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REVIEW

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Novel therapeutic approaches for treatment of COVID-19

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Abstract
To date, there is no licensed treatment or approved vaccine to combat the coronavirus disease of 2019 (COVID-19), and the number of new cases and mortality multiplies every day. Therefore, it is essential to develop an effective treatment strategy to control the virus spread and prevent the disease. Here, we summarized the therapeutic approaches that are used to treat this infection. Although it seems that antiviral drugs are effective in improving clinical manifestation, there is no definite treatment protocol. Lymphocytopenia, excessive inflammation, and cytokine storm followed by acute respiratory distress syndrome are still unsolved issues causing the severity of this disease. Therefore, immune response modulation and inflammation management can be considered as an essential step. There is no doubt that more studies are required to clarify immunopathogenesis and immune response; however, new therapeutic approaches including mesenchymal stromal cell and immune cell therapy showed inspiring results.

Keywords COVID-19 · Coronavirus · Therapeutic approaches · Severe acute respiratory syndrome · Acute respiratory distress syndrome · Cell therapy

Introduction

Corona viruses are a large family of enveloped, positive-sense RNA viruses that have the largest RNA genome (rage from 26 to 32 kb) [1, 2]. Several coronavirus epidemics such as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) have occurred during the past years [2, 3]. At the end of 2019, a novel coronavirus infection named coronavirus disease of 2019 (COVID-19) was first identified in Wuhan, China [4–7]. Due to the fast transmission, it is reported in almost all countries and has become a global crisis. Therefore, COVID-19 pandemic becomes an international threat for human health and economy [1, 8].

COVID-19 spreads fast among people and the mortality rate is controversial; however, it was less than 2% in some

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studies. The main manifestations of the disease include fever, dry caught, headache, shortness of breath, pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and even death [3, 11, 12].

The genome sequencing of this virus revealed more than 82% identity to SARS-CoV [9]. Analysis indicated that the binding affinity of virus S protein to the angiotensin-converting enzyme 2 (ACE2) receptor on human alveolar epithelial cells is higher compared with the SARS-CoV [10].

Since SARS-CoV-2 is a new pathogen, little is known about it. Moreover, there is no licensed treatment or approved vaccine and the number of new cases and mortality multiplies daily [8]. Therefore, it is vital to develop an effective treatment strategy to control the virus spread and prevent the disease [1, 11].

Immunopathogenesis of COVID-19

Although the pathogenesis of this disease has not been fully understood, it seems that the host immune responses play an important role. Aberrant host immune response causes lung tissue damage, reduced lung capacity, and finally respiratory failure [4]. Studies indicated that dendritic cells (DCs) and macrophages are playing crucial role in innate immune responses [12, 13]. These cells produce inflammatory cytokines and chemokines including TNF-α, IL-12, IL-6, IFNγ, and IL-8, and monocyte chemoattractant protein (MCP-1), macrophage colony-stimulating factor (GM-CSF), and granulocyte-colony-stimulating factor (G-CSF) [6, 14]. These inflammatory responses may lead to systemic inflammation [6, 7, 13, 14].

Adoptive immunity plays a major role in viral infections [15]. Cytotoxic T cells (CD8+ T cells) are the main T cell subsets that destroy infected cells [16]. Therefore, the number of these cells is one of the major factors for clearance of the viral infection [17, 18]. Preliminarily, it was indicated that the number of total T cells, CD4+ and CD8+ T cells, reduced significantly in COVID-19 patients. This decrease was more intensive in ICU admitted patients compared with that in non-ICU admitted individuals [19]. It is also reported that T cell clonal exhaustion occurred during the infection and the expression of certain T cell surface markers like PD1 (programmed cell death protein 1) and TIM-3 (T cell immunoglobulin and mucin domain-containing molecule-3) markedly increased [19, 20]. The cytokine storm occurred in response to SARS-CoV-2 infection that led to increased expression of NKG2A (natural-killer group 2, member A) on cytotoxic T cells (CTLs) and NK cells. This upregulation suppressed CTL and NK function and cytokine secretion [19, 21, 22]. It is suggested that inflammatory cytokines, TNF-α and IL-6, mainly originated from apoptotic monocytes (CD14+CD16+) and macrophages and induced T CD4+ and T CD8+ cells [19, 23]. These excessive inflammatory responses might result in respiratory system pathology and dysfunction [23].

Perhaps it takes many years to achieve a specific and effective therapeutic protocol, efficient vaccine, or suitable medicine for the treatment of COVID-19. There is a wide range of existing and current treatment strategies categorized into antiviral drugs, immunotherapy protocols including convalescent serum and monoclonal antibodies, cell-based therapies, hydroxychloroquine, Chinese medicine, and steroids (just for patients who suffer from ARDS) [24]. A schematic figure (Fig. 1) summarized the novel therapeutic approaches in treatment of COVID-19 patients. Moreover, there are a growing number of clinical trials registered for the treatment of COVID-19 (Table 1).

