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 article

The immune system as a target for therapy of SARS-CoV-2: A systematic review of the current immunotherapies for COVID-19

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ABSTRACT

Aims: The immune response is essential for the control and resolution of viral infections. Following the outbreak of novel coronavirus disease (COVID-19), several immunotherapies were applied to modulate the immune responses of the affected patients. In this review, we aimed to describe the role of the immune system in response to COVID-19. We also provide a systematic review to collate and describe all published reports of the using immunotherapies, including convalescent plasma therapy, monoclonal antibodies, cytokine therapy, mesenchymal stem cell therapy, and intravenous immunoglobulin and their important outcomes in COVID-19 patients.
Material and methods: A thorough search strategy was applied to identify published research trials in PubMed, Scopus, Medline, and EMBASE from Dec 1, 2019, to May 4, 2020, for studies reporting clinical outcomes of COVID-19 patients treated with immunotherapies along with other standard cares.
Key findings: From an initial screen of 80 identified studies, 24 studies provided clinical outcome data on the use of immunotherapies for the treatment of COVID-19 patients, including convalescent plasma therapy (33 patients), monoclonal antibodies (55 patients), interferon (31 patients), mesenchymal stem cell therapy (8 patient), and immunoglobulin (63 patients). Except for nine severe patients who died after treatment, most patients were recovered from COVID-19 with improved clinical symptoms and laboratory assessment.
Significance: Based on the available evidence, it seems that treatment with immunotherapy along with other standard cares could be an effective and safe approach to modulate the immune system and improvement of clinical outcomes.

1. Introduction

The newly emerged SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), is a positive-sense single-stranded RNA (+ssRNA) virus that causes COVID-19 (coronavirus disease 2019), which has been getting global concern since December 2019 [1–4]. Coronaviruses belong to the subfamily *Coronavirinae*, in the family *Coronaviridae* of the order *Nidovirales*. Like the other strains of coronavirus, SARS-CoV-2 has phospholipid bilayers envelop and the genome codes almost five types of structural proteins [5–8] (Fig. 1). The typical clinical manifestations of COVID-19 include a non-productive cough, fever, and dyspnea, while acute respiratory distress syndrome (ARDS) is the leading cause of death in COVID-19 [9,10]. Unfortunately, the outbreak is rapidly spreading worldwide. In the absence of effective treatments or vaccines to prevent or treat this infection, its rapid dissemination may affect public healthcare systems and severe economic and social distress worldwide [11,12]. Up to now, several immunotherapy strategies have been used to treat or prevent virus infection in patients with COVID-19 [13]. These approaches, including convalescent plasma therapy, monoclonal antibodies against IL-6 receptor and complement protein C5, cytokine therapy, mesenchymal stem cell therapy, and intravenous immunoglobulin, have been applied with varied efficiency in COVID-19 [14–17]. Interaction of the virus with the immune system mediators leads to triggering an immune response that may determine the outcome of the viral infection [18]. Controlling viral replication in the early phase of the disease could be applied through virus recognition by Pattern recognition receptors (PRRs), including toll-like receptor (TLR), NOD-like receptor (NLR), RIG-I-like receptor (RLR), melanoma

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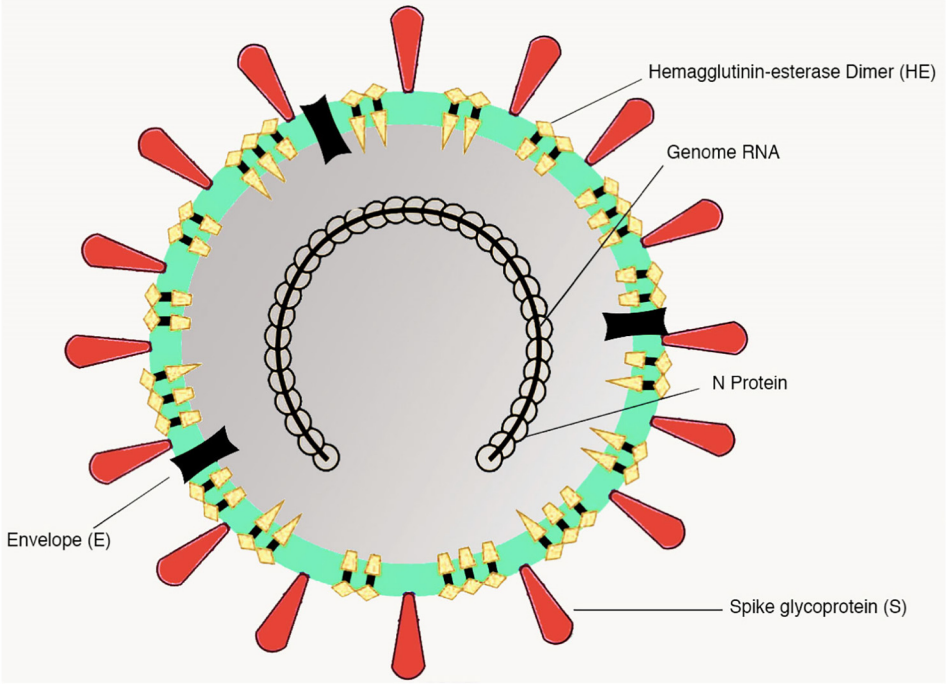

Fig. 1. Structural proteins of SARS-CoV-2: Sprotein (spike glycoprotein trimmer), M protein (a type III transmembrane glycoprotein), E protein (located among the S proteins in the virus envelope), N proteins (nucleocapsid), HE (hemagglutinin-esterase) dimer (exists in some CoVs).

differentiation-associated gene 5 (MDA5), C-type lectin-like receptors (CLR), complement proteins, and the other unclassified receptors in the cytoplasm, like Stimulator of interferon genes (STING), DAI, and other innate immune mediators as a part of the innate immune system that may limit SARS-CoV-2 spread within the host [19–23].

According to the recent findings, SARS-CoV-2 replication starts when the S (Spike) proteins attach to the membrane of the lung cells via angiotensin-converting enzyme 2 (ACE2) receptor, by the clathrin-dependent and -independent endocytosis, and release their RNA that senses by endosomal TLRs (TLR3, TLR7, TLR8, and TLR9), RIG-I, MDA5 and cGAS (nucleotidyltransferase cyclic GMP-AMP synthase) in the cytoplasm [24–26]. Interactions between SARS-CoV-2 and alveolar cells, trigger downstream signaling pathway via TIR-domain-containing adapter-inducing interferon-β (TRIF), and STING adaptor molecules lead to triggering MyD88 adaptor molecule, following that activation of the NF-κB and interferon regulatory factor 3 (IRF3) [27–29]. The result of this complex pathway is the production of IFN-α and -β and varied set of pro-inflammatory mediators. According to the recently published researches, increased levels of some plasma mediators, including IL-1, IL-2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, TNF-α, MIP-1α, IP-10, IFN-γ, GCSF, MCP-1, MCSF, and hepatocyte growth factor (HGF) lead to the lung injury in some patients with COVID-19 [30–33]. The viral invasion occurred, when the virus particles fuse to the respiratory mucosal tissue and infect other cells, resulting in a chain of the immune system responses and cytokine storm, which may be associated with the severe condition of COVID-19 patients [34–36]. In most studies, it was obviously proved that severe pneumonia and consequently respiratory failure and death are due to acute inflammation rather than a direct damaging effect of the virus itself [37,38].

