ9Vδ2 T cells is substantially lower than in matched healthy controls. Further analysis indicated that the number of Vγ9Vδ2 T cells in the blood was returned to normal in the patients who survived, but the number of Vγ9Vδ2 T cells in the blood was significantly lower in the six deceased patients, compared to healthy controls.

In the context of the data presented herein, it is suggested that using allogenic γδ T cells could be a promising and feasible complementary candidate for COVID-19 treatment. This suggestion should be investigated in more extensive CTs. Table 5 provides γδ T cell-based immunotherapy-related CT.

5.4. Mesenchymal stem cell therapy

An anti-inflammatory and immunosuppressive role for MSCs was proved by Meisel et al. [189] when they demonstrated that MSCs derived from BM suppress allogeneic T-cell responses via indoleamine 2,3-dioxygenase. Innumerable studies have indicated that these cells secrete anti-inflammatory molecules such as IL-10, TGF-β, and Prostaglandin E2 (PGE2) [190-192]. In addition, Xu et al. [193] have indicated that MSCs attenuated lung injury, improved the survival rate, and reduced the levels of inflammatory cytokines in the murine model of lipopolysaccharide (LPS)-induced acute lung injury. Another inhibitory role of MSCs cells is Treg cell induction [194-196]. Regarding the data presented herein, there is a rationale to modulate the severity of COVID-19 using these cells. Table 5 provides extensive evidence from MSC

Table 5
Adoptive cell therapy-related clinical trials in COVID-19.

Type of Intervention	Drug/Product/Biological Agent	Participants (N)	NCT identifier or Registration Number	Phase	Results	References
NK cell Therapy	NK Cells	30	NCT04280224	I	NR	
	NK Cells	24	NCT04634370	I	NR	
	CYNK-001 (an allogeneic off the shelf cell therapy enriched for $CD56^{+}/CD3^{-}$ NK cells expanded from human placental $CD34^{+}$ cells)	86	NCT04365101	I/II	NR	
	The CAR-NK cells expressing IL-15 superagonist, NKG2D, ACE-2, and GM-CSF-neutralizing scFv.	90	NCT04324996	I/II	NR	
	Umbilical cord blood CIK and NK cells	90	ChiCTR2000030329	0	NR	
	Cord blood NK cells combined with cord blood MSCs	60	ChiCTR2000029817	0	NR	
	FT516	5	NCT04363346	I	NR	
	DVX201	18	NCT04900454	I	NR	
	KDS-1000 (Off-the-shelf NK Cells)	54	NCT04797975	I/II	NR	
	Allogeneic NK Cells	14	IRCT20200621047859N2	I	NR	
Regulatory T cell Therapy	CK0802	45	NCT04468971	I	NR	
	RAPA-501-ALLO Cells	88	NCT04482699	I	NR	
γδ T cell Therapy	TCB008 (Expanded Gamma/Delta T cell Lymphocytes)	12	NCT04834128	II	NR	
T lymphocyte Therapy	Allogeneic SARS-CoV2-Specific T Cells	58	NCT04401410	I	NR	
	CTL	24	NCT04765449	I	NR	
	SARS-CoV-2 Antigen-Specific CTL	16	NCT04742595	I	NR	
	SARS-CoV-2 Specific T Cells	8	NCT04351659	–	NR	
	COVID-19 Specific T Cell-derived exosomes	60	NCT04389385	I	NR	
MSC Therapy	AT-MSC	20	NCT04611256	I	NR	
	PrimePro	40	NCT04573270	I	NR	
	hUC-MSCs (MPC)	70	NCT04565665	I/II	NR	
	hCT-MSCs	30	NCT04399889	I/II	NR	
	MSCs	9	NCT04466098	II	NR	
	Longeveron MSCs	70	NCT04629105	I	NR	
	BM-MSCs	45	NCT04397796	I	NR	
	ULSC	60	NCT04494386	I/II	NR	
	Remestemcel-L (BM-MSCs)	223	NCT04371393	III	NR	
	Descartes 30 (MSCs RNA-engineered to secrete a combination of DNases)	30	NCT04524962	I/II	NR	
	PLX-PAD (Mesenchymal-like adherent stromal cells)	140	NCT04389450	II	NR	
	Allogenic AT-MSC	100	NCT04348435	II	NR	
	Allogenic AT-MSC	100	NCT04362189	II	NR	
	Allogenic AT-MSC	56	NCT04349631	II	NR	
	Allogenic MSCs	20	NCT04615429	II	NR	
	hUC-MSCs	18	ChiCTR2000031494	I	CRP ↓, IL-6 ↓, Time for the Lymphocyte count returning ↓, Lung Inflammation ↓, time to clinical improvement ↓, Clinical symptoms ↓, shortness of breath↓, oxygen saturation↑	Shu et al. [214]
	hUC-MSCs	16	NCT04269525	II	$CD4^{+}$ T cells↑, $CD8^{+}$ T cells↑, NK cells↑, Pulmonary involvement↓, CRP↓, procalcitonin↓, oxygenation index↑	Feng et al. [215]
	hUC-MSCs	31	–	–	oxygenation index↑, CRP↓, procalcitonin↓, IL-6↓, D-dimer↓, Lymphocyte count↑	Guo et al. [216]
	hUC-MSCs	18	NCT04252118	I	oxygenation index↑, lung lesions↓, Inflammatory cytokines (IL-6, IFN-γ, TNF-α, MCP-1, IP-10, IL-22, IL-1RA, IL-18, IL-8) ↓	Meng et al. [217]
	hUC-MSCs	100	NCT04288102	II	lung lesions↓, walking distance in a 6-minute walk test↑, no significant difference in the lymphocyte counts	Shi et al. [218]
	hUC-MSCs	24	NCT04355728	I/II	pro-inflammatory cytokines↓, patient survival↑, time to recovery↓	Lanzoni et al. [219]
	Allogenic MB-MSCs	2	ChiCTR2000029606	0	IL-6↓, CRP↓, $CD4^{+}$ lymphocytes↑, Oxygen saturation↑, partial pressure of oxygen↑, the fraction of inspired O2↓, bilateral lung exudate lesions↓	Tang et al. [220]
	$ACE\text{-}2^{-}$ MSCs	10	ChiCTR2000029990	I/II	Pulmonary function↑, Clinical symptoms↓, Lymphocyte count↑, CRP↓, TNF-α↓, IL-10↑,	Leng et al. [221]