Passive immunotherapy

Convalescent serum

Antibody injection to the patients and susceptible people provides rapid immunity to treat or prevent the disease [25–27]. Past experiences from SARS and MERS viral infections indicated that passive immunotherapy could be a potential treatment strategy for the patients [27–29]. It is considered that passive immunotherapy could also be beneficial in SARS-CoV-2 infection [30]. Extracting neutralizing antibodies from recovered individuals with high titer of antibodies in sera and transfusion to infected patient could deactivate the virus. However, neutralization activity of these antibodies is not fully understood. It has been showed that neutralizing antibodies are not long lasting and only the recently recovered patients are suitable candidates [31]. It has also been reported that the neutralizing antibody titers vary among the patients and elderly patients had higher antibody titer compared with young recovered individuals [32]. It is supposed that convalescent serum administration may induce phagocytosis and antibody-mediated cellular cytotoxicity [25, 27]. One important implications for using convalescent serum is the risk for antibody-dependent enhancement (ADE) [33]. It is supposed that these neutralizing antibodies may enhance other viral infections [34]. Another major limitation of this strategy is donor shortage. However, by increasing the number of recovered individuals, this limitation would be solved [25].

Monoclonal antibodies

It has been shown that monoclonal antibodies (mAbs) could be an effective tool for the treatment of viral infectious diseases [35–37]. Different techniques have been used to develop mAbs including phage display library, hybridoma, single B cell isolation, and transgenic mice [37]. Various monoclonal antibodies developed against MERS and SARS infections include m396, 80R, and S3.1 against SARS and LCA60 for the

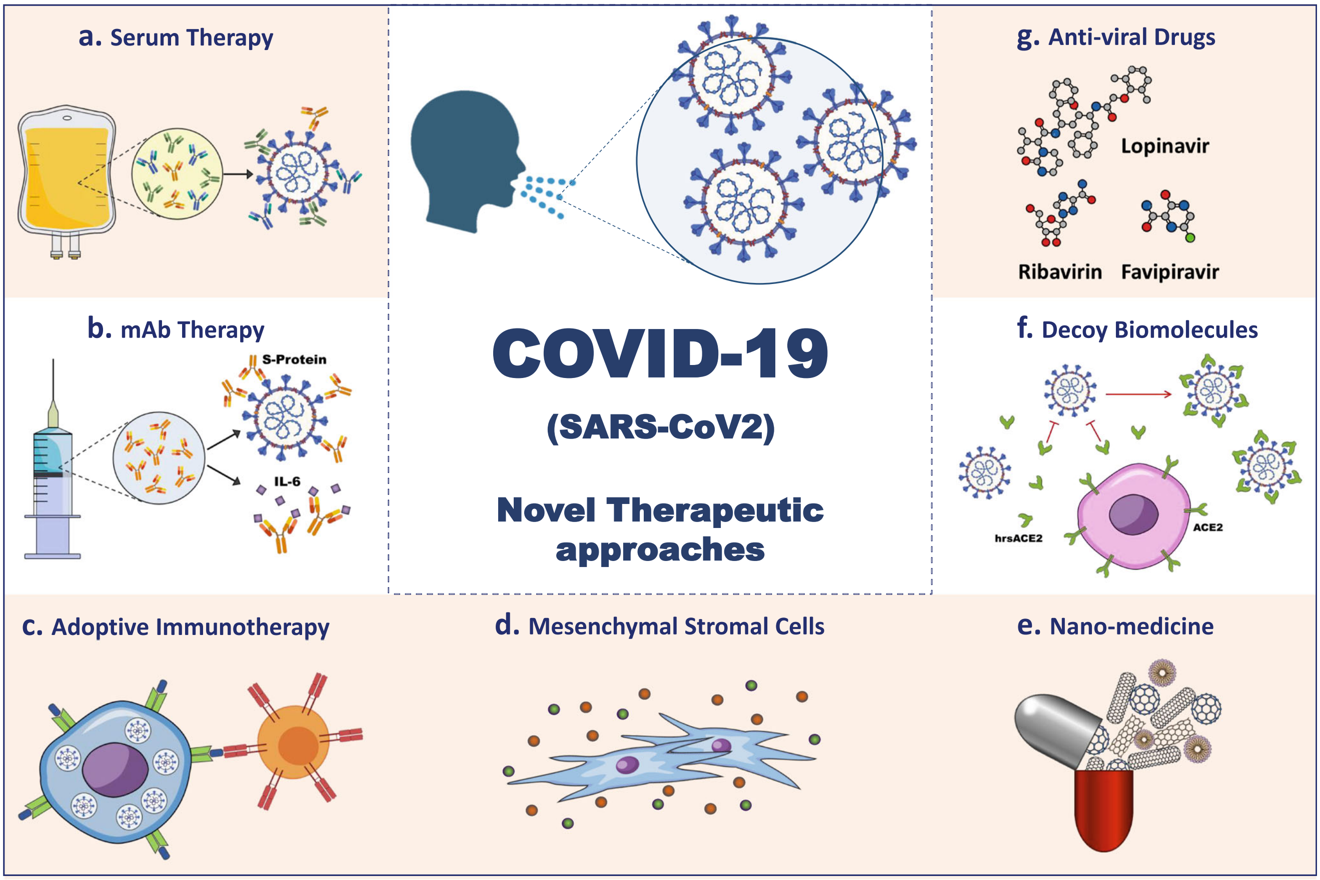

Fig. 1 Novel therapeutic strategies for treatment of clinical complications of COVID-19. (a) Passive immunotherapy using serum of immunized individuals. (b) Monoclonal antibodies can directly target virus particles. Also, mAbs can be used to eliminate crucial cytokines in progression of inflammation, e.g., IL-6. (c) The effector cells in adoptive immunotherapy can be used to specifically target infected cells and enhance anti-viral immune responses. (d) Mesenchymal stromal cells are key players in immunomodulation of severe immune response. The paracrine effect of these cells can tune down immune reaction. (e) Using nanostructures for drug delivery in different medical applications. (f) Recombinant ACE2 receptor protein in soluble form attaches to viral particles. (g) Antiviral medicines can prohibit viral proliferation

