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 (range 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
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 chemotactant 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 cytotoxic 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
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...
| Group | Therapeutic agent | Example of clinical trials registered at ClinicalTrials.gov |
|-------|-------------------|----------------------------------------------------------|
| 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 |
|       | Sarilumab | NCT04324073 France Recruiting Phase II/III |
|       | Avdoralimab | NCT04319367 France Recruiting Phase II |
|       | Gimsilumab | NCT04351243 USA Recruiting Phase II |
|       | Siltuximab | NCT04329650 Spain Recruiting Phase II |
|       | Bevacizumab | NCT04275414 China Recruiting Phase II/III |
|       | Eculizumab | NCT0428713 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 |
|       | Lenzihamab | NCT04351152 USA Recruiting Phase III |
|       | Leronlimab | NCT04343651 USA Recruiting Phase II |
|       | Ravulizumab | NCT04369469 USA Not yet recruiting Phase III |
|       | Nivolnab | NCT04343144 France Not yet recruiting Phase II |
|       | Meplazumab | NCT04275245 China Recruiting Phase I/II |
| 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 |
| TJ03234 | 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 | NCT04320236 | China | Recruiting | Phase III |
| IFN-α | NCT04350671 | Iran | Enrolling by invitation | Phase IV |
| Interferon beta-1A | NCT04293887 | China | Not yet recruiting | Early Phase I |
| Recombinant human interferon α1β | NCT04320238 | China | Recruiting | Phase III |
| Recombinant human interferon alpha-1b | NCT0431899 | USA | Recruiting | Phase II |
| Peginterferon lambda-1a | NCT04343976 | USA | Not yet recruiting | Phase II |
| Pegylated interferon lambda | NCT04324996 | Colombia | Not yet recruiting | Phase I |
| NK cells | NCT04280224 | China | Recruiting | Phase I |
| iPSC-derived NK cells | NCT04344548 | Colombia | Not yet recruiting | Phase I/II |
| 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 | NCT04362137 | UK | Recruiting | Phase III |
| Ruxolitinib | NCT04348071 | USA | Not yet recruiting | Phase II/III |
| | NCT04355793 | USA | Available | NA |
| | NCT0434714 | 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 | NCT04280588 | China | Recruiting | Phase II |
| Fingolimod | NCT04341675 | USA | Recruiting | Phase II |
| 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 II    |
| Antivirals      |             |         |                   |             |
| Remdesivir      | NCT04292899 | USA     | Recruiting         | Phase III   |
| Favipinavir     | NCT04336904 | Italy   | Active, not recruiting | Phase III   |
| Umifenovir      | NCT04350684 | Iran    | Enrolling by invitation | Phase IV   |
| Abidol hydrochloride vs. oseltamivir vs. lopinavir/ritonavir | NCT04330690 | Canada | Recruiting | Phase II |
| Lopinavir/ritonavir | NCT04307693 | Korea   | Recruiting         | Phase II    |
| 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    | NCT04359680 | USA     | Not yet recruiting | Phase III   |
| Hydroxychloroquine | NCT04329611 | Canada | Recruiting | Phase III |
| Antibiotics     |             |         |                   |             |
| Azithromycin    | NCT04332107 | USA     | Not yet recruiting | Phase III   |
| Doxycycline     | NCT04371952 | France  | Not yet recruiting | Phase III   |
| Carnimycin      | NCT04286503 | China   | Not yet recruiting | Phase IV    |
| Decoy biomolecules | rhACE2, rhACE2 | China   | Withdrawn           | NA          |
|                 | NCT04287686 | China   | Recruiting | Phase II |
|                 | NCT0435136 | Austria, Denmark, Germany | Not yet recruiting | Phase I |
|                 | NCT04375046 | Egypt   | Not yet recruiting | Phase I     |
| 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 |
| 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 |
| BM-MSC                                    |                                          | NCT04366323 | Spain   | Not yet recruiting | Phase I/II |
|                                          |                                          | NCT04346368 | China   | Not yet recruiting | Phase I/II |
| 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 |
| 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       |
| Methylprednisolone sodium succinate        | NCT04274071 | USA     | Completed          | NA       |
| Sedatives, antidepressants, neuroleptics   | Chlorpromazine | NCT04366739 | France | Not yet recruiting | Phase III |
|                                            | Etoposide | NCT04356690 | USA     | Not yet recruiting | Phase II |
|                                            | Thalidomide | NCT04273529 | Egypt  | Not yet recruiting | Phase I/II |
|                                            | Fluvoxamine | NCT04342663 | USA | Recruiting         | Phase II |
|                                            | Fluoxetine | NCT04377308 | USA | Recruiting         | Phase IV |
|                                            | Dexametomidine | 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 | NCT04349998 | 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 |
|                                            | Domase 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 |
| Group | Therapeutic agent | Example of clinical trials registered at ClinicalTrials.gov |
|-------|-------------------|----------------------------------------------------------|
|       | CT number         | Country         | Recruitment status | Phase |
|       | Dapagliflozin     | NCT04350593    | Recruiting         | Phase III |
|       | Isotretinoin      | NCT04361422    | Not yet recruiting | Phase III |
|       | Deferoxamine      | NCT04333550    | Recruiting         | Phase I/II |
|       | SnPP protoporphyrin | NCT04371822  | Not yet recruiting | Phase I |
|       | Ascorbic acid     | NCT04363216    | Not yet recruiting | Phase II |
|       | BACTEK-R          | NCT04363814    | Not Yet Recruiting | Phase III |
|       | Traditional Chinese medicine | NCT04323332 | China | Not yet recruiting | Phase III |
|       | Huaier granule    | NCT04291053    | Not yet recruiting | Phase II/III |
| Combined | Favipiravir, hydroxychloroquine | NCT04359615 | Iran | Not recruiting | Phase IV |
|       | Favipiravir, tocilizumab | NCT04310228  | China | Recruiting | NA |
|       | Hydroxychloroquine, azithromycin | NCT04328272 | Pakistan | Not yet Recruiting | Phase III |
|       | 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 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 a 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 phosphorylated 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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