While SARS-CoV-2 attaches and enters the alveolar cells, its antigen will be presented to virus-specific cytotoxic T lymphocytes (CTLs) via major histocompatibility complex (MHC) class I (and less via MHC II) existing on the surface of antigen presentation cells (APC). Antigen presentation subsequently stimulates the cellular and humoral immunity. According to the researches, multiple HLA alleles polymorphisms such as HLA-B*0703, HLA-B*4601, HLA-Cw*0801, HLA-DR B1*1202 have shown a correlation to the susceptibility of SARS-CoV-2 [39,40], while polymorphisms in the HLA-A*0201, HLA-DR0301, and HLA-Cw1502 are related to the protection from SARS infection [41].

According to Wang et al., different subsets of lymphocyte, including CD4+ and CD8+T lymphocytes, B lymphocytes as well as natural killer (NK) cells are decreased in COVID-19 patients, and this reduction is more significant in the severe cases compared to moderate ones. Peripheral lymphocyte subset alteration is associated with clinical outcome and treatment efficacy of COVID-19 [42].; the number of CD8+ T cells and CD4+/CD8+ ratio showed a significant association with inflammatory status in COVID-19; CD4+/CD8+ ratio was indicated as independent predictors of poor efficacy [41]. While the virus enters the cells, its antigen will be presented to the APC. According to Li et al., the number of TCD4+ and CD8+ in the peripheral blood of COVID-19 patients is significantly reduced. In contrast, they are excessively active, as evidenced by high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions [43].

According to the various case studies, those patients who have been infected with SARS-CoV-2 developed a protective antibody, but it is not apparent how long this protection lasts. The quantity and quality of the antibody response may determine the fate of a viral infection [44]. High-affinity neutralizing antibodies can recognize particular viral epitopes without additional mediators via Fc regions. It seems that similar to SARS-CoV infection, in the case of SARS-CoV-2, viral fusing via ACE2 to the lung epithelia is blocked, when neutralizing antibodies recognize the particular domains on the S protein [45,46]. Moreover, these antibodies can also interact with the other immune cells, including NK cells, phagocytes, and complement systems, as a bridge between acquired immune responses and innate immune responses. After recognizing viral antigens via specific antibodies, phosphorylation of ITAMs in the cytoplasmic tail segments of the Igα and Igβ in B cells occurs by SRC kinase family, lead to trigger downstream signaling to up-regulate pro-inflammatory cytokines and down-regulate anti-inflammatory cytokines [47,48]. Viral components in the endosomes recognized by multiple endosomal TLRs, including TLR3, TLR7, and TLR8, resulting in immunopathology. In this systematic review, we provide an update on the treatment of the COVID-19 patients with focused on the immunotherapies. Immunology knowledge along with

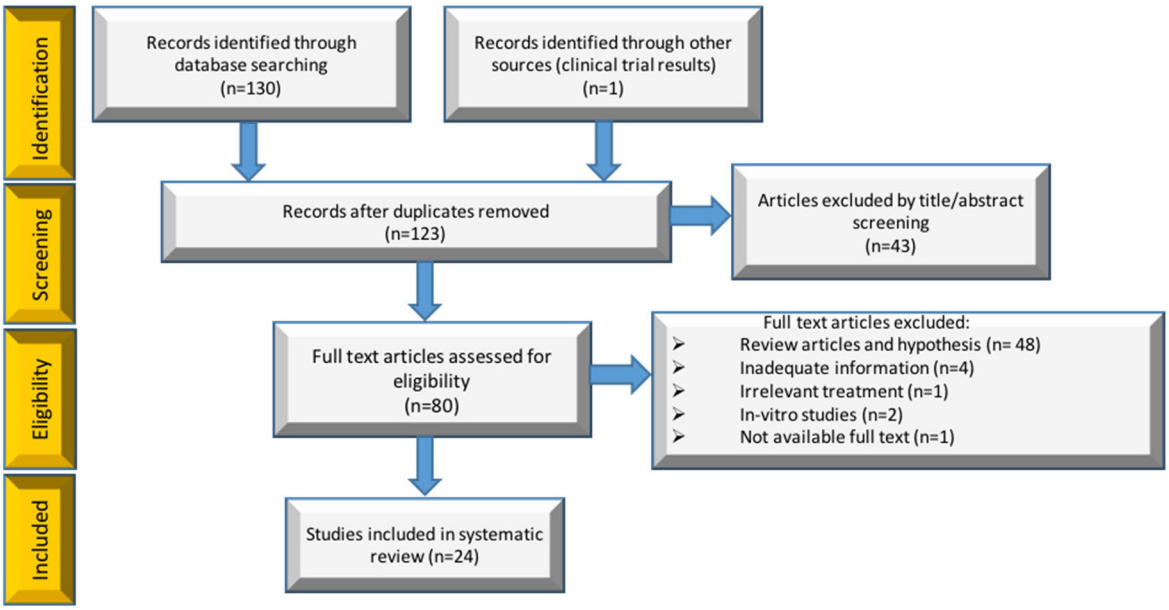

Fig. 2. PRISMA flowchart.

advanced vaccine technology is expected to help us find more effective ways to cure the disease.

2. Methods

This systematic review was conducted based on the Preferred Reporting Items for systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist (Supplementary data, Table 1) [49].

2.1. Search strategy

To identify published research trials in PubMed, Scopus, Medline, and EMBASE from Dec 1, 2019, to May 4, 2020, comprehensive search strategies were performed (Fig. 2). The language was not restricted. We also searched the Clinical Trials.gov, clinicaltrialsregister.eu, and chictr.org for registered ongoing clinical trials. The search keywords are available in Supplementary data, Table 2.

2.2. Study eligibility criteria

Two authors (M.A.H. and S.M.) screened the titles and abstracts from the search results, using the predefined inclusion criteria and excluded duplicate publications. The authors recorded the reasons for excluding studies. Disagreement was resolved through discussion with two more authors (R.N. and M.M.H.R.).

To be eligible, studies had to meet the following criteria:

1) The studies included COVID-19 patients with no restrictions on patient age, sex, and ethnicity.
2) Enrolled patients in the intervention group must have treated with the immunotherapy agents alone or in combination with other drugs, including anti-viral agents, corticosteroids, and antibiotics.

Meanwhile, trials were excluded directly, if:

1) The review articles, systematic reviews, and hypothesis articles.
2) The articles about other respiratory infected diseases such as SARS and MERS.
3) The patients were received other therapies except for immunotherapies, as mentioned above.

2.3. Study quality assessment

Two authors (S.M. and M.M.H.R.) independently evaluated the quality of each publication according to the PRISMA checklist.

2.4. Data extraction

Three authors (M.A.H., S.M., and M.M.H.R.) reviewed the full texts of potentially relevant articles for eligibility according to the inclusion criteria. Then excluded ineligible studies, and documenting reasons for exclusion. The authors extracted data from all included articles to Tables 1 and 2.

3. Results

From an initial screen of 80 identified studies, 24 studies provided clinical outcome data on the use of immunotherapies for the treatment of COVID-19 patients, including convalescent plasma therapy, monoclonal antibodies, interferon, mesenchymal stem cell therapy, and immunoglobulin. Totally, 157 patients met our inclusion criteria that were included in this study. Characteristics of included studies and patient outcomes are summarized in Tables 1 and 2.

3.1. Convalescent plasma therapy

Of 24 studies screened, 6 studies with a total of 33 patients were identified that provided clinical outcomes data on the use of convalescent plasma (CP) therapy for the treatment of COVID-19 patients. These studies include two case reports [50,51], one descriptive study [52], one preliminary uncontrolled case series [53], one pilot study [54], and one retrospective study [55].