treatment of MERS disease [29, 37–41]. These mAbs limited virus replication and facilitated lung recovery in animal models [42–44]. S protein is also the most immunogenic determinant of coronaviruses [40]. Several mAbs target receptor-binding domain (RBD) in the virus spike (S) glycoprotein and inhibit the virus to invade the host cell [9]. It is reported that mAbs against SARS-CoV-1 could cross react with SARS-CoV-2 [45]. It is indicated in the preprint that mAb 1A9 that targets the S protein of SARS-CoV-1 could interact with SARS-CoV-2 [46].

Tocilizumab is a humanized monoclonal antibody against IL-6 receptor cytokine. Tocilizumab targets both membrane and soluble-bound IL-6 receptors. This mAb is used for the treatment of COVID-19 patients [47]. It is shown that the IL-6 level is considerably high in severe COVID-19 cases. Treatment of 21 severe COVID-19 cases with tocilizumab indicated that using this monoclonal antibody is an effective treatment and well tolerated in these patients. In the preprinted study, tocilizumab caused body temperature and CRP returned to the normal levels and improved lung function [48]. There are also many registered clinical trials on efficiency and safety of tocilizumab for the treatment of COVID-19 (Table 1).

VEGF is one of the main mediators of vascular permeability and progression of ARDS. Bevacizumab is a humanized monoclonal antibody that targets VEGF and employed in a phase II/III clinical trial for the treatment of COVID-19 patients (NCT04275414).

As described earlier, during the SARS-CoV-2 infection, exhaustion of T and NK cells happens. In order to restore these cells, using monoclonal antibodies to block the PD-1/PD-L1 and TIM3 pathways may have beneficial therapeutic effects as well [49].

Kinase inhibitors

It is suggested that an inhibitor of Janus kinase (JAK) called baricitinib could prevent the entry of SARS-CoV-2 into the host cells and also inhibit the inflammation [50, 51]. Cyclin G-associated kinase (GAK) and AP2-associated protein kinase 1

Table 1 Variety of therapeutic agents used in clinical trials registered to treat COVID-19

Group	Therapeutic agent	Example of clinical trials registered at ClinicalTrials.gov			
		CT number	Country	Recruitment status	Phase
Serum	Convalescent serum	NCT04327349	Iran	Enrolling by invitation	Phase I
	Convalescent plasma	NCT04372979	France	Not yet recruiting	Phase III
		NCT04343755	USA	Recruiting	Phase II
		NCT04363034	USA	Available	NA
		NCT04333355	Mexico	Recruiting	Phase I
	Inactivated convalescent plasma	NCT04292340	China	Recruiting	Phase I
	Immunoglobulin of cured patients	NCT04264858	China	Not yet recruiting	NA
	Immunoglobulins obtained with DFPP	NCT04346589	Italy	Recruiting	NA
Monoclonal antibodies	Tocilizumab	NCT04322773	Denmark	Recruiting	Phase II
		NCT04317092	Italy	Recruiting	Phase II
		NCT04331795	USA	Recruiting	Phase II
		NCT04377659	USA	Recruiting	Phase II
		NCT04345445	Malaysia	Not yet recruiting	Phase III
	Sarilumab	NCT04315298	USA	Recruiting	Phase II/III
		NCT04324073	France	Recruiting	Phase II/III
	Avdoralimab	NCT04371367	France	Recruiting	Phase II
	Gimsilumab	NCT04351243	USA	Recruiting	Phase II
	Siltuximab	NCT04329650	Spain	Recruiting	Phase II
	Bevacizumab	NCT04275414	China	Recruiting	Phase II/III
	Eculizumab	NCT04288713	USA	Available	Phase I
	Emapalumab	NCT04324021	Sweden	Recruiting	Phase II/III
	Clazakizumab	NCT04381052	USA	Not yet recruiting	Phase III
	Canakinumab	NCT04362813	USA, Spain, UK	Recruiting	Phase III
		NCT04348448	Italy	Not yet recruiting	NA
	Olokizumab	NCT04380519	Russia	Recruiting	Phase II/III
	Otilimab	NCT04376684	UK	Not yet recruiting	Phase III
	Sirukumab	NCT04380961	USA	Recruiting	Phase II
	Emapalumab	NCT04324021	Sweden	Recruiting	Phase II/III
	Lenzilumab	NCT04351152	USA	Recruiting	Phase III
	Leronlimab	NCT04343651	USA	Recruiting	Phase II
	Ravulizumab	NCT04369469	USA	Not yet recruiting	Phase III
	Nivolumab	NCT04343144	France	Not yet recruiting	Phase II
	Meplazumab	NCT04275245	China	Recruiting	Phase I/II

Table 1 (continued)

