

REVIEW

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# The role of mesenchymal stromal cells in immune modulation of COVID-19: focus on cytokine storm

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## Abstract

The outbreak of coronavirus disease 2019 (COVID-19) pandemic is quickly spreading all over the world. This virus, which is called SARS-CoV-2, has infected tens of thousands of people. Based on symptoms, the pathogenesis of acute respiratory illness is responsible for highly homogenous coronaviruses as well as other pathogens. Evidence suggests that high inflammation rates, oxidation, and overwhelming immune response probably contribute to pathology of COVID-19. COVID-19 causes cytokine storm, which subsequently leads to acute respiratory distress syndrome (ARDS), often ending up in the death of patients. Mesenchymal stem cells (MSCs) are multipotential stem cells that are recognized via self-renewal capacity, generation of clonal populations, and multilineage differentiation. MSCs are present in nearly all tissues of the body, playing an essential role in repair and generation of tissues. Furthermore, MSCs have broad immunoregulatory properties through the interaction of immune cells in both innate and adaptive immune systems, leading to immunosuppression of many effector activities. MSCs can reduce the cytokine storm produced by coronavirus infection. In a number of studies, the administration of these cells has been beneficial for COVID-19 patients. Also, MSCs may be able to improve pulmonary fibrosis and lung function. In this review, we will review the newest research findings regarding MSC-based immunomodulation in patients with COVID-19.

**Keywords:** Mesenchymal stromal cells, COVID-19, Immune regulatory, Cytokine storm

## Introduction

The city of Wuhan was the origin of coronavirus disease (COVID-19), a severe acute respiratory syndrome with SARS-CoV-2 as its causative agent. Presently, COVID-19 infection has spread to all continents of the world [1]. Due to unknown reasons, COVID-19 infection has been widely distributed in various geographical regions with high population densities [2]. Moreover, the profile of symptoms and severity of COVID-19 infection show extensive variation in different parts of the world [3].

Worldwide assessments suggest that only 3.4% of those infected with SARS-CoV-2 have perished as a result of COVID-19, which also shows high difference in various parts of the world [4].

Constant fever, non-productive cough, dyspnea, myalgia, fatigue, normal or reduced WBC counts, hyperferritinemia, and radiographic evidence of pneumonia are among the clinical signs of patients with COVID-19, which are similar to the symptoms of infection by other members of this family, namely SARS-CoV and the Middle East respiratory syndrome-related coronavirus (MERS-CoV) [5–7]. The mortality rate of the new coronavirus, known as SARS-CoV-2, is high because of insufficient knowledge about the pathogenesis of COVID-19, and no specific treatment has been recognized for it

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[8]. On the other hand, the response to COVID-19 infection can be overwhelmed in many patients. When SARS-CoV-2 enters into the lungs, it unleashes an immune response, attracting immune cells to the region attacked by the virus and resulting in localized inflammation [9]. In some cases, excessive or unchecked levels of cytokines are released that can be fatal due to an overreaction of the immune system, which is referred to as a cytokine storm [10]. The cytokine storm can trigger organ injury and cause edema, gas exchange dysfunction, acute respiratory distress syndrome (ARDS), acute cardiac injury, and secondary infection, which can be potentially fatal [11].

Consequently, the inhibition of cytokine storm is a main factor in the treatment of patients who are infected with SARS-CoV-2. Currently, available therapies for COVID-19 include non-specific antiviral drugs, antibiotics used for the treatment of secondary bacterial infections, sepsis, and reduction of inflammation [12]. A large number of anti-inflammatory medications have been developed, including NSAIDs, glucocorticoids, chloroquine/hydroxychloroquine, antagonists of inflammatory cytokines (such as IL-6R monoclonal antibodies, TNF inhibitors, IL-1 antagonists), and Janus kinase JAK inhibitors [13, 14]. However, in severe cases of ARDS, it is a difficult task to treat the cytokine storm induced by the virus. The findings suggest that stem cell-based therapy is applicable to treat infected patients.

### Mesenchymal stromal cells and their features

Mesenchymal stromal cells (MSCs) are the cells with the unique ability to exert suppressive and regulatory effects on the immune system [15]. MSCs have been the focus of research because evidence has indicated that MSCs are able to migrate to and return from damaged tissues, exercise potent anti-inflammatory and immune regulatory activities, support the regeneration and repair of tissues, resist against apoptosis, inhibit tissue fibrosis, and decrease tissue injury [16]. MSCs are able to migrate to site of lesion and differentiate into tissue-specific active cells such as lung, smooth muscle, and nerve cells [17]. Following intravenous or intra-arterial infusion of MSCs, these cells are primarily trapped in capillary beds of the liver and lungs [18]. MSC homing processes are not fully realized but are known to involve a variety of molecules such as chemokine receptors, including CCR2, CCR4, CCR7, CCR10, CXCR5, CXCR6, and CXCR4, adhesion proteins, and matrix metalloproteinase (MMPs), namely molecules also implicated in the well-known process of leukocyte extravasation [19, 20]. Hypoxia and inflammation are frequent indications of an injured tissue capable of affecting paracrine features of MSCs, which are mainly mediated via VEGF, FGF2, IGF-1, and HGF [21].

When MSCs are trapped in the lungs, a wide range of soluble mediators are secreted by them, including anti-microbial peptides, anti-inflammatory cytokines, extracellular vesicles, and angiogenic growth factors [22]. The release pattern of anti-inflammatory mediators is unique to the inflammatory lung environment, which is adjusted by differential damage and pathogen-associated molecular receptors that are expressed on MSCs [23], namely TLRs (toll-like receptors). As for COVID-19, TLRs are stimulated by viral unmethylated CpG-DNA (TLR9) as well as viral RNA (TLR3), leading to sequential cellular signaling pathways and the activation of MSCs [24].