Except for one retrospective study that out of 6 patients with COVID-19, only one patient recovered after CP therapy, five studies have shown optimistic results in using CP therapy to treat severe COVID-19 patients.

In one pilot study, one dose of CP collected from recently recovered COVID-19 patients was administered to 10 sever COVID-19 patients. In this trial, the neutralizing antibody titers greater than 1:640 were transfused to the patients in addition to anti-viral drugs and corticosteroid therapy. The outcome was the amelioration of clinical symptoms, pulmonary lesions, pulmonary function, improved lymphocytopenia,

Table 1
The extracted data from 24 included studies.

#	Author	Type of immunotherapy	Treatment by	Number of treated patients	Outcomes	Fatality	Ref
1	Ahn JY et al	Plasma therapy	CP	2	Subsiding the fever, decrease oxygen demand, decreased level of CRP and IL-6 to normal range, chest X-ray improvement, negative SARS-CoV-2 RNA	None	[50]
2	Zhang B et al	Plasma therapy	CP	4	Decreased viral load, increased anti-SARS-COV-2 titer in serum, chest X-ray improvement	None	[51]
3	Mingxiang et al.	Plasma therapy	CP	6	Improvement of clinical symptoms, chest X-ray improvement, increased anti-SARS-COV-2 titer in serum	None	[52]
4	Shen C et al	Plasma therapy	CP	5	Changes of body temperature, improvement Sequential Organ Failure Assessment (SOFA) score, decrease viral load, increased serum antibody titer, decreased CRP level and procalcitonin to the normal range	None	[53]
5	Duan K et al	Plasma therapy	CP	10	Improvement of clinical symptoms, decreased pulmonary lesions, improved pulmonary function, improved lymphocytopenia, decreased SARS-CoV-2 RNA to undetectable level	None	[54]
6	Zeng QL et al	Plasma therapy	CP	6	Decreased viral load, decreased SARS-CoV-2 RNA to undetectable level	5 patients	[55]
7	Xu X et al	Monoclonal antibody	TCZ	21	Subsiding the fever, decreased level of CRP to normal range (in 16 patients), decreased oxygen demand (in 15 patients), chest X-ray improvement (in 19 patients), little improvement in chest X-ray (in 3 patients)	None	[57]
8	Giambenedetto SD et al	Monoclonal antibody	TCZ	3	Subsiding the fever, PaO2/FiO2 ratio improvement, decreased level of CRP to normal range	None	[58]
9	Diurno F et al	Monoclonal antibody	Eculizumab	4	Improvement of clinical symptoms and laboratory tests, improvement in chest X-ray	None	[59]
10	Fontana F et al	Monoclonal antibody	TCZ, IVIg	1	Subsiding the fever, decreased oxygen demand, *Pseudomonas aeruginosa* infection in urine culture	None	[60]
11	Michot JM	Monoclonal antibody	TCZ	1	Improvement of clinical symptoms, subsiding the fever, decreased oxygen consumption, chest X-ray improvement, decreased level of CRP to normal range	None	[61]
12	Zhang X et al	Monoclonal antibody	TCZ	1	Disappeared chest tightness, decreased level of IL-6, chest X-ray improvement, decreased the SARS-CoV-2 RNA to undetectable level	None	[62]
13	Mihai C et al	Monoclonal antibody	TCZ	1	Control of arthritis, improvement of musculoskeletal and respiratory symptoms, lung function and chest X-ray improvement The patients developed cough, headache and general malaise 4 weeks after the last TCZ transfusion	None	[63]
14	Morrison AR et al	Monoclonal antibody	TCZ	2	Subsiding the fever, decreased level of inflammatory markers, hypertriglyceridemia, acute pancreatitis (elevated level of lipase and amylase) in one patient with 65 years old age.	None	[64]
15	Luna GD et al	Monoclonal antibody	TCZ	1	Improvement of clinical symptoms	None	[65]
16	Cellina Met al	Monoclonal antibody	TCZ	1	Improvement of clinical symptoms and laboratory tests	None	[66]
17	Hammami MB et al	Monoclonal antibody	TCZ	1	Subsiding the fever, chest pain and abdominal pain improvement	None	[67]
18	Odievre MH et al	Monoclonal antibody	TCZ	1	Improvement of clinical symptoms, decreased oxygen demand, improvement in chest X-ray	None	[68]
19	Radbel J et al	Monoclonal antibody	TCZ	2	Worsened the clinical symptoms, myocarditis in one patient, cytopenias, hypertriglyceridemia, elevated ferritin and lactate dehydrogenase, hypofibrinogenemia, decreased level of CRP	1 patient	[69]
20	Luo P et al	Monoclonal antibody	TCZ	15	Death 3/15 Clinical stabilization 9/15 Clinical improvement 1/15 Disease aggravation 2/15	3 patients	[70]
21	Liang B et al	Cell therapy	hUCMSC IVIg	1	The pneumonia greatly relieved, Improvement of clinical symptoms and laboratory tests, the throat swabs tests reported negative	None	[71]
22	Leng Z et al	Cell therapy	MSC	7	Increased the peripheral lymphocytes, decreased level of CRP The overactivated cytokine-secreting immune cells including CXCR3 + CD4 + T cells, CXCR3 + CD8 + T cells, and CXCR3 + NK cells disappeared in 3–6 days Increased CD14 + CD11c + CD11b regulatory DC cell population, decreased level of TNF-α, increased level of IL-10	None	[74]
23	Xie Y et al	Immunoglobulin G	IVIg, Thymosin	58	Outcomes in treated patients with IVIg within 48 h ($\leq$48 h) after admission: reduced the 28-day mortality rate, shorter length of stay in the hospital and/or in ICU, reduced ventilator use. Outcomes in treated patients with IVIg $>$ 48 h after admission: high mortality rate in 28-day follow up, longer length of stay in the hospital and/or in ICU, increased ventilator use *23 of the 58 patients died within 28 days of admission	None	[75]
24	Cao W et al	Immunoglobulin G	IVIg	3	Improvement of clinical symptoms, recovered lymphocyte count, decreased level of ESR and CRP to normal range, chest X-ray improvement	None	[76]

CP: convalescent plasma therapy; TCZ: Tocilizumab; hUCMSC: human umbilical cord mesenchymal stem cell.

Table 2
Demographic and clinical data of included studies.