Group	Therapeutic agent	Example of clinical trials registered at ClinicalTrials.gov			
		CT number	Country	Recruitment status	Phase
	CD24Fc	NCT04317040	USA	Not yet recruiting	Phase III
	TJ003234	NCT04341116	USA	Recruiting	Phase I/II
	IC14	NCT04346277	Italy	Available	NA
	Anakinra	NCT04362111	UK	Not yet recruiting	Phase III
	Anakinra vs. siltuximab vs. tocilizumab	NCT04330638	Belgium	Recruiting	Phase III
Interferons	IFN-α	NTC04320236	China	Recruiting	Phase III
	Interferon beta-1A	NCT04350671	Iran	Enrolling by invitation	Phase IV
	Recombinant human interferon α1β	NCT04293887	China	Not yet recruiting	Early Phase I
	Recombinant human interferon alpha-1b	NCT04320238	China	Recruiting	Phase III
	Peginterferon lambda-1a	NCT04331899	USA	Recruiting	Phase II
	Pegylated interferon lambda	NCT04343976	USA	Not yet recruiting	Phase II
NK cells	NK cells	NCT04280224	China	Recruiting	Phase I
		NCT04344548	Colombia	Not yet recruiting	Phase I/II
	iPSC-derived NK cells	NCT04324996	USA	Not yet recruiting	Phase I
	IL15-NK cells vs. NKG2D CAR-NK cells vs. ACE2 CAR-NK cells vs. NKG2D-ACE2 CAR-NK cells	NCT04324996	China	Recruiting	Phase I/II
	CYNK-001	NCT04365101	USA	Not yet recruiting	Phase I/II
Kinase inhibitors	Ruxolitinib	NCT04362137	UK	Recruiting	Phase III
		NCT04348071	USA	Not yet recruiting	Phase II/III
		NCT04355793	USA	Available	NA
		NCT04354714	USA	Not yet recruiting	Phase II
		NCT04377620	USA	Recruiting	Phase III
	Baricitinib	NCT04340232	USA	Not yet recruiting	Phase II/III
		NCT04358614	Italy	Completed	Phase II/III
		NCT04346147	Spain	Recruiting	Phase II
	Acalabrutinib	NCT04346199	Spain	Not yet recruiting	Phase II
		NCT04380688	USA	Not yet recruiting	Phase II
	Duvelisib	NCT04372602	USA	Not yet recruiting	Phase II
	Tofacitinib	NCT04332042	Italy	Not yet recruiting	Phase II
	Imatinib	NCT04346147	Spain	Recruiting	Phase II
	Ibrutinib	NCT04375397	USA	Not yet recruiting	Phase II
	Nintedanib	NCT04338802	China	Not yet recruiting	Phase II
Other immunosuppressors	Fingolimod	NCT04280588	China	Recruiting	Phase II
	Sirolimus	NCT04341675	USA	Recruiting	Phase II

Table 1 (continued)

Group	Therapeutic agent	Example of clinical trials registered at ClinicalTrials.gov			
		CT number	Country	Recruitment status	Phase
	Tacrolimus	NCT04341038	Spain	Recruiting	Phase III
	Lenalidomide	NCT04361643	Spain	Not yet recruiting	Phase IV
	Methotrexate	NCT04352465	Brazil	Not yet recruiting	Phase I/II
Antivirals	Remdesivir	NCT04292899	USA	Recruiting	Phase III
		NCT04280705	USA	Recruiting	Phase III
		NCT04365725	France	Available	NA
	Favipiravir	NCT04336904	Italy	Active, not recruiting	Phase III
		NCT04346628	USA	Not yet recruiting	Phase II
		NCT04349241	Egypt	Not yet recruiting	Phase III
	Umifenovir	NCT04350684	Iran	Enrolling by invitation	Phase IV
	Abidol hydrochloride vs. oseltamivir vs. lopinavir/ritonavir	NCT04255017	China	Recruiting	Phase IV
	Lopinavir/ritonavir	NCT04330690	Canada	Recruiting	Phase II
		NCT04307693	Korea	Recruiting	Phase II
		NCT04346147	Spain	Recruiting	Phase II
		NCT04328285	France	Recruiting	Phase III
	Galidesivir	NCT03891420	Brazil	Recruiting	Phase I
	Danoprevir, ritonavir	NCT04345276	China	Recruiting	Phase IV
	Darunavir/cobicistat	NCT04252274	China	Recruiting	Phase III
	Virazole	NCT04356677	USA	Not yet recruiting	Phase I
	Clevudine	NCT04347915	Korea	Not yet recruiting	Phase II
	Nitazoxanide	NCT04348409	Brazil	Recruiting	NA
		NCT04359680	USA	Not yet recruiting	Phase III
	Hydroxychloroquine	NCT04329611	Canada	Recruiting	Phase III
		NCT04323631	Israel	Not yet recruiting	Early Phase I
		NCT04340544	Germany	Not yet recruiting	Phase III
		NCT04345692	USA	Recruiting	Phase III
		NCT04362332	Netherlands	Recruiting	Phase IV
Antibiotics	Azithromycin	NCT04332107	USA	Not yet recruiting	Phase III
	Doxycycline	NCT04371952	France	Not yet recruiting	Phase III
	Carrimycin	NCT04286503	China	Not yet recruiting	Phase IV
Decoy biomolecules	rhACE2, rhACE2	NCT04287686	China	Withdrawn	NA
		NCT04335136	Austria, Denmark, Germany	Recruiting	Phase II
	rbACE2	NCT04375046	Egypt	Not yet recruiting	Phase I

Table 1 (continued)