(*continued on next page*)

Table 5 (*continued*)

Type of Intervention	Drug/Product/Biological Agent	Participants (N)	NCT identifier or Registration Number	Phase	Results	References
					overactivated cytokine-secreting immune cells↓, regulatory DC cells↑	
	AT-MSC	13	NCT04348461/EudraCT: 2020–001266-11	II	clinical improvement↑, inflammatory parameters↓, Lymphocyte count↑	Guijo et al. [222]
	ExoFlo™ or DB-001 (Exosomes Derived from BM-MSCs)	120	NCT04493242	II	clinical status↑, Oxygene pressure ↑, Neutrophils and lymphocytes count↑, CRP↓, ferritin↓, D-dimer↓	Sengupta et al. [223]

Abbreviations: NK: Natural killer; CTL: Cytotoxic T lymphocyte; MSCs: Mesenchymal stem cells; UCB: Umbilical cord blood; CIK: Cytokine-induced killer; GM-CSF: Granulocyte-Macrophage colony-stimulating factor; CB: Cord blood; scFV: Single-chain variable fragment; CAR: Chimeric antigen receptor; ACE-2: Angiotensin-converting enzyme-2; NR: Not released; hUC-MSCs: Human umbilical cord-derived mesenchymal stem cells; AT-MSC: Adipose tissue-derived MSCs; MB-MSCs: Menstrual blood-MSCs; BM-MSCs: Bone Marrow-MSCs; CRP: C-reactive protein; hCT-MSCs: Human cord tissue-MSCs; MPC: Mesenchymal progenitor cell; ULSC: Umbilical cord lining stem cells; ↑: Increased or Improved; ↓: Decreased.