N	Gender	Age (y)	Comorbidities	IAI (days)	CPI	TI	Dose/times of transfusion	OT	Ref
2	Male	71	None	10	Fever, cough, pneumonia, acute respiratory distress syndrome	CP	Two doses of 250 mL of CP (500 mL in total) at 12 h interval	Lopinavir/ritonavir, methylprednisolone	[50]
	Female	67	HTN	6	Fever, myalgia, pneumonia, acute respiratory distress syndrome	CP	Two doses of 250 mL of CP (500 mL in total) at 12 h interval	Lopinavir/ritonavir	
4	Female	69	None	17	Fever	CP	900 mL of CP in three doses	Arbidol, lopinavir/ritonavir, oseltamivir, IFN-alpha-2b	[51]
	Male	55	COPD	11	Nausea, poor appetite, cough	CP	900 mL of CP in three doses	Arbidol, lopinavir/ritonavir, IFN-alpha-2b	
	Male	73	HTN, chronic renal failure	14	Cough	CP	900 mL of CP in three doses	Arbidol, lopinavir/ritonavir, oseltamivir, IFN-alpha-2b, ribavirin	
	Female	31	None	19	Pharyngalgia, fever, dyspnea	CP	900 mL of CP in three doses	Lopinavir/ritonavir, ribavirin	
6	Male	69	None	13	Fever, myalgia, dyspnea	CP	Three doses of 200 mL of CP (600 mL in total)	Arbidol, corticosteroids	[52]
	Female	75	None	28	Fatigue, dyspnea	CP	Two doses of 200 mL of CP (400 mL in total)	Arbidol, corticosteroids	
	Male	56	Bronchitis	31	Fever, cough	CP	Three doses of 200 mL of CP (600 mL in total)	Arbidol, corticosteroids	
	Female	63	Sjogren syndrome	27	Fever, cough, fatigue, dyspnea	CP	One dose of 200 mL of CP	Arbidol	
	Female	28	None	8	None	CP	One dose of 200 mL of CP	Arbidol, corticosteroids	
	Male	57	None	6	Fever, cough, myalgia, dyspnea	CP	One dose of 200 mL of CP	Arbidol, corticosteroids	
5	Male	70	None	22	Bacterial pneumonia; ARDS; multiple organ dysfunction syndrome	CP	Two doses of 200 to 250 mL (400 mL in total) of CP on the same day	Lopinavir/ritonavir, IFN-alpha-1b, favipiravir, methylprednisolone	[53]
	Male	60	HTN, MI	10	Bacterial pneumonia; fungal pneumonia; ARDS; myocardial damage	CP	Two doses of 200 to 250 mL (400 mL in total) of CP on the same day	Lopinavir/ritonavir, arbidol; darunavir, methylprednisolone	
	Female	50	None	20	ARDS	CP	Two doses of 200 to 250 mL (400 mL in total) of CP on the same day	Lopinavir/ritonavir, IFN-alpha-1b, methylprednisolone	
	Female	30	None	19	ARDS	CP	Two doses of 200 to 250 mL (400 mL in total) of CP on the same day	IFN-alpha-1b, favipiravir, methylprednisolone	
	Male	60	None	20	ARDS	CP	Two doses of 200 to 250 mL (400 mL in total) of CP on the same day	Lopinavir/ritonavir, IFN-alpha-1b, methylprednisolone	
10	Male	46	HTN	11	Fever, cough, sputum production, shortness of breath, chest pain	CP	One dose of 200 mL of CP	Arbidol, ribavirin	[54]
	Female	34	None	11	Cough, shortness of breath, chest pain, nausea and vomiting	CP	One dose of 200 mL of CP	Arbidol	
	Male	42	HTN	19	Fever, cough, sputum production, shortness of breath, sore throat, diarrhea	CP	One dose of 200 mL of CP	Arbidol, methylprednisolone	
	Female	55	None	19	Fever, cough, sputum production, shortness of breath	CP	One dose of 200 mL of CP	Ribavirin, methylprednisolone	
	Male	57	None	14	Fever, shortness of breath	CP	One dose of 200 mL of CP	Arbidol, remdesivir, IFN-alpha, methylprednisolone	
	Female	78	None	17	Fever, cough, sputum production, shortness of breath, muscle ache	CP	One dose of 200 mL of CP	Arbidol, methylprednisolone	
	Male	56	None	16	Fever, cough, sputum production, arthralgia	CP	One dose of 200 mL of CP	Arbidol, methylprednisolone	
	Male	67	CD	20	Fever, cough, headache, diarrhea, vomiting	CP	One dose of 200 mL of CP	Arbidol, ribavirin	
	Female	49	None	10	Cough, shortness of breath	CP	One dose of 200 mL of CP	Arbidol, oseltamivir, Peramivir	
	Male	50	HTN	20	Shortness of breath	CP	One dose of 200 mL of CP	Arbidol, IFN-alpha, methylprednisolone	

(*continued on next page*)

Table 2 (*continued*)

N	Gender	Age (y)	Comorbidities		IAI (days)	CPI		TI	Dose/times of transfusion	OT	Ref
6	Male: 5/6 Female: 1/6	Median age: 61.5	None HTN CVD	4/6 1/6 1/6	Median: 21.5 days	Fever Cough Fatigue Shortness of breath Dyspnea	6/6 6/6 5/6 5/5 4/5	CP	Median volume of CP: 300 mL (200–600)	N/A	[55]
21	Male: 18/21 Female: 3/21	Range: 56.8 ± 16.5	HTN Diabetes CHD COPD Brain Infarction Bronchiectasis Auricular fibrillation CKD	9/21 5/21 2/21 1/21 1/21 1/21 1/21 1/21	N/A	Fever Cough dyspnea Phlegm Fatigue Nausea Rhinorrhea Chest pain	21/21 14/21 6/21 9/21 6/21 4/21 1/21 1/21	TCZ	8 mg/kg IV 18/21 patients received one dose 3/21 patients received two doses (due to fever within 12 h)	All patients: Lopinavir, ritonavir, IFN alpha, ribavirin For patients with rapid progress in respiratory function: Methylprednisolone was also administered	[57]
3	Male	71	HTN		9	Flu-like symptoms, dyspnea		TCZ	Two dose of TCZ at 8 mg/kg IV, 12 h apart	Lopinavir/ritonavir, hydroxycholoroquine	[58]
	Male	45	None		4	Fever, dyspnea, chest pain		TCZ	Two doses of TCZ at 8 mg/kg IV, 12 h apart	Lopinavir/ritonavir, hydroxycholoroquine	
	Male	53	HTN		2	Flu-like symptoms, dyspnea		TCZ	Three doses of TCZ 12 h after the first and a third dose after further 24–36 h	Lopinavir/ritonavir, hydroxycholoroquine	
4	Female	54	β-Thalassemia		N/A	Fever, cough, dyspnea, respiratory failure		Eculizumab	Two doses of Eculizumab at 900 mg	Enoxaparin 4000, Lopinavir/ritonavir, hydroxycholoroquine	[59]
	Male	73	HTN		N/A	Fever, cough, respiratory failure		Eculizumab	Two doses of Eculizumab at 900 mg		
	Female	82	HTN		N/A	Fever, cough, dyspnea, respiratory failure		Eculizumab	Two doses of Eculizumab at 900 mg		
	Male	53	HTN		N/A	Fever, cough, dyspnea, respiratory failure		Eculizumab	Two doses of Eculizumab at 900 mg		
1	Male	61	Kidney transplant, chronic kidney disease stage IIIa, lymphoma, unprovoked pulmonary embolism, urinary tract infection		11	Fever		TCZ IVIg	324 mg of TCZ via subcutaneous route 0.3 g/kg IVIg	Methylprednisolone, hydroxycholoroquine, IVIg	[60]
1	Male	42	MRC		8	Fever, cough, dyspnea		TCZ	Two doses of TCZ, at 8 mg/kg intravenously (IV) for each dose, 8 h apart	Lopinavir/ritonavir	[61]
1	Male	60	MM		9	chest tightness and shortness of breath without fever and cough		TCZ	One dose of TCZ at 8 mg/kg IV	Arbidol, methylprednisolone	[62]
1	Female	57	SSC, IDDM, WHO grade I obesity		N/A	Cough, dyspnea, arthritis		TCZ	8 mg/kg every 4 weeks IV	N/A	[63]
2	Male	65	None		9	Fever, ARDS		TCZ	Two doses of TCZ	Lopinavir/ritonavir, ribavirin/ hydroxycholoroquine	[64]
	Male	43	None		13	Respiratory failure, ARDS, fever		TCZ	Two doses of TCZ	Lopinavir/ritonavir, ribavirin	
1	Male	45	SCD		2	Fever, pneumonia, acute chest syndrome		TCZ	One dose of TCZ at 8 mg/kg IV	Hydroxycholoroquine	[65]
1	Male	65	None		7	Syncope, fever, dyspnea		TCZ	Two doses of TCZ at 8 mg/kg IV, 12 h apart	N/A	[66]
1	Male	63	Liver cancer, liver transplant (end-stage renal disease), HTN, diabetes, peripheral vascular disease, heart failure, smoking		12	Fever, cough, fatigue, headache, myalgia, malaise		TCZ	One dose of TCZ at 800 mg (9 mg/kg)	Hydroxycholoroquine	[67]
1	Female	16	SCD		N/A	Fever, acute chest syndrome, respiratory distress syndrome,		TCZ	One dose of TCZ at 8 mg/kg	N/A Red blood cell exchange transfusion	[68]
2	Male	40	None		4	Fever, cough, dyspnea, ARDS, septic shock		TCZ	One dose of TCZ at 400 mg	N/A	[69]
	Female	69	Type II diabetes mellitus, rheumatoid arthritis, aplastic anemia		4	Fever, cough, chest pain, fatigue, abdominal pain		TCZ	Two dose of TCZ at 560 mg and 700 mg		