Group	Therapeutic agent	Example of clinical trials registered at ClinicalTrials.gov			
		CT number	Country	Recruitment status	Phase
	PUL-042, PUL-042	NCT04313023	USA	Not yet recruiting	Phase II
		NCT04312997	USA	Not yet recruiting	Phase II
	Rhu-pGSN	NCT04358406	USA	Not yet recruiting	Phase II
	Piclidenoson	NCT04333472	Israel	Not yet recruiting	Phase II
ACE inhibitors and AR blockers	Ramipril	NCT04366050	USA	Not yet recruiting	Phase II
	Valsartan	NCT04335786	Netherlands	Recruiting	Phase IV
	Losartan	NCT04335123	USA	Recruiting	Phase I
	Telmisartan	NCT04355936	Argentina	Recruiting	Phase II
		NCT04360551	USA	Not yet recruiting	Phase II
MSC and other cells	Cardiosphere-derived cells	NCT04338347	USA	Available	NA
	Dental pulp mesenchymal stem cells	NCT04302519	China	Not yet recruiting	Phase I
	Dental pulp stem cells	NCT04336254	China	Recruiting	Phase I/II
	MSC exosomes	NCT04276987	China	Not yet recruiting	Phase I
	MSC	NCT04252118	China	Recruiting	Phase I
		NCT04361942	Spain	Not yet recruiting	Phase II
		NCT04377334	Germany	Not yet recruiting	Phase II
	AD MSC	NCT04362189	USA	Not yet recruiting	Phase II
		NCT04352803	USA	Not yet recruiting	Phase I
		NCT04366323	Spain	Not yet recruiting	Phase I/II
	BM-MSC	NCT04346368	China	Not yet recruiting	Phase I/II
		NCT04345601	USA	Not yet recruiting	Early Phase I
	UC-MSC	NCT04355728	USA	Recruiting	Phase I/II
		NCT04273646	China	Not yet recruiting	NA
		NCT04333368	France	Recruiting	Phase I/II
		NCT04269525	China	Recruiting	Phase II
		NCT04339660	China	Recruiting	Phase I/II
		NCT04366271	Spain	Not yet recruiting	Phase II
	WJ-MSC	NCT04313322	Jordan	Recruiting	Phase I
Corticosteroids	Ciclesonide	NCT04330586	Korea	Not yet recruiting	Phase II
		NCT04381364	Sweden	Not yet recruiting	Phase II
	Budesonide	NCT04355637	Spain	Recruiting	Phase IV
	Dexamethasone	NCT04325061	Spain	Not yet recruiting	Phase IV
		NCT04360876	USA	Not yet recruiting	Phase II

Table 1 (continued)

Group	Therapeutic agent	Example of clinical trials registered at ClinicalTrials.gov			
		CT number	Country	Recruitment status	Phase
	Prednisone	NCT04344288	France	Recruiting	Phase II
	Prednisone vs. hydrocortisone	NCT04359511	France	Not yet recruiting	Phase III
	Methylprednisolone	NCT04273321	China	Suspended	NA
		NCT04274071	USA	Completed	NA
	Methylprednisolone sodium succinate	NCT04343729	Brazil	Recruiting	Phase II
Sedatives, antidepressants, neuroleptics	Chlorpromazine	NCT04366739	France	Not yet recruiting	Phase III
		NCT04354805	Egypt	Not yet recruiting	Phase I/II
	Thalidomide	NCT04273529	China	Not yet recruiting	Phase II
	Fluvoxamine	NCT04342663	USA	Recruiting	Phase II
	Fluoxetine	NCT04377308	USA	Recruiting	Phase IV
	Dexmedetomidine	NCT04358627	Spain	Not yet recruiting	NA
Others	Azoximer bromide	NCT0438177	Russia	Recruiting	Phase II/III
	Etoposide	NCT04356690	USA	Not yet recruiting	Phase II
	Bicalutamide	NCT04374279	USA	Not yet recruiting	Phase II
	Selinexor	NCT04349098	USA	Recruiting	Phase II
	Melphalan	NCT04380376	Russia	Recruiting	Phase II
	Bromhexine	NCT04355026	Slovenia	Recruiting	Phase IV
	N-acetylcysteine	NCT04374461	USA	Recruiting	Phase IV
	Sargramostim	NCT04326920	Belgium	Recruiting	Phase IV
	Angiotensin peptide (1-7) derived plasma	NCT04375124	Turkey	Recruiting	NA
	Defibrotide	NCT04335201	Italy	Not yet recruiting	Phase II
	Aviptadil	NCT04311697	USA	Not yet recruiting	Phase II
	Dornase alpha	NCT04355364	France	Recruiting	Phase III
	Nafamostat mesilate	NCT04352400	Italy	Not yet recruiting	Phase II/III
	Camostat mesilate	NCT04321096	Denmark	Not yet recruiting	Phase I/II
		NCT04353284	USA	Not yet recruiting	Phase II
	Almitrine	NCT04357457	France	Not yet recruiting	Phase III
	Sildenafil citrate	NCT04304313	China	Recruiting	Phase III
	Progesterone	NCT04365127	USA	Recruiting	Phase I
	Colchicine	NCT04375202	Italy	Recruiting	Phase II
		NCT04355143	USA	Recruiting	Phase II
	Tetrandrine	NCT04308317	China	Enrolling by invitation	Phase IV
	Vazegepant	NCT04346615	USA	Recruiting	Phase II/III