On the other hand, inflammation leads to nuclear factor-kappa B (NF- $\kappa$ B) and c-Jun NH2-terminal kinase (JNK) signaling, which is also controlled through the factors secreted by MSCs. In addition, lung damage improves during the response of MSCs to oxidative stress, cytoprotection, and phosphoinositide 3-kinase/protein kinase B (PI3K / Akt) signaling pathway [25]. Administration of BM-MSCs alleviated lung injury in a preclinical study via potentiating the PI3K/Akt signaling pathway [26, 27].

For example, the release of IL-1ra through MSCs inhibits IL- $\alpha/\beta$  activity via generating TSG-6, which is followed by the downregulation of NF- $\kappa$ B signaling and reduced production of inflammatory cytokines. Secretion of prostaglandin E2 (PGE2) is another efficient way to decrease inflammation by MSCs, which is a function of IL-10 production as a strong anti-inflammatory cytokine. Khakoo et al. showed that MSCs prevent PKB signaling of target cells via a contact-dependent way [28].

MSCs encounter a complex setting specified by various chemical and physical stimuli while moving toward an injured tissue and the microenvironment impacts MSCs' behavior [29]. MSCs are able to release many types of cytokines through paracrine release or direct interaction with immune cells, which leads to immunomodulation [30]. These cells have the capacity to interact with immune cells in innate and adaptive immune systems [31]. Besides, MSC-mediated immunosuppression depends on the combined reaction of chemokines, inflammatory cytokines, and effector factors, as along with the microenvironment and the rate of inflammatory stimulus [32]. Owing to their powerful immunomodulatory ability, MSCs might have beneficial effects for preventing or attenuating the cytokine storm of SARS-CoV-2 infection [33, 34]. This paper tries to explain the significant role of MSCs in secreting important factors for immune regulation in COVID-19.

### The SARS-CoV-2 infection and cytokine storm

ARDS caused by cytokine storm is the main mortality factor in COVID-19 [35]. The lethally uncontrolled systemic inflammatory response is stimulated by the

secretion of a large number of pro-inflammatory cytokines such as interleukin (IL)-1 $\beta$ , IL-2, IL-6, IL-7, IL-12, IL-18, IL-33, interferon (IFN)- $\alpha$ , IFN- $\gamma$ , tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), granulocyte colony-stimulating factor (G-CSF), interferon- $\gamma$  inducible protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1- $\alpha$  (MIP1A), and transforming growth factor-beta (TGF- $\beta$ ) such as chemokines by immune effector cells within coronavirus infection (Fig. 1) [36–38].

Huang et al. reported the level of inflammatory factors among patients with COVID-19. They measured cytokines of patients with COVID-19 and indicated increasing levels of IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), IFN- $\gamma$ , G-CSF, IP10, MCP1, MIP1A, PDGF, TNF $\alpha$ , and vascular endothelial growth factor (VEGF) in their specimens, among which TNF $\alpha$  levels were higher in patients with severe disease. Remarkably, no significant difference was observed in serum IL-6 levels between ICU and non-ICU admitted patients [8]. Nevertheless, in a retrospective, multicenter cohort study, the same research group reported a significant elevation of IL-6 levels in patients not surviving COVID-19 as compared with survivors [39]. Several other reports have also confirmed increasing IL-6 levels among critically ill COVID-19 patients [24, 40]. Moreover, the result of another study demonstrated that a majority of severe COVID-19 patients in ICU had persistently elevated levels of ESR and CRP, as well as high levels of IL-6, TNF $\alpha$ , IL-1 $\beta$ , IL-8, and IL2R, and experienced ARDS, hypercoagulation, and disseminated intravascular coagulation (DIC) [13].

The cytokine storm was followed by ARDS and multiple organ failure, which causes death in severe cases of COVID-19. For example, the findings of Huang et al. showed that out of 41 infected patients who were admitted in the early stages, 6 patients died as a result of ARDS [8]. Like common acute viral infections, both humoral and cellular immunity are activated in COVID-19. Therefore, inhibition of cytokine storm may be the key to the treatment of COVID-19 patients.