(*continued on next page*)

Table 2 (*continued*)

N	Gender	Age (y)	Comorbidities		IAI (days)	CPI		TI	Dose/times of transfusion	OT	Ref
15	Male: 12/15 Female: 3/15	71 ± 9	HTN HTN + stroke history HTN+ diabetes Stroke history	3/15 2/15 4/15 1/15	0	Critically ill Seriously ill Moderately ill	7/15 6/15 2/15	TCZ	80–600 mg of TCZ per time. 10/15 patients received one dose of TCZ, 3/15 patients received two dose of TCZ, 2/15 patients received three dose of TCZ	Methylprednisolone: 8/15 None: 2/15	[70]
1	Female	65	N/A		10	Fatigue, fever, cough chest tightness		hUCMSC IVIg	Three doses of MSC at 5×10^7 cells	Lopinavir/ritonavir, IFN-alpha, oseltamivir, methylprednisolone	[71]
7	Male Female Female Female Male Male Male	65 63 65 51 57 45 53	N/A N/A N/A N/A N/A N/A N/A		8 6 10 1 2 10 3	Fever, shortness of breath, cough, poor appetite, diarrhea (1/7)		MSC	1×10^6 cells per kilogram of weight	Standard treatments	[74]
58	Male: 36/58 Female: 22/58	Median age: 63	N/A		> 48 h ≤48 h	N/A		IVIg	N/A	Arbidol + all other treatment according to WHO (not detected)	[75]
3	Male Male Female	56 34 35	None HTN None		7 2 6	Sore throat, fever, cough, dyspnea Fever, cough, dyspnea Fever, cough, dyspnea		IVIg IVIg IVIg	25 g per day for five days (body weight: 66 kg) 25 g per day for five days (body weight: 63 kg) 25 g/day for five days (body weight: 56 kg)	Oseltamivir None Lopinavir/ritonavir, corticosteroids	[76]

Y: years; N: number of patients; IAI: interval between admission and immunotherapy (days); CPI: complication prior to immunotherapy or principal symptoms; TI: type of immunotherapy; OT: other anti-viral and steroid therapies; CP: convalescent plasma therapy; TCZ: Tocilizumab; MSC: mesenchymal stem cell; hUCMSC: human umbilical cord mesenchymal stem cell; ARDS: acute respiratory distress syndrome; HTN: hypertension; MI: mitral insufficiency; CD: cardiovascular and cerebrovascular diseases; MRC: metastatic sarcomatoid clear cell renal cell carcinoma; SSC: systemic sclerosis; IDDM: insulin-dependent type 2 diabetes mellitus; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; MM: multiple myeloma; SCD: homozygous sickle cell disease; N/A: not applicable; CVD: cardiovascular disease.

and decreased the SARS-CoV-2 RNA to an undetectable level [54].

In a case series trial, five COVID-19 patients with severe pneumonia were assessed who were treated with CP therapy. The neutralizing antibody titers above 1:40 were transfused to the patients in addition to anti-viral drugs and corticosteroid therapy. The outcome was an improvement of the clinical symptoms and laboratory assessments including, changes in body temperature, improvement Sequential Organ Failure Assessment (SOFA) score, decrease viral load, increased serum antibody titer, and decreased CRP level to the normal range [53].

One case report study has shown a favorable outcome after CP therapy in two COVID-19 patients with severe pneumonia. Both two cases showed chest X-ray improvement, decrease oxygen demand, and subsiding the fever. Their laboratory assessments showed a reduced level of CRP and IL-6 to the normal range and negative SARS-COV-2 RNA [50].

In a descriptive study by Mingxiang et al., six COVID-19 patients were treated with CP therapy. An increased titer of anti-SARS-COV-2 and computed tomography (CT) scan improvement were observed in all six patients [52].

Zhang B et al. evaluated the efficiency of CP therapy in 4 patients. The viral load significantly dropped in one case after CP transfusion. Totally, decreased viral load was observed in 3–22 days and anti-SARS-COV-2 IgG was developed in all patients in this trial 14 days after CP therapy [51]. On the other hand, researchers at Johns Hopkins University obtained FDA approval to test CP therapy for COVID19 patients in large-scale clinical trials [56]. By 4th May 2020, there were 11 clinical trials registered in China (Supplementary data, Table 3) and 43 trials have registered in clinicaltrials.gov (Supplementary data, Table 4) for large-scale treatment of COVID-19 patients with CP.

3.2. Monoclonal antibodies

Of the 24 included studies screened, 14 studies with a total of 55 patients have identified that met inclusion criteria for monoclonal antibodies, including 3 case series [57–59], 10 case reports [60–69], and one retrospective study [70].

Except for four patients who were successfully treated with Eculizumab [59], the others (51 patients) were treated with Tocilizumab (TCZ). One patient also received intravenous immunoglobulin (IVIg) in combination with TCZ [60]. 47 patients were recovered after TCZ; among them, 4 patients have shown adverse effects [60,64,69]. The fatality was also reported in 4 patients, who received TCZ [69,70].

In a case series study, 21 severe COVID-19 patients were treated with TCZ. Improvement of clinical symptoms in this trial was observed within a few days. Fifteen of the 20 patients had reduced demand for oxygen, and one patient did not require oxygen therapy within five days after TCZ. In 16 of the 19 patients, the elevated C-reactive protein (CRP) levels returned to normal range. Improvement in Chest X-rays was observed in 19 cases, and other patients showed little improvement in their chest X-rays [59]. In accordance with this trial, 3 studies have also shown improved clinical symptoms and laboratory tests after TCZ treatment [58,65,66].

Three studies have assessed the TCZ effectiveness in treating patients with cancer or autoimmune disorders. In the first study, treatment with TCZ with favorable outcome was reported in a patient with metastatic sarcomatoid clear cell renal cell carcinoma, including gradually decreased oxygen consumption, improvement in chest CT, and decreased level of CRP. However, it should be noted that this patient had an immunosuppressed condition due to his cancer [61]. The second study reported a patient with multiple myeloma (MM) who was successfully treated with TCZ. The outcomes in this trial were improved in chest tightness and chest CT, decreased level of IL-6, and decreased the SARS-CoV-2 RNA to undetectable levels [62]. Another study demonstrated TCZ performance in a patient with systemic sclerosis and IDDM. Treatment with TCZ in this trial improved musculoskeletal and respiratory symptoms, lung function, and CT imaging [63].