Table 1 (continued)

Group	Therapeutic agent	Example of clinical trials registered at ClinicalTrials.gov			
		CT number	Country	Recruitment status	Phase
	Dapagliflozin	NCT04350593	USA	Recruiting	Phase III
	Isotretinoin	NCT04361422	Egypt	Not yet recruiting	Phase III
	Deferoxamine	NCT04333550	Iran	Recruiting	Phase I/II
	SnPP protoporphyrin	NCT04371822	Egypt	Not yet recruiting	Phase I
	Ascorbic acid	NCT04363216	USA	Not yet recruiting	Phase II
	BACTEK-R	NCT04363814	Spain	Not yet Recruiting	Phase III
	Traditional Chinese medicine	NCT04323332	China	Not yet recruiting	Phase III
	Huaier granule	NCT04291053	China	Not yet recruiting	Phase II/III
Combined	Favipiravir, hydroxychloroquine	NCT04359615	Iran	Not yet recruiting	Phase IV
		NCT04376814	Iran	Enrolling by invitation	NA
	Favipiravir, tocilizumab	NCT04310228	China	Recruiting	NA
	Hydroxychloroquine, azithromycin	NCT04328272	Pakistan	Not yet Recruiting	Phase III
		NCT04329832	USA	Recruiting	Phase II
		NCT04359316	Iran	Not yet recruiting	Phase IV
	Hydroxychloroquine, nitazoxanide	NCT04361318	Egypt	Not yet recruiting	Phase II/III
	Hydroxychloroquine, azithromycin, tocilizumab	NCT04332094	Spain	Recruiting	Phase II
	Hydroxychloroquine vs. hydroxychloroquine, lopinavir/ritonavir vs. hydroxychloroquine, azithromycin	NCT04359095	Colombia	Not yet recruiting	Phase II/III
	Hydroxychloroquine, famotidine	NCT04370262	USA	Recruiting	Phase III
	Ivermectin, Nitazoxanide	NCT04360356	Egypt	Not yet recruiting	Phase II/III
	Lopinavir/ritonavir, ribavirin, interferon beta-1B	NCT04276688	China	Completed	Phase II
	Met-enkephalin, tridecactide	NCT04374032	Bosnia and Herzegovina	Recruiting	Phase II/III

ACE angiotensin-converting enzyme; *AR* angiotensin receptor; *DFPP* double-filtration plasmapheresis; *MSC* mesenchymal stem (stromal) cells; *AD MSC* adipose-derived MSC; *BM-MSC* bone marrow–derived MSC; *UC-MSC* umbilical cord–derived MSC; *WJ-MSC* Wharton jelly–derived MSC; *NK cells* natural killer cells; *rhACE2* recombinant human angiotensin-converting enzyme 2; *rbACE2* recombinant bacterial angiotensin-converting enzyme 2; *Rhu-pGSN* recombinant human plasma gelsolin

(AAK1) are endocytosis regulators. Baricitinib might inhibit SARS COV-2 entry by disruption of these regulators. Other JAK inhibitors such as fedratinib and ruxolitinib are also candidates for decreasing inflammatory cytokines in COVID-19 individuals [51]. Although JAK inhibitors have wide effects and can inhibit cytokine secretion such as IFN-α, more studies need to confirm their safety and efficiency [14].

Adoptive immunotherapy

Adoptive transfer of antigen-specific T cells has been developed for the treatment of cancers, autoimmunity, and viral infections including hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus (CMV) [24–26]. In this approach, anti-viral-specific T cell clones are generated, expanded, and purified in vitro [26]. It is shown that engineered SARS-specific CD8+ T cells had normal activity and function and may be a potential therapeutic tool for SARS infection [27]. Recently, it has been indicated that the number of CD8+ T cells decreased dramatically and the ratio of CD4+/CD8+ T cells increased during the SARS-CoV-2 infection. This decrease in the number of CD8+ lymphocytes has been correlated with the disease severity and clinical outcome [52]. It has also indicated that CD8+ T cells and the CD4+/CD8+ ratio decreased and increased respectively after the treatment. It seems that CD8+ T cells play an important role in COVID-19 and could be a potential biomarker of the disease [52, 53]. Due to these findings, adoptive transfer of COVID-19-specific CD8+ T cells may be an effective treatment strategy [28]. NK cells are innate immune cells that play a crucial role in host immune response after viral infections [54]. Preprinted studies indicated that NK cell population decreased remarkably during the disease [55, 56]. It has been indicated that during SARS-CoV-2 infection, increased amount of IL-6 inflammatory cytokine had negative correlation with the number of NK cells [52]. Thus, it is assumed that adoptive transfer of NK cells may have an effective therapeutic approach. Therefore, recently, an ongoing phase I clinical trial has been registered in which NK cell therapy in combination with conventional therapies for COVID-19 patients was proposed (NCT04280224). Altogether, it seems that cell-mediated immunity plays an important role in host immune response against SARS-CoV-2 [57].

Mesenchymal stromal cells

Persistence of inflammatory cytokines in COVID-19 patients leads to lung dysfunction and even death. Using corticosteroids for dampening cytokine storm suppresses immune system and makes delay in virus elimination [58].