### Immunomodulatory effects of MSCs

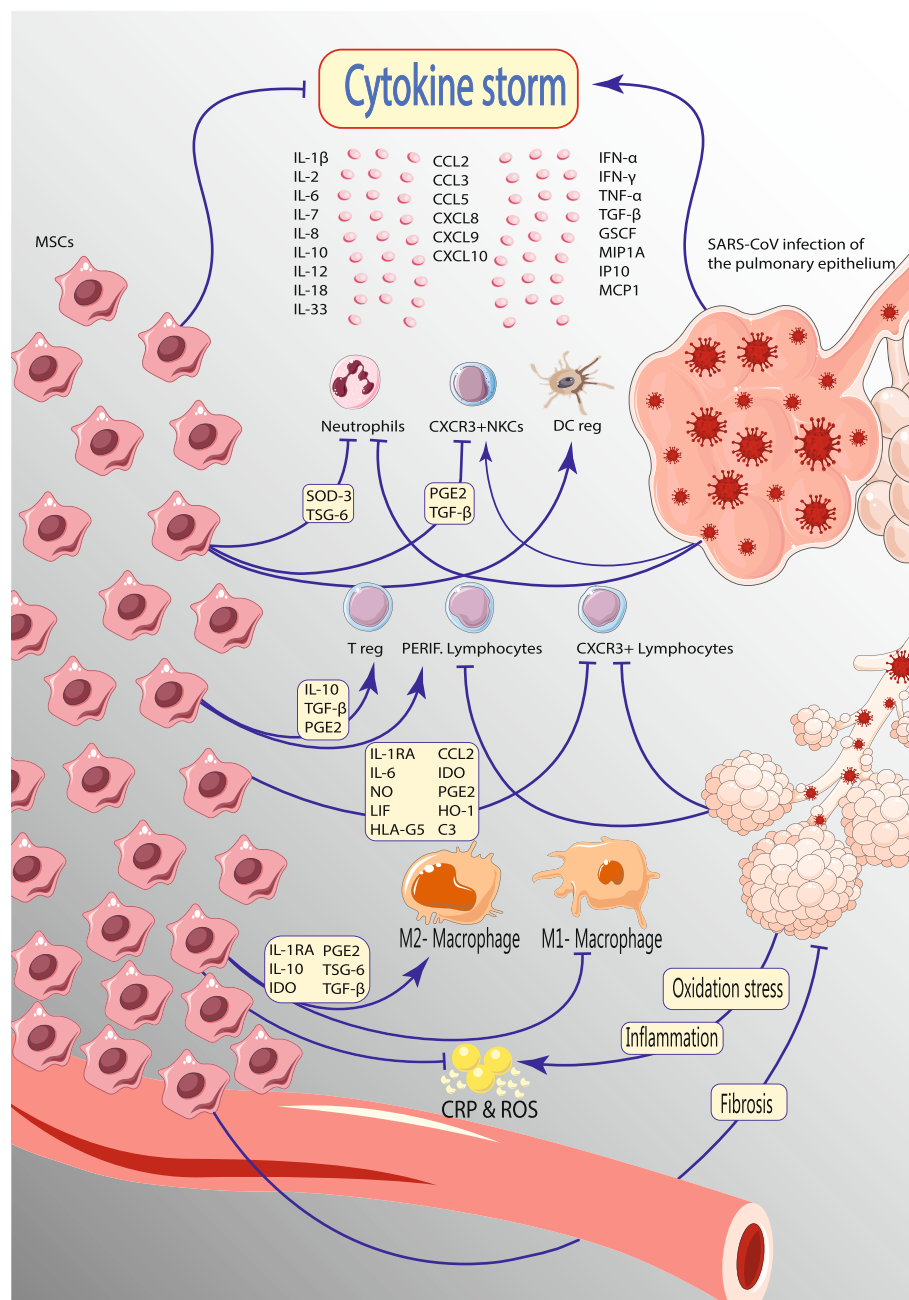
MSCs show remarkable immunomodulatory capacity and are implicated in both innate and adaptive immune systems. Former investigations on immune regulation of MSCs have concentrated on interactions of MSCs and B lymphocytes, natural killer (NK) cells, and dendritic cells (DC) [41]. Lately, the application of MSCs in repairing damaged tissue and adjustment of inflammatory reactions have become noticed considering macrophage and T lymphocyte regulation (Fig. 1) [16]. Interaction mechanisms have been shown to be dependent upon cell-cell contact along with the release of soluble immune factors

to induce MSC-regulated immunosuppression [42]. The cells that express immunosuppressive ligands like programmed death-ligand 1 (PD-L1) and Fas ligand (Fas-L) on their surface bind receptors present on the surface of immune cells, which leads to loss of function in immune cells [43, 44].

Several studies have revealed that the anti-inflammatory effect of MSCs can alleviate virus-induced lung injury and mortality in mice [45, 46]. Research has indicated that MSCs are able to significantly reduce acute lung injury by H9N2 and H5N1 viruses in mice by decreasing levels of pro-inflammatory cytokines and chemokines as well as diminishing the recruitment of inflammatory cells into the lungs [47, 48]. Applying MSCs to interfere in endotoxin (LPS)-induced acute lung injury of mice proved that MSCs can remarkably lead to reduction of inflammatory cell infiltration in lung tissue, alleviate inflammation, and improve the lung tissue from endotoxin-induced damage [49, 50].

Intravenous infusion of MSCs normally results in their accumulation within lungs, whereby they secrete many paracrine factors [51]. Evidence suggests that MSCs bind activated immune cells, which could keep them in close proximity and hence potentiate immunosuppressive effects [52]. Moreover, MSCs can also prevent the function of immune cells via releasing cytokines such as TGF- $\beta$ , HGF, and prostaglandin E2 (PGE2), as along with other anti-inflammatory factors [53]. For example, MSCs secrete TGF- $\beta$  and other factors promoting the induction of regulatory T lymphocytes (Tregs) and M2 macrophages, transmitting the immunosuppressive effects to other cells in order to activate various immunosuppressive mechanisms [54]. MSCs express TNF $\alpha$ -stimulated gene/protein 6 (TSG-6) that mediates the regulation of immune inflammation (Fig. 1) [55]. TSG-6 is another key factor with a crucial role in tissue repair activity of human MSCs that has been proven in mouse models of myocardial infarction, peritonitis, and acute corneal and lung injury [23, 56]. TSG-6 antagonizes the binding of CXCL8 to heparin via interaction with the GAG-binding site of CXCL8, which inhibits CXCL8-mediated chemotaxis of neutrophils. Furthermore, TSG-6 can prevent the extravasation of leukocytes (especially neutrophils and macrophages) at the inflammation site [57].