Two studies evaluated the efficacy of TCZ in two patients with organ transplantation [60,67]. Subsiding the fever, decreased oxygen demand, and *Pseudomonas aeruginosa* infection in urine culture were seen in one of them who was treated with TCZ and IVIg [60]. Another patient showed the reduced fever, improved chest pain and abdominal pain [67].

The adverse effects of TCZ were reported in three studies. Two studies have shown hypertriglyceridemia in four COVID-19 patients treated with TCZ. Hypertriglyceridemia could be related to the disruption of triglyceride uptake which caused by TCZ. Besides, cytopenias, hypertriglyceridemia, elevated ferritin and lactate dehydrogenase, hypofibrinogenemia [69] and acute pancreatitis (elevated level of lipase and amylase) [64] have been also shown in two studies. In another study [60], in a patient with chronic kidney disease stage IIIa, *Pseudomonas aeruginosa* infection was found in the urinary culture as an adverse effect of TCZ.

One study [70] reported disease aggravation after treatment with TCZ in COVID-19 patients. In this trial, among 15 patients who were treated with TCZ, two patients showed disease aggravation, nine patients showed clinical stabilization, one patient showed clinical improvement, and three patients died.

One study reported treatment with TCZ in COVID-19 pediatric patients with homozygous sickle cell disease (SCD) who was treated successfully [68].

A total number of 29 clinical trials were registered in clinicaltrials.gov until 4 May 2020 in order to evaluate the efficacy of TCZ for treatment of COVID-19 patients (Supplementary data, Table 5). Moreover, some of the clinical trials have been approved for the efficacy assessment of other monoclonal antibodies, including Adalimumab, Camrelizumab, Eculizumab, Meplazumab, PD-1 mab, Anakinra, and Siltuximab to treatment of COVID-19 patients. These monoclonal antibodies are summarized in Supplementary data, Table 6.

3.3. Cytokines and interferons

Of the 24 studies included, 5 studies [51,53,54,57,71] with a total of 31 patients included that received type 1 interferon (IFN) apart from other immunotherapies. These studies include one case report [51], one preliminary uncontrolled case series [53], one pilot study [54], one retrospective study [57], and one case report in registered clinical trials in china [71].

Three patients received IFN-α-2b apart from CP therapy and anti-viral drugs. Among them, two patients had comorbidities including chronic obstructive pulmonary disease (COPD) and chronic renal failure. In this trial, decreased viral load, increased anti-SARS-COV-2 titer in serum, and improvement in chest X-rays were observed in all three patients [51].

Four patients received IFN-α-1b apart from CP therapy, anti-viral drugs, and methylprednisolone. The outcome was including changes in body temperature, improved Sequential Organ Failure Assessment (SOFA) score, decreased viral load, increased serum antibody titer, decreased CRP and procalcitonin levels to the normal range [53].

Type of IFN-α has not mentioned in 24 other patients [54,57,71]. Among them, two patients received IFN-α apart from CP therapy, anti-viral drugs, and methylprednisolone. Amelioration of clinical symptoms, decreased pulmonary lesions, improved pulmonary function, improved lymphocytopenia, and decreased the SARS-CoV-2 RNA to an undetectable level were observed upon treatment [54].

21 patients received IFN-α apart from Tocilizumab, anti-viral drugs, with or without methylprednisolone [57].

One patient received IFN-α apart from human umbilical cord mesenchymal stem cell (hUCMSC), IVIg, anti-viral drugs, and methylprednisolone. The outcome was an improvement of clinical symptoms and laboratory tests [71].

Treatment with IFN-α in combination with anti-viral drugs such as ribavirin is recommended for treatment COVID-19 patients in china

[72,73].

There are also 20 registered clinical trials up to 4 May 2020 to evaluate the treatment efficiency of COVID-19 patients with IFN in clinicaltrials.gov (Supplementary data, Table 7). Besides, there were two ongoing clinical trials in China for evaluating the efficacy of recombinant human interleukin-2 [ChiCTR2000030167] and G-CSF [ChiCTR2000030007] in combination with standard treatment in COVID-19 patients.

3.4. Mesenchymal stem cell therapy (MSCT)

Out of the 24 studies included, two studies, with a total of 8 patients included a case-control study with 7 patients in the treatment group and 3 in the control group [74], a case report in registered china clinical trials [71] were identified that received MSCT.

In the first case study carried out in China, a 65 years old woman with severe pneumonia was treated with the umbilical cord stem cells, apart from IVIg, IFN-α, anti-viral drugs, and methylprednisolone [71]. Before stem cell therapy, the patient had respiratory and multi-organ failure requiring mechanical ventilation. She was not responding to conventional therapy. So, she received three doses of allogeneic stem cells (50 million per dose) within three days, along with conventional therapy. One day after the second infusion, her vital signs were stabilized and she was no longer requiring the ventilator. Two days upon the third dose, she was getting out of the ICU and most of the laboratory indexes were normal. Two days upon the third dose, her throat specimen was negative for Coronavirus. Finally, six days after the third infusion, the CT scan of her lungs significantly improved.

Another study was a short-term (14 days' follow-up) and a small clinical trial with only 10 coronavirus patients [74]. The patients were divided into 7 patients (including 1 critically serious, 4 serious, and 2 commons) who were treated with one dose of stem cells and 3 serious patients in the control group who did not. The patients were not responding to standard conventional therapy. All 7 patients were recovered following the receiving stem cell therapy. Conversely, the results obtained from the control group were one dead, one patient with developed ARDS, and only one patient with stable conditions. In the treated group within a few days, the oxygen saturation, the laboratory indexes such as CRP, aspartic aminotransferase, creatine kinase activity, and myoglobin changed to normal. Furthermore, significant improvements were observed in the signs in CT scans of the lungs in the treatment group [74].

There are also 29 registered clinical trials up to 4 May, to evaluate the treatment efficiency of COVID-19 patients by cell therapy including MSCT in clinicaltrials.gov (Supplementary data, Table 8).

3.5. Intravenous immunoglobulin (IVIg)

Of the 24 studies included, 4 observational studies with a total of 63 patients were identified that received IVIg apart from anti viral drugs or other immunotherapies. These studies included one case report [60], one case report in registered china clinical trials [71], one retrospective study [75], and one case series [76].

Among them, one patient received IVIg alone [76], 60 patients received IVIg apart from anti-viral drugs or corticosteroids [75,76], one patient received IVIg apart from Tocilizumab, corticosteroid, and hydroxychloroquine [60], and one patient received IVIg apart from hUCMSC, IFN-alpha, anti viral, and corticosteroid [71].

In the first clinical trial, three patients were treated with anti-viral drugs and IVIg (0.3–0.5 g per kg weight per day for five days) in about one week after admission (in two patients) and 2 days after admission (in one patient). The clinical observations in all three patients were improved, including fever, CT-scan, and oxygen consumption [76].

In the second study, 28-day mortality rate was assessed in 58 sever COVID-19 patients who were treated with IVIg in China. The patients were divided into two groups, the patients who received IVIg within 48 h ($\leq$48 h) after admission and the patients who received IVIg > 48 h after admission. All patients received IVIg when their total lymphocyte count decreased to < 0.5 × 109/L at 20 g/day. The patients were also treated with Thymosin if the total number of lymphocytes had not increased 5 days after IVIg administration. The results showed the reduced 28-day mortality rate, reduced ventilator use, and shorter length of stay in hospital in the patients who received IVIg within 48 h after admission in comparison to the patients who received IVIg > 48 h after admission [75].