Mesenchymal stromal cells (MSCs) are characterized with their immunomodulatory and anti-inflammatory properties [59, 60]. Because of these characteristics, they have been used for the treatment of various inflammatory and autoimmune disorders including diabetes, graft-versus-host disease (GvHD), and multiple sclerosis [59]. It is proven that MSCs and MSC extracellular vesicle (EV) infusion have beneficial effects in the treatment of virus-induced pneumonia by reducing the lung inflammation [61, 62]. EVs are stable, could distribute to the lungs, and have the same immunomodulatory and anti-inflammatory properties of parental MSCs [63]. MSCs decreased inflammatory cytokines and chemokines in animal model of avian influenza. They could also prevent immune cell infiltration into the lungs and improved alveolar injury [61]. Recently, there are studies evaluating allogenic MSCs and MSC-derived exosomes as potential therapeutic tools for reducing inflammation and improving COVID-19-related ARDS [47, 64]. It is indicated that adoptive transfer of allogenic umbilical cord mesenchymal stem cells (UC-MSCs) could inhibit inflammation and attenuate symptoms in patients with advanced COVID-19. Four days after cell therapy, patients are disconnected from the ventilator. UC-MSC therapy also elevated T cell numbers and boosted the immune system [58]. Administration of ACE negative MSCs to seven COVID-19 patients improved clinical symptoms with no side effects just 2 days after injection. The number of inflammatory cytokine secreting cells reduced significantly. Regulatory DC subpopulation (CD14+CD11c+CD11b^{mid}) elevated. The levels of IL-10 anti-inflammatory cytokine increased while TNF-α decreased [65]. Infusion of MSCs also induced lung tissue regeneration by modulating inflammatory microenvironment in COVID-19 patients [66]. There are several ongoing clinical trials using different sources of MSCs for the treatment of COVID-19 (Table 1). Taken together, MSC therapy could inhibit excessive immune system reaction, modulate inflammatory milieu, and prevent virus-mediated cytokine storm [65]. It seems that MSC therapy could be a novel therapeutic approach for the treatment of COVID-19 [64].

Nanomedicine

LIF (leukemia inhibitory factor) is one of the important cytokines to protect the respiratory system and promote lung homeostasis during viral infections [67, 68]. This cytokine modulates severe adverse events during ARDS [67]. Up to now, there is no study investigating the role of LIF in SARS-CoV-2 infection. However, in respiratory syncytial virus (RSV) model, it has been shown that overexpression of LIF enhanced the recovery of lungs during pneumonia. Neutralization of the LIF induced alveolar damage and chemokine secretion [69]. According to these data, LIF might also have protective effects in SARS-CoV-2 infection.

LIF nanoparticles (LIF-NPs) indicated clinical benefits in experimental autoimmune encephalomyelitis (EAE) animal models. LIF-NPs possessed immunomodulatory effects and increased self-tolerance in animal models for ARDS [70].

These inhalable NPs could be a novel strategy for lung tissue repair and cytokine storm inhibition [64]. Activation and polarization of macrophages play a major role in the initiation and intensity of inflammation, respectively, in ALI/ARDS. Peptide-coated gold nanoparticles could alleviate lung inflammation through inducing M1-to-M2 macrophage phenotype transition and increasing the anti-inflammatory cytokine (IL-10) in the lung of acute lung injury (ALI) mice [71].

Decoy biomolecules

As mentioned above, SARS-COV-2 attaches to ACE2 receptor to invade the host cells, particularly alveolar epithelial cells. SARS-CoV-2 spike protein has strong affinity to ACE2 receptor [72–74]. This attachment may enhance viral entry and replication [74, 75]. It is assumed that targeting this interaction and using soluble form of ACE2 could be a potential therapeutic approach [76]. Studies on COVID-19 indicated that ACE2 injection could competitively neutralize the virus and improve lung injury [77]. Recently, a novel therapeutic approach was developed based on soluble ACE2 interaction with the virus. It has been shown that human recombinant soluble ACE2 (hrsACE2) could inhibit SARS-CoV-2 from entering the host cells, decreasing the viral load in a dose-dependent manner. This molecule inhibits viral infection of human blood vessels and kidney organoids. These data indicated that hrsACE2 was effective in early-stage patients [78]. Since the inhibitory effects of hrsACE2 were not complete, it is preliminarily considered that the virus may use a second receptor or co-factor such as transmembrane protease serine 2 (TMPRSS2) [79]. In this regard, TMPRSS2 inhibitor was approved for clinical application in COVID-19 to inhibit the entry of virus [74].

Antiviral drugs

Remdesivir is claimed to be an option to treat COVID-19 [80]. It is a nucleoside analog and has broad-spectrum activities against RNA viruses such as MERS; remdesivir can effectively diminish the viral load in lung tissue infected with MERS-CoV and improve lung function in animal model [81]. The in vitro study revealed that, compared with ribavirin or favipiravir, remdesivir in combination with emetine showed the inhibition in viral yield that might achieve 64.9% [82]. Regarding its clinical application, Grein et al. reported the good improvement among severe COVID-19 cases (68%, $n = 53$) after treatment with remdesivir [83]. It also showed promising results in the treatment of a patient with COVID-19 in the USA [84]. However, its efficacy is doubted because, e.g., in a randomized, double-blind, placebo-controlled, multicenter trial, Wang et al. reported no statistically significant clinical benefits [85].