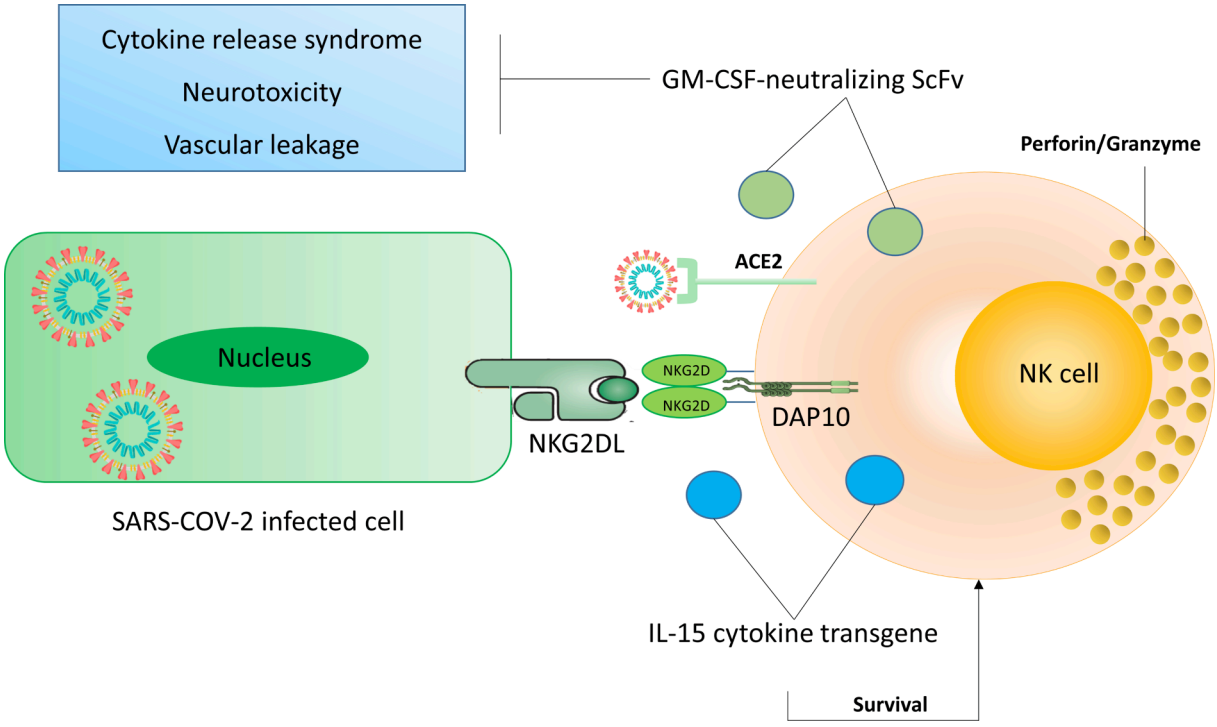

Fig. 5. NKG2D-ACE-2 CAR-NK cells secreting IL-15 superagonist and GM-CSF-neutralizing single-chain variable fragment for Therapy of COVID-19. The universal, off-the-shelf IL15 superagonist- and GM-CSF neutralizing scFv-secreting NKG2D-ACE2 CAR-NK generated from cord blood has been constructed. Using ACE2 and NKG2D to target the S protein of SARS-CoV-2 and NKG2DL on the surface of infected cells, as well as the robust synergistic effect of IL15 superagonist in order to NK cells survival and prevention of cytokine release syndrome (CRS) and neurotoxicity through GM-CSF neutralizing scFv, can remove the SARS-CoV-2 virus particles and their infected cells, providing a safe and effective cell therapy for COVID-infected patients.

therapy in COVID-19 treatment.

5.5. $CD4^+$ /$CD8^+$ T cell therapy

SARS-CoV-2-directed T-cell immunotherapy targeting structural proteins is feasible for preventing or early infection treatment in immunocompromised patients with blood disorders or after BM transplantation. This approach would allow for antiviral control while also mitigating uncontrolled inflammation [197]. Bange et al. [198] have suggested that when humoral immunity is deficient, $CD8^+$ T cells may aid in the recovery from COVID-19 infection. Emerging evidence has demonstrated the role of $CD4^+$/$CD8^+$ T cells in the control of SARS-CoV-2 in both non-hospitalized and hospitalized cases of COVID-19 [199]. Table 5 provides conventional T cell-based immunotherapy-related CTs.

6. Conclusion

To sum up, current research has comprehensively presented evidence-based approaches and CTs regarding the effects of passive immunotherapy strategies in ameliorating and treating COVID-19 patients. However, the results of the approaches in different human CTs are controversial. Given the challenges of global vaccination against COVID-19, particularly vaccine efficacy limitations against emerging SARS-CoV-2 variants, the utilization and development of these approaches are urgently needed.

Exacerbated inflammatory cascades are a hallmark of the immunopathology of COVID-19. Therefore, passive immunotherapy targeting inflammatory pathways would be beneficial in COVID-19 patients. From this point of view, the inhibition of several inflammatory cytokines concomitantly has a tremendously positive effect on patient recovery. It should be noted that this approach should be utilized in the disease's inflammatory state. In addition, codifying a therapeutic protocol for

passive immunotherapies, including the appropriate treatment window and the optimal dose, is an essential issue that should be addressed via further CTs.

Further empirical investigations are needed to identify novel cellular receptors involving COVID-19 immunopathogenesis. These investigations shed light on our understanding of immunopathologic processes and will lead to the development of innovative passive immunotherapies for COVID-19. In addition, we propose using combined passive immunotherapies that concomitantly use mAbs-based products and immune cell therapy to synergize the intervention. More CTs with larger samples are needed to validate this therapeutic option. Finally, due to the mAbs-related redundancy effects, it is proposed that approaches based on inhibiting several inflammatory cytokines be used.

Author contributions

PF, NR, MA, and AAD conceptualized the study. PF, SD, ARS, SVF, and MG were contributed in drafting the manuscript. MA, and AAD supervised and revised the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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