One study assessed the efficiency of IVIg in a COVID-19 patient with chronic kidney disease stage IIIa. In this trial, the patient received IVIg at the dose of 0.3 g/kg, Tocilizumab, hydroxychloroquine, corticosteroid, and cyclosporine A. The outcome was a subsiding the fever and normal peripheral oxygen saturation. Progressive leukopenia and neutropenia, stopped oxygen treatment, and stability in kidney function were observed after Tocilizumab, and then IVIg was administered to immune system modulation [60].

3.6. Other registered clinical trials

In addition to the mentioned ongoing clinical trials, we found five clinical trials for Thymosin (Supplementary data, Table 9) and four clinical trials for immunosuppressive drugs, including Fingolimod, Leflunomide, Thalidomide (Supplementary data, Table 10) in order to evaluate their efficiency in COVID-19 patients.

4. Discussion

SARS-CoV-2 is a newly emerged pathogen that spreads quickly and could result in acute respiratory distress syndrome in infected patients. SARS-CoV-2 and SARS-CoV share about 79% genomic similarity, caused to bind to the same receptor (ACE2R) that found in the lung epithelium and some other tissues. No efficient drug is available for treatment at the moment [48,77]. Meanwhile, the immune system is facing many challenges and there is still a lot of uncertainty about the immune responses in this disease as well as the role of the individual components of the immune system, the effect of antibody responses, duration of immunity, the most effective treatment, and so on. So the efficacy of the innate, cellular, and humoral immunity determines the outcome of viral infections. It means a proper immune response mediates protection, while an overwhelming immune response is associated with immune-mediated pathogenesis in viral infections. Many efforts are currently being made to find effective treatment worldwide, and each has shown different outcomes. Since a lot of different immunotherapies are in processing, we hope that we could see the elimination of this virus via immunotherapy like the other previous viral pandemics (Fig. 3).

Convalescent plasma therapy is referred to use plasma containing antibodies from a person who has recovered from an illness. Accumulating evidence suggests the effective role of CP therapy in various viral respiratory disorders. The hopeful outcomes of CP therapy, including improved survival rate and reduced mortality of the patients have been reported in SARS-CoV related pneumonia and influenza A (H1N1) [78–82].

It seems that CP therapy could be used in newly infected COVID-19 patients to improve the immune response, probably through neutralizing the virus, suppress viremia, and viral clearance. No adverse effects were observed in all included patients in this study. Nevertheless, some precautions should be considered, including evaluating the neutralizing Ab activity titer and accurate time for plasma collection and administration [83]. Besides, CP therapy might be more effective if administered at the initial stage of the disease [55,79].

Immunotherapy using monoclonal antibodies as another inspiring approach is progressing to treat COVID-19 patients [84]. Up to now, most clinical trials have been performed on TCZ. However, one study reported good results in treating patients with Eculizumab, a

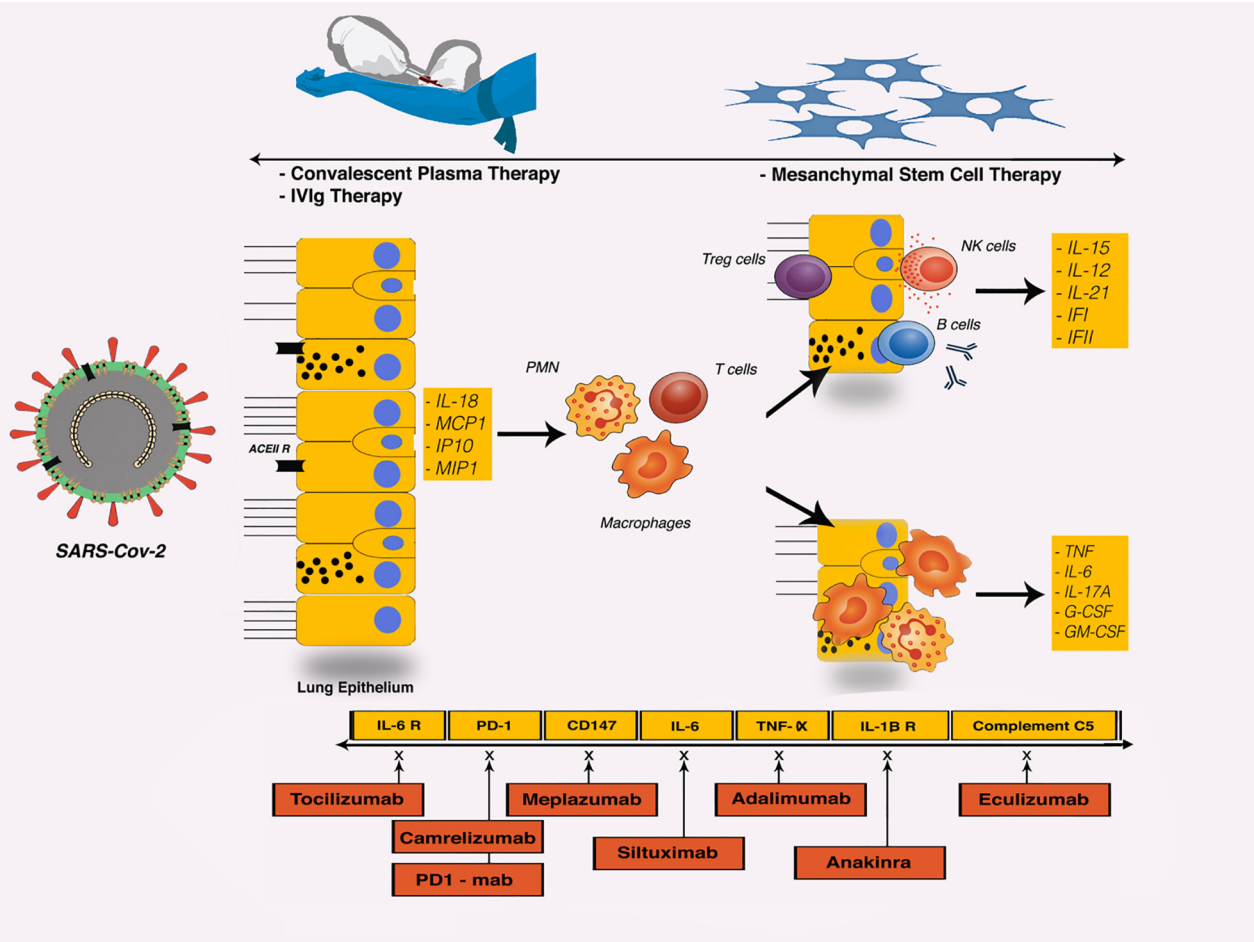

Fig. 3. The mechanism of the innate and acquired immune response following by attaching the virus to the ACE2 receptor and the current immunotherapies for treatment the COVID-19 patients. Viral interactions with the innate and acquired immune system play a central role in determining the outcome of infection. Local inflammation formed in the site of the infection, triggers immune cells to limit viral spread within the host during the early phases of the disease via producing cytokines and other chemokines. Current immunotherapies including monoclonal antibodies, convalescent plasma therapy, IVIg, mesenchymal stem cell therapy in COVID-19 patients are also shown. Up to now, most clinical trials have been performed on Tocilizumab and convalescent plasma therapy with inspiring outcomes. Depicted monoclonal antibodies are currently being evaluated by registered clinical trials. ACE2R: angiotensin-converting enzyme 2 receptor; IL: interleukin; MCP1: monocyte chemoattractant protein1; IP10: interferon-inducible protein 10; IF: interferon; PD-1: programmed cell death protein 1; MIP1: macrophage inflammatory proteins1; TNF: tumor necrosis factor; PMN: polymorphonuclear granulocyte; NK: natural killer; Treg cell: regulatory T cell; CSF: colony stimulating factor; IVIg: intravenous immunoglobulin.

humanized monoclonal antibody against complement protein C5.