Chloroquine is a drug used to treat malaria [86]. It is taught that chloroquine has a great potential to treat COVID-19 [87]; chloroquine can prevent pH-dependent steps of the replication of several viruses such as SARS-CoV [88]. Additionally, chloroquine has immunomodulatory effects by suppressing the production/release of TNF-α and IL-6. It also might interfere with viral infection and replication, as an autophagy inhibitor [89]. In preprinted paper, Chen et al. showed that hydroxychloroquine use can shorten the time to clinical recovery in COVID-19 patients [90]. Gautret et al. claimed that the treatment of COVID-19 patients with hydroxychloroquine (chloroquine analog) caused the significant viral load reduction/disappearance [91]. However, other researchers did not reveal the same effect. Moreover, high-dose chloroquine diphosphate in combination with azithromycin or oseltamivir resulted in high rates of death and adverse cardiac events [92]. Clinicians also cautioned that the increased consumption of chloroquine and hydroxychloroquine can lead to their shortage that might create a problem for people suffering systemic lupus erythematosus, other rheumatological disorders, primary Sjögren syndrome, dermatological diseases, and antiphospholipid syndrome [93].

It has been previously reported that the protease inhibitors such as lopinavir and ritonavir, used to treat infection with human immunodeficiency virus (HIV) [94], could improve the outcome of MERS-CoV- [95] and SARS-CoV [96]–infected patients. Initially, lopinavir and ritonavir were hypothesized to inhibit the 3-chymotrypsin-like protease of SARS and MERS, and seemed to be associated with improved outcomes of patients with SARS in a non-randomized open-label trial. In a case report from Korea, it has been shown that the viral loads of a SARS-CoV-2 significantly decreased after lopinavir/ritonavir treatment [97]. However, it is controversial whether HIV protease inhibitors could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of SARS-CoV-2. HIV protease belongs to the aspartic protease family, whereas the two coronavirus proteases are from the cysteine protease family. Moreover, HIV protease inhibitors were specifically optimized to fit the C2 symmetry in the catalytic site of the HIV protease dimer; however, this C2-symmetric pocket is absent in coronavirus proteases. If HIV protease inhibitors alter host pathways to indirectly interfere with coronavirus infections, their potency remains a concern [98].

Favipiravir is a new type of RNA-dependent RNA polymerase inhibitor. Additionally, it is capable of blocking the replication of other RNA viruses [99]. Favipiravir is converted into an active phosphoribosylated form (favipiravir-RTP) in cells and is recognized as a substrate by viral RNA polymerase, therefore inhibiting RNA polymerase activity [100]. Favipiravir may have potential antiviral action on SARS-CoV-2, which is a RNA virus. In a clinical trial on favipiravir for the treatment of COVID-19, the preliminary results indicated that favipiravir had more potent antiviral action than lopinavir/ritonavir [101].

BCG vaccine

Bacillus Calmette-Guérin (BCG; weakened strain of *Mycobacterium bovis*) vaccination could have protective effects against COVID-19 infection. There are several mechanisms that ensure BCG-induced non-specific protection and are actively studied. BCG and viral antigens have similar molecular structure; so after vaccination, B and T cells can recognize both pathogen types. Moreover, BCG vaccination results in the so-called trained immunity—epigenetic reprogramming of innate immune cell types [102]. Monocytes of vaccinated individuals had higher expression of different surface markers of activation and synthesis of cytokines (IL-1β, IL-6, IFNγ, and TNF) in response to infection than those of non-vaccinated ones; so non-mycobacterium pathogens, e.g., staphylococci, yellow fever virus, and influenza, can be removed faster [103]. In several preprints, it is claimed that BCG vaccination program could reduce the number of SARS-CoV-2-infected individuals and their mortality [104, 105]. However, the WHO does not recommend BCG vaccination to prevent COVID-19 because there is still no direct evidence that it can protect against SARS-CoV-2 infection, and all related clinical trials are ongoing [106].

Corticosteroids

Corticosteroids are well-known with their immunosuppressive activity, which are essential to stop or delay the progression of the pneumonia and have been proved to be beneficial for the treatment of ARDS [107]. Additionally, corticosteroids have an anti-inflammatory effect to diminish systemic inflammation, reduce exudative fluid in the lung tissue, and inhibit further diffused alveolar damage, which can relieve hypoxemia which can protect the lungs effectively and prevent further progression of respiratory insufficiency [108]. The use of corticosteroids for the treatment of COVID-19 is controversial due to their negative impact on anti-viral immune responses [109]. However, it has been shown that corticosteroids could improve mortality in severe COVID-19 patients with systemic hyperinflammation [110]. It is supposed that patient selection, half-life, formulation, and dosage of the corticosteroids are important factors determining the clinical outcome. In this regard, a preprinted study indicated that in severe COVID-19 patients with ARDS early short-term and low dose of corticosteroid (methylprednisolone) improved clinical manifestation and long lesions [111].

Conclusion

Although it seems that antiviral drugs are effective in improving clinical manifestation and controlling the SARS-CoV-2 infection, until now, there is no definite treatment protocol for this novel virus infection. Lymphocytopenia alongside with excessive inflammation and cytokine storm followed by ARDS in these patients are still unsolved problems that cause severity of the disease [14]. Therefore, it is considered that immune response modulation and inflammation management are essential steps. Based on the abovementioned, more studies needed to be conducted on immunopathogenesis and immune response during the SARS-CoV-2 infection. In this regard, new therapeutic approaches including mesenchymal stromal cell therapy and immune cell therapy showed promising results.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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