In COVID-19 cases, MSCs are able to increase the lymphocyte count and regulatory DCs to raise their antiviral characteristic which results in the decreased level of C-reactive protein and pro-inflammatory cytokines (IL-6, TNF $\alpha$ , IL-8, and so on) that are the main markers of inflammation and ROS to diminish the inflammation and oxidative stress [58]. On the other hand, MSCs can increase the level of IL-10 as an anti-inflammatory protein activating regulatory cells such as Tregs (Fig. 1)



**Fig. 1** Immunomodulation effect of mesenchymal stem cells on cytokines storm led by COVID-19. When SARS-CoV-2 enters the lungs, it attracts immune cells to infection areas and localizes inflammation. The lethal unchecked systemic inflammatory response is caused by the secretion of large levels of pro-inflammatory cytokines such as interleukin, interferons, chemokines, and other factors by immune effector cells in this infection. After MSC therapy, these cells reach the lung tissue and secrete factors that can modulate the immune system; they also can prevent ROS and even fibrosis of the lung tissue. Abbreviation: ARDS: acute respiratory distress syndrome, COVID-19: coronavirus disease 2019, CCL: chemokine (C-C motif) ligand, CXCL: chemokine (C-X-C motif) ligand, C3: Complement component 3, CRP: C-reactive protein, DC reg: regulatory dendritic cells, GSCF: granulocyte colony-stimulating factor, HO-1: Heme oxygenase-1, HLA-G5: human leukocyte antigen-G, IL: interleukin, IFN: interferon, IP10: IFN-γ-Inducible Protein 10, IL-1RA: interleukin-1 receptor antagonist, LIF: leukemia inhibitory factor, IDO: Indoleamine 2,3-dioxygenase, MSCs: mesenchymal stem cells, MIP1A: Macrophage Inflammatory Protein 1 Alpha, MCP1: *monocyte chemoattractant protein 1*, NKCs: natural killer cells, NO: nitric oxide, PERIF: peripheral, PGE2: Prostaglandin E<sub>2</sub>, ROS: *reactive oxygen species*, SARS-CoV: severe acute respiratory-associated coronavirus, SOD-3: *superoxide dismutase*, TSG-6: TNFα-stimulated gene-6, TGF-β: transforming growth factor, Treg: regulatory T

[59]. Therefore, MSCs play a central role in immune homeostasis by interacting with cytokines, chemokines, and cell surface molecules. Put together, all these immunomodulatory features contribute to the extensive potential of MSCs in clinical therapies.

#### MSC-based therapy in COVID-19 patients

The capacity of MSCs in multilineage differentiation and immunomodulation signifies that these somatic progenitor cells are extremely versatile in many therapeutic applications [60]. In fact, as of April 2016, more than 500 MSC-related clinical trials have been recorded on the NIH Clinical Trial Database (<https://clinicaltrials.gov/>) [61].

The safety and efficacy of transplanted MSCs for the alleviation of inflammatory lung diseases appears to be demonstrated in experimental models [62]. MSCs have been extensively used in cell-based therapies from basic research to clinical trials [63–65]. Inflammation has been recognized to affect several morbid processes in the pulmonary system, which include obstructive diseases such as chronic obstructive pulmonary diseases (COPD) and asthma, along with restrictive diseases such as idiopathic pulmonary fibrosis (IPF) and (ARDS). The acute and chronic lung injury observed in these diseases always involves abnormal immune activity and fibrosis either as a cause or a consequence [66, 67]. Similar to most cell therapies, MSC therapy could be useful in lung disease because it has been demonstrated that many intravenously delivered MSCs (80–90%) will rapidly reach the lungs when delivered through intravenous injection [68]. Following systemic administration, a majority of MSCs lodge in the pulmonary vascular bed through unknown interactions with the capillary endothelial cells. Tracking studies using labeled MSCs demonstrate that most MSCs are cleared within 24–48 h although there can be longer persistence of them in injured or inflamed lungs [69]. Several phase I/II clinical trials have been done to determine the safety of MSC infusions in patients afflicted with ARDS. In China, Zheng et al. observed no serious adverse events associated with MSC administration in 12 patients with ARDS [70]. Besides, Wilson et al. showed that a single intravenous MSC infusion up to  $10^6$  cells/kg was well tolerated in nine patients with moderate to severe ARDS [71]. Matthay and colleagues reported a prospective, double-blind, randomized clinical trial evaluating the effect of a single systemic dose of allogeneic bone marrow-derived MSCs ( $10^7$  cells/kg) in comparison with placebo (2:1 ratio). This research demonstrated that no hemodynamic or respiratory abnormal events associated with MSC infusion were seen over a follow-up period of 60 days and that the 28-day death rate was higher in the MSC group relative to the placebo, which was not remarkably different between the groups [72]. Furthermore, the novel avian-origin

influenza A (H7N9) virus with single-stranded RNA segments and COVID-19 has comparable complications (e.g., ARDS and lung failure), as well as corresponding multi-organ dysfunction together with inflammatory lung lesions and structural damage [73, 74]. Thus, advances in finding a therapeutic approach for H7N9 infection in human beings would be essential for treating COVID-19, especially severe ARDS-induced pneumonia that has presently provoked panic in every corner of the world [8, 75, 76]. Wilson et al. [71] have recently found that the administration of allogeneic MSCs for nine patients with ARDS did not lead to any particular adverse events such as cardiac arrhythmia, hypoxemia, and ventricular tachycardia. MSCs taken from menstrual blood have recently become attractive because of easy access, high rate of proliferation, and a non-invasive procedure lacking ethical issues [77–79]. Chen et al. argue that MSCs are capable of reducing inflammatory effects and avoiding cytokine storm. MSCs are an encouraging tool for treatment of acute pneumonia for prospective clinical application [14]. A recent study in China revealed that administration of intravenous injection of MSCs significantly improved the inflammation situation in severe COVID-19 patients. Ultimately, the patients with severe COVID-19 pneumonia survived the worst condition and entered recovery. Also, they said that the level of TNF $\alpha$  was significantly decreased, while IL-10 increased in MSC treatment group [80].

It should be mentioned that just a few cell therapy studies for ARDS and sepsis have reached their primary goals in randomized investigations [81, 82]. Scientists approve that targeted clinical research is essential whilst the first reports of MSC use for COVID-19 over the early phase of COVID-19 breakout in China have presented valuable clues that the therapeutic measures could be rather safe and efficient [83–85]. Few conclusions can be derived from these early studies because of the low number of subjects (typically  $\leq 10$ ) and the absence of adequate control groups [58, 80, 86]. Proper design of clinical trials and the observation of quality factors such as the documentation of patients, inclusion/exclusion criteria, classification of treatment approaches, primary and secondary statistics, timing and dosing of treatments, and comedication are immediately needed [85, 87]. While preliminary results may appear to be promising, the previous failures of innovative clinical research with MSCs as well as the low number of registered MSC products should be kept in mind [88–92]. Several problems have been identified in this respect, including failed upscaling of the product to large-scale supply and the absence of translation to efficient clinical application (e.g., cell expansion from the starting material, cell viability problems after thawing, and suboptimal delivery route) [82, 93–96], which could account for the

failure of different studies [88, 89]. A key issue for sustainable marketing would be the technological adequacy of the products and manufacturers in case some of the advanced phase II/III clinical studies show solid evidence supporting the approval of product in future (as discussed below) [90, 91]. The unprecedented dynamics of COVID-19 pandemic as well as the high number of deaths all over the world indicate that large-scale manufacturing and comprehensive logistic capacity are required to supply enough doses of high-quality cellular products in a reproducible and chronological manner [97]. SARS-CoV-2 enters into cells through the recognition of cellular transmembrane protease serine 2 (TMPRSS2) and angiotensin I converting enzyme 2 receptor (ACE2). ACE2 receptors have been detected in the heart (endothelium of coronary arteries, myocytes, fibroblasts, epicardial adipocytes), blood vessels (vascular endothelial and smooth cells), gut (intestinal epithelial cells), lung (tracheal and bronchial epithelial cells, type 2 pneumocytes, macrophages), kidney (luminal surface of tubular epithelial cells), brain, and testis [98]. In the human lung, the wide surface area of alveolar epithelial cells could account for the vulnerability of this organ to negative sequelae of COVID-19 infiltration. A main point is that ACE2 receptors are largely expressed in type II pneumocytes, i.e., small cylinder-shaped cells representing 5% of all pneumocytes [99] that are responsible for the generation of alveolar surfactant while acting as “stem” cells and progenitors of type I pneumocytes (95% of pneumocytes) performing gas exchanges in lungs [100–102].

SARS-Cov and SARS-CoV2 bind ACE2 receptors, leading to membrane fusion and virus penetration into the cell, thereby causing the downregulation of these receptors [98, 103]. In other words, the virus seems to enter into the cell together with the membrane receptor, which is subsequently removed from the external surface of the membrane.

The ACE2 gene lies on X chromosome and it has been shown that potential functional variants of ACE2 gene alter its transcriptional activity. Nevertheless, the pattern of population distribution influencing differential susceptibility to SARS-CoV-2 and the genetic origin of differential ACE2 expression and its functional implications among different populations are barely known [104]. Hypertension and diabetes mellitus (DM) are the most frequent comorbid conditions in COVID-19 and both are modulated by ACE2. Loss of ACE2 disturbs the balance of renin-angiotensin system, impairing vascular function and exacerbating cardiovascular complications of diabetes [105]. It appears that higher severity of COVID-19 among those suffering from high blood pressure and DM could be driven at least partially by pathological deviations from the ACE2 pathway. Accordingly, ACE2 appears to be crucial in the outcome of COVID-19 as well as the role it plays in susceptibility [106].

A major function of ACE2 has also been proven in inflammatory processes [107]. Genetic deficiency of ACE2 leads to upregulated expression of cytokines, inducing vascular inflammation in ApoE knockout mouse models [108]. In a recent research, ACE2 expression was related with several immune signatures such as markers of T cells, B cells, and NK cells, as well as interferon response in various human tissues [109]. These results suggest that ACE2 not only acts as a receptor of SARS-CoV-2 but takes part in mediation of post-infection downstream processes, including inflammatory responses. Furthermore, the gene expression profile of MSCs shows that ACE2 and TMPRSS2 are not expressed in these cells, so MSCs are not infected by a coronavirus. RNA-seq survey to identify 12,500 transplanted MSC during follow-up revealed that the cells had not been differentiated and remained ACE2 negative. ACE2 expression is observed in other tissues like the heart, liver, kidney, and digestive organs [80].

Such an expression pattern explains the reason why infected ICU patients are afflicted not only with ARDS but also other complications of multiple organ dysfunction syndromes [110]. The mechanisms that account for the improvement observed following MSC infusion in COVID-19 patients seem to be indicative of the strong anti-inflammatory activity of these cells [80]. Two recent studies from China on COVID-19 patients reveal a marked reversal of symptoms even in severe and critical conditions [58, 80]. Consequently, their clinical researches recognize a new remedial strategy and the presence of natural mechanisms capable of defeating acute inflammatory pneumonia. One study was a case report of a critically ill COVID-19 patient on a ventilator with progressive disease despite undergoing intensive therapy with markers showing liver injury. The patient was treated using allogeneic human umbilical cord MSC (hUC-MSC) and three intravenous infusions of  $5 \times 10^7$  hUC-MSC 3 days later. Within 4 days of the first cell infusion, the patient was detached from the ventilator and was able to walk. All the parameters under study such as circulating T lymphocytes returned to normal. Low levels of lymphocytes could be due to their sequestration within the inflamed lungs and tissues. No noticeable side effects were observed [58].

The second study [80] by Leng et al. demonstrated that intravenous MSC infusion prevents the immune system from overactivation and repairs the lung microenvironment affected by SARS-CoV-2 infection even in older patients. Intravenous infusion of MSCs normally results in the accumulation of these cells in the lungs and release of several paracrine factors [111]. MSC infusion is useful especially in older people infected with SARS-CoV-2 because this group is more susceptible to pneumonia from SARS-CoV-2, resulting in severe

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
1.	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-ADMSCs) to Provide Protection Against COVID-19 Sponsor: Hope Biosciences	NCT04348435	Texas, USA	Randomized, placebo-controlled, double-blinded, clinical trial to assess effectiveness of HB-allogeneic adipose-derived mesenchymal stem cells to supply immune support against coronavirus illness.N:100.	<ul style="list-style-type: none"> <li>Incidence of hospitalization for COVID-19</li> <li>Incidence of symptoms associated with COVID-19</li> </ul>	Enrolling by invitation April 16, 2020	Phase 2
2.	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-ADMSCs) to Provide Protection Against COVID-19 Sponsor: Hope Biosciences	NCT04349631	Texas, USA	Open label, single-center, and clinical trial to assess effectiveness of HB-ADMSCs to produce immune support against coronavirus illness.N:56.	<ul style="list-style-type: none"> <li>Incidence of hospitalization for COVID-19</li> <li>Incidence of symptoms associated with COVID-19</li> </ul>	Enrolling by invitation April 16, 2020	Phase 2
3.	Natural Killer Cell (CYNK-001) Infusions in Adults With COVID-19 (CYNK-001-COVID-19) (CYNK001COVID) Sponsor: Cellularity Incorporated	NCT04365101	?	Open label, randomized, phase I can assess the safety and effectivity of multiple doses of CYNK-001 (days 1, 4, and 7) in 14 patients. Phase II can utilize a randomized, open-label design: multiple doses of CYNK-001 are compared to the control group. Up to 72 patients are enclosed within the phase II clinical trial portion of the study with a 1:1 randomization ratio.	<ul style="list-style-type: none"> <li>Frequency and severity of adverse events (AE)</li> <li>Time to clearance of SARS-CoV-2</li> </ul>	Not yet recruiting April 28, 2020	Phase 1 Phase 2
4.	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV) (COVID_MSV) Sponsor: Red de Terapia Celular	NCT04361942	Valladolid, Spain	Double-blind, placebo-controlled, N:24, mesenchymal stromal cells, evaluate safety and efficacy of mesenchymal stromal cells from allogenic tissue for treatment of acute respiratory failure in patients with COVID-19.	<ul style="list-style-type: none"> <li>Proportion of patients who have achieved withdrawal of invasive mechanical ventilation</li> <li>Rate of mortality</li> </ul>	Recruiting April 24, 2020	Phase 2

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
5.	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019 Sponsor: Fuzhou General Hospital	NCT04371601	Fuzhou, Fujian, China	Open label, randomized, N: 60, control group: standard symptomatic treatments like antiviral (Oseltamivir), hormones, oxygen therapy, mechanical ventilation, and different accessory therapies; Experimental group: On the basis of the above-named standard symptomatic treatment and supportive medical aid, UC-MSCs were given at 106 / kg weight / time, once each 4 days for four times. iv infusion was given at intervals 3 days of 1st admission.	<ul style="list-style-type: none"> <li>• Changes of oxygenation index (PaO<sub>2</sub>/FIO<sub>2</sub>), blood gas test</li> </ul>	Active, not recruiting May 1, 2020	Early Phase 1
6.	Novel Adoptive Cellular Therapy With SARS-CoV-2 Specific T Cells in Patients With Severe COVID-19 Sponsor: KK Women's and Children's Hospital	NCT04351659	Singapore	Observational, novel adoptive cellular therapy with SARS-CoV-2-specific T cells in patients with severe COVID-19; N:8	<ul style="list-style-type: none"> <li>• Success rate in production of SARS-CoV-2 specific T cells from convalescent donor</li> </ul>	Recruiting April 17, 2020	....
7.	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19) Sponsor: Guangzhou Institute of Respiratory Disease	NCT04346368	Guangzhou, Guangdong, China	Randomized controlled trial, parallel, N = 20, BM-MSCs in severe patients with coronavirus disease 19.	<ul style="list-style-type: none"> <li>• Changes of oxygenation index (PaO<sub>2</sub>/FIO<sub>2</sub>)</li> <li>• Side effects in the BM-MSCs treatment group</li> </ul>	Not yet recruiting April 15, 2020	Phase 1 Phase 2
8.	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease) Sponsor: Baylor College of Medicine	NCT04345601	Houston, Texas, USA	Pilot study, N = 30, BM-MSCs for the treatment of SARS-CoV-2 induced acute respiratory failure	<ul style="list-style-type: none"> <li>• Incidence of unexpected adverse events</li> <li>• Improved oxygen saturations ≥93%</li> </ul>	Not yet recruiting April 20, 2020	Early Phase 1
9.	Phase I / II Clinical Study of Immunotherapy Based on Adoptive Cell Transfer as a Therapeutic Alternative for	NCT04344548	Bogota, Cundinamarca, Colombia	Open label, single group assignment, N = 10, allogeneic NK transfer	<ul style="list-style-type: none"> <li>• Adverse effects and safety</li> </ul>	Not yet recruiting April 14, 2020	Phase 1 Phase 2



**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
	Patients With COVID-19 in Colombia Sponsor: Universidad Nacional de Colombia						
10.	NK Cells Treatment for COVID-19 Sponsor: Xinxiang medical university	NCT04280224	Xinxiang, Henan, China	Open label, randomized, N = 30, natural killer cells treatment in pneumonia patients infected with 2019 novel coronavirus	<ul style="list-style-type: none"> <li>Improvement of clinical symptoms including duration of fever</li> <li>Improvement of clinical symptoms including respiratory frequency</li> </ul>	Recruiting February 21, 2020	Phase 1
11.	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS (STROMA-CoV2) Sponsors: Assistance Publique - Hôpitaux de Paris	NCT04333368	Paris, France	Triple, randomized N = 60 patients, 20 patients will be cell-treated whereas the remaining 40 patients will be injected with a placebo in addition to the standard of care.	<ul style="list-style-type: none"> <li>Respiratory efficacy evaluated by the increase in PaO<sub>2</sub>/FIO<sub>2</sub> ratio from baseline to day 7 in the experimental group compared with the placebo group [time frame: from baseline to day 7]</li> </ul>	Not yet recruiting April 3, 2020	Phase 1 Phase 2
12.	ASC Therapy for Patients With Severe Respiratory COVID-19 (ASC COVID-19) Sponsors: Rigshospitalet, Denmark	NCT04341610	Copenhagen, Denmark	Double-blind placebo-controlled, randomized, N = 40 participants, allogeneic adipose-derived, mesenchymal stem cells or placebo will be injected to COVID-19 patients having severe pulmonary dysfunction.	<ul style="list-style-type: none"> <li>Changes in clinical critical treatment index [time frame: day 7 from randomization]</li> </ul>	Not yet recruiting April 10, 2020	Phase 1 Phase 2
13.	Safety and Efficacy of CAStem for Severe COVID-19 Associated With/Without ARDS Sponsors: Chinese Academy of Sciences	NCT04331613	Beijing, China	Open label, single group, CAStem will be injected to severe COVID-19 associated respiratory distress syndrome (ARDS), CAStem will be administered iv route.	<ul style="list-style-type: none"> <li>Adverse reaction (AE) and severe adverse reaction (SAE)</li> <li>Frequency of adverse reaction (AE) and severe adverse reaction (SAE) within 28 days after treatment</li> <li>Changes of lung imaging examinations</li> <li>Evaluation by chest CT</li> </ul>	Recruiting April 3, 2020	Phase 1 Phase 2
14.	A Phase I/II Study of Universal Off-the-shelf NK/G2D-ACE2 CAR-NK Cells for Therapy of	NCT04324996	Chongqing, China	Interventional, quadruple/randomized, a phase I/II study of	<ul style="list-style-type: none"> <li>Clinical response [time frame: up to 28 days]</li> <li>Side effects in the</li> </ul>	Recruiting, March 27, 2020	Phase 1 Phase 2

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
	COVID-19 Sponsors: Chongqing Public Health Medical Center			universal off-the-shelf NKG2D-ACE2 CAR-NK cells secreting IL15 super agonist and GM-CSF-neutralizing scFv for treatment of COVID-19	treatment group [time frame: up to 28 days]		
15.	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia Sponsors: Puren Hospital Affiliated to Wuhan University of Science and Technology	NCT04339660	Wuhan, Hubei, China	Triple, randomized, N = 30 Human mesenchymal stem cells in the treatment of COVID-19 pneumonia	<ul style="list-style-type: none"> <li>The immune function (TNF<math>\alpha</math>, IL-1<math>\beta</math>, IL-6, TGF-<math>\beta</math>, IL-8, PCT, CRP)</li> <li>Blood oxygen saturation</li> </ul>	Recruiting April 9, 2020	Phase 1 Phase 2
16.	Stem Cell Educator Therapy Treat the Viral Inflammation Caused by Severe Acute Respiratory Syndrome Coronavirus 2 Sponsor: Tianhe Stem Cell Biotechnologies Inc.	NCT04299152	?	Randomized = 20 Two-arm, partially masked, single center clinical study to assess the safety, feasibility, and efficacy of SCE therapy for the treatment of patients with SARS-CoV-2.	<ul style="list-style-type: none"> <li>Determine the number of COVID-19 patients who were unable to complete SCE therapy</li> </ul>	Not yet recruiting March 6, 2020	Phase 2
17.	Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019(COVID-19) Sponsors: Beijing 302 Hospital	NCT04288102	Hubei, China	Prospective, double- blind, multicenter, randomized trial N = 60 severe COVID-19 patients randomized 2:1 to 3 iv doses of mesenchymal stem cells (MSCs) or placebo (saline).	<ul style="list-style-type: none"> <li>Improvement time of clinical critical treatment index within 28 days</li> <li>Side effects in the MSCs treatment group</li> </ul>	Recruiting; August 31, 2020/ December 31, 2020	Phase 2
18.	Therapy for Pneumonia Patients infected by 2019 Novel Coronavirus Sponsors: Puren Hospital Affiliated to Wuhan University of Science and Technology	NCT04293692	China, Hubei	Triple-blinded RCT. N = 48 with moderate to severe COVID-19 randomized to UC- MSCs or placebo	<ul style="list-style-type: none"> <li>Size of lesion area by chest imaging</li> <li>Blood oxygen saturation</li> </ul>	Recruiting; May 12, 2020/ Feb 1, 2021	Not Applicable
19.	Clinical Trial for Human Mesenchymal Stem Cells in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19) Sponsor: Chinese PLA General Hospital	ChiCTR2000030138	Hainan, China	Randomized, double- blind, placebo- controlled trial N = 60 randomized to human umbilical cord mesenchymal stem cells (UC-MSC),	<ul style="list-style-type: none"> <li>Clinical index</li> </ul>	Not yet recruiting; From 2020-02-24 to 2020-05-31	Phase 2

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
20.	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With 2019 Novel Coronavirus Sponsors: Beijing 302 Hospital	NCT04252118	China	or placebo in COVID-19. Open-label, non-randomized intervention study N = 20 patients with COVID-19 Treatment: N = 10 treated with MSN N = 10 treated with conventional treatment.	<ul style="list-style-type: none"> <li>• Size of lesion area by chest radiograph or CT (time frame day 28)</li> <li>• Side effects day (time frame day 180)</li> </ul>	Recruiting; Dec 2020/ December, 2021	Phase 1
21.	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia Sponsors: Ruijin Hospital	NCT04276987	China	Open-label pilot study N = 30 with severe COVID-19. Single group assignment	<ul style="list-style-type: none"> <li>• Adverse reactions</li> <li>• Time to clinical improvement (28 days)</li> </ul>	Not yet recruiting; Estimated study completion: July 31, 2020	Phase 1
22.	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia Sponsor: Wuhan Union Hospital, China	NCT04273646	China, Hubei	Open-label, randomized study N = 48 with severe COVID-19; Randomized to stem cell therapy or placebo	<ul style="list-style-type: none"> <li>• Pneumonia severity index</li> <li>• Oxygenation index (PaO<sub>2</sub>/FIO<sub>2</sub>)</li> </ul>	Not yet recruiting; June 30,2020/February 15, 2022	Not Applicable
23.	Safety and efficacy of umbilical cord blood mononuclear cells conditioned medium in the treatment of severe and critically novel coronavirus pneumonia (COVID-19): a randomized controlled trial Sponsor: Xiangyang 1st People's Hospital	ChiCTR2000029569	China, Hubei	Open label N = 30 with severe and critical COVID-19. Randomized to stem cell or conventional treatment.	<ul style="list-style-type: none"> <li>• PSI</li> </ul>	Not recruiting From 2020-02-05 to 2021-04-30	0
24.	Umbilical Cord(UO)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus (nCoV) Pneumonia Sponsor: ZhiYong Peng	NCT04269525	China, Hubei	Open label N = 10, serious or critical COVID-19	<ul style="list-style-type: none"> <li>• Oxygenation index day 14</li> <li>• Partial arterial oxygen pressure (PaO<sub>2</sub>) / oxygen concentration (FIO<sub>2</sub>)</li> </ul>	Recruiting; April 30, 2020/ Sept 30, 2020	Phase 2
25.	Clinical Study for Human Menstrual Blood-Derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) Sponsor: The First Affiliated Hospital, College of Medicine, Zhejiang	ChiCTR2000029606	Zhejiang, China	Open-label, 5-arm study. Critically ill patients treated with stem cells, conventional treatment, artificial liver therapy, artificial liver therapy + stem	<ul style="list-style-type: none"> <li>• Mortality in patients</li> </ul>	Recruiting; From 2020-01-15 to 2022-12-31	0

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
	University			cells, or conventional treatment			
26.	Canceled by the investigator Clinical Study for Umbilical Cord Blood Mononuclear Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) Sponsor: Guangzhou reborn health management consultation co., LTD	ChiCTR2000029812	Guangdong, China	Open label, N = 60 patients with COVID-19 randomized to umbilical cord blood mononuclear cells or conventional treatment	• Time to disease recovery	Not recruiting; From 2020-02-20 to 2021-02-20	0
27.	NK Cells Combined with Cord Blood Mesenchymal Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) Sponsor: Guangzhou Reborn Health Management Consultation Co., LTD	ChiCTR2000029817	Guangdong, china	Open label, N = 60 patients with COVID-19 randomized to high-dose NK cells, and mesenchymal stem cells, conventional dose NK cells and mesenchymal stem cells, or preventive dose NK cells and mesenchymal stem cells.	• Time to disease recovery	Not recruiting; From 2020-02-20 to 2021-02-20	0
28.	Canceled by the investigator Clinical Study for Umbilical Cord Blood Plasma in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) Sponsor: Guangzhou reborn health management consultation co., LTD	ChiCTR2000029818	Guangdong, china	Open label, N = 60 patients with COVID-19 randomized to high-dose NK cells, and mesenchymal stem cells, conventional dose NK cells and mesenchymal stem cells, or preventive dose NK cells and mesenchymal stem cells.	• Time to disease recovery	Not recruiting; From 2020-02-20 to 2021-02-20	0
29.	Clinical trials of mesenchymal stem cells for the treatment of pneumonitis caused by novel coronavirus pneumonia (COVID-19) Sponsor: Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences	ChiCTR2000029990	Beijing, Hubei, Shanghai	N = 120, severe COVID-19 randomized to MSCs or saline	• Improved respiratory system function (blood oxygen saturation) recovery time	Recruiting; From 2020-01-30 to 2020-03-31	Phase 1-2
30.	Umbilical cord Wharton's Jelly derived mesenchymal stem	ChiCTR2000030088	Beijing, China	Type of study not stated. Blinding not	• The nucleic acid of the novel coronavirus is	Not yet recruiting; From 2020-03-01 to	0

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
	cells in the treatment of severe novel coronavirus pneumonia (COVID-19) Sponsor: The Sixth Medical Center of PLA General Hospital			stated N = 40 with critical COVID-19. Treatment: stem cells (n = 20) 40 ml saline (n = 20)	negative • CT scan of ground-glass shadow disappeared	2021-12-31	
31.	Safety and effectiveness of human umbilical cord mesenchymal stem cells in the treatment of acute respiratory distress syndrome of severe novel coronavirus pneumonia (COVID-19) Sponsor: The First Affiliated Hospital of Nanchang University	ChiCTR2000030116	Jiangxi, China	N = 16 with critical COVID-19; different stem cell doses	• Time to leave ventilator on day 28 after receiving MSCs infusion	