TCZ is a humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that has long been used to treat various inflammatory disorders including rheumatoid arthritis (RA), systemic juvenile idiopathic arthritis, Castleman disease, and Crohn's disease. The effective use of TCZ is also reported in the treatment of cytokine release syndrome (CRC) that has occurred in various conditions such as CAR-T cell therapy, organ transplantation, and virus infection [85–90].

The high level of serum cytokines, including IL-6, IL-1, IL-8, IL-12, and tumor necrosis factor-alpha (TNF-a) is reported to be associated with the severe acute respiratory syndrome (SARS) in coronavirus infection [33,91–93]. It has been described that the COVID-19 patients had a high level of cytokines and chemokines in serum including IL-6, IL-2, TNF-a, IL-10, interferon-gamma inducible protein (IP-10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein (MIP1a) that was related to an inflammatory condition in the patients known as cytokine storm that is associated with the severity of the disease [94]. TCZ can modulate immune responses through the interaction with soluble or membrane-bound IL-6R and subsequently inhibits IL-6 signaling [95]. Interestingly, anti-virus immune response by plasma B cells and CD8+ T cells were seen in the treated patients with TCZ suggesting the specific effect of TCZ on inflammatory cascade [96].

Treatment with TCZ in COVID-19 patients who have elevated levels of inflammatory cytokine IL-6 might be effective in modulating inflammatory response caused by cytokines storm.

Although treatment with TCZ had inspiring outcomes, some adverse effects were also reported such as hypertriglyceridemia in four patients and *Pseudomonas aeruginosa* infection in urine culture in one patient with chronic kidney disease [60,64,69]. Besides, two patients have shown disease aggravation after treatment with TCZ [70]. As a result, more investigations in large scale trials are needed for evaluating the efficacy of TCZ in COVID-19 patients.

Two in-vitro studies by Wang et al., and Tian et al., also revealed two types of monoclonal antibodies named 47D11 [97] and CR3022 [98] with the neutralizing effect of SARS-COV-2. These studies could be helpful to improve our knowledge to design effective monoclonal antibodies to treat COVID-19 patients.

Cytokine therapy is also another approach to treat COVID-19 patients. Type 1 interferons (IFN-I) are a group of cytokines produced by various types of immune cells, particularly plasmacytoid dendritic cells during the first stages of a response against viral infection [99]. Different subtypes of IFN-I are recognized including α, β, ε, ω, and κ [100].

It has been shown that IFN-I could be an efficient agent against

various viral infections including hepatitis B, C, and HIV [101]. An in vitro study showed that SARS-CoV-2 is more sensitive to IFN-I compared to SARS-CoV. This discrepancy may be due to the changes that occurred in proteins of SARS-CoV-2, such as the loss of ORF3b, that would be resulted in a changed response to IFN-I [102]. After treatment COVID-19 patients with IFN-I along with other standard cares, favorable outcomes were observed due to improvement of the anti-viral response.

IVIg is referred to as polyclonal IgG isolated from healthy donors. IVIg has long been used to treat the patients, who suffered from primary antibody deficiencies, vasculitis, rheumatologic disorders, chronic inflammatory diseases, systemic lupus erythematosus (SLE) as well as treat several hematological and neurological disorders [103]. Treatment with IVIg has also been effective in the treatment or prevention of the infectious disease caused by viruses, bacteria, and fungi in human patients [104,105].

Previous studies were shown the encouraging outcomes in patients with SARS and MERS after treatment with IVIg [106–108]. Using IVIg for COVID-19 treatment has been performed only in a small number of patients. Good results were observed after treatment with IVIg in combination with other standard anti-viral drugs. The immune system modulation by IVIg could be conducted by improving passive immunity and anti-inflammatory response. Although the role of IVIg in COVID-19 patients requires more investigations, it seems that this approach has promising effects, if administered in the early stage of disease.

Cell-based therapies have been used to management of several illnesses including pulmonary [109–111], cardiovascular [112,113], hepatic [114], and renal [115] diseases. Also, the safety and effectiveness of the treatment with stem cells have been documented in many clinical trials, especially in immune-mediated inflammatory diseases, such as SLE and graft-versus-host disease (GVHD) [110,116].

In line with finding effective drug therapies and immunological treatments for COVID-19, mesenchymal stem cells (MSCs) may have significant immunomodulatory ability. On the other hand, these cells secret many anti-inflammatory factors through paracrine route or direct interactions with immune cells, including T and B cells, macrophages, dendritic cells (DCs), and NK cells. The outcome of these events may lead to preventing or inhibiting the cytokine storm, regulating the inflammatory response as well as decreased morbidity and mortality in the treated patients.

Until now, many worldwide health centers have released several guidelines related to treating coronavirus patients using MSCs. For example, the Italian College of Anesthesia, Analgesia, Resuscitation, and Intensive Care has stated that stem cells have a significant potential to treat COVID-19 patients by decreasing the need to ICU care. Based on FDA regulations, stem cell therapy is commonly used to treat various morbidity conditions. In this way, some clinical trials (mainly performed in China) have shown the safety and efficacy of this type of therapy method [116–118]. The reported findings from these clinical trials showed that stem cell therapy likely is ideal to treat coronavirus as a serious systemic illness. The primary sources of stem cells available for this purpose are autologous bone marrow stem cells [116], adipose stem cells, amniotic stem cells, and umbilical cord stem cells. Among them, the umbilical cord as a promising source of MSCs, due to transplantation across MHC barriers seems to be the most desirable source to treat coronavirus [69,71,112].

Two potential mechanisms have been proposed by which MSCs can treat COVID-19 patients, including the immune system modulation and also promote tissue repair and regeneration. The most complications induced by the coronavirus in the vital organs occurred in the lungs. Studies have reported that upon intravenous infusion, the majority of the MSCs accumulate in the lung, which could potentially result in the improvement of the pulmonary microenvironment of the alveolar epithelial cells and also inhibition of pulmonary fibrosis.

Besides, several studies reported that MSCs also show the antimicrobial effects during infection and inflammation that occurred in preclinical models of sepsis, ARDS, and cystic fibrosis infection. The mechanism of action proposed for their antimicrobial activities are the dynamic coordination of the pro- and anti-inflammatory elements of the immune system or increasing the activity of phagocytes, and also the secretion of antimicrobial factors and molecules [119,120]. In conclusion, umbilical cord MSCs as a main type of the stem cells show a gene expression profile more similar to that of embryonic stem cells due to the fact that they have faster doubling times, more plasticity, and possibly more potency. Fortunately, unlike embryonic stem cells, they are not tumorigenic [121]. Thus, MSCs therapy against COVID-19 could be a promising approach to managing this world-threatening disease. However, the appropriate cell dose, cell concentration, the cell infusion rate should be determined to maximize efficacy and safety. Cell passage numbers should be limited to increase potency and decrease cell size.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

Author contributions

R.N. directed the project. M.A.H., S.M., and R.N. designed research. Data extraction performed by M.A.H., S.M., and M.M.H.R. The paper was drafted by M.A.H., S.M., and M.M.H.R.

R.N. did critical revision of the paper. All the authors contributed to protocol development, read and finally approved the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2020.118185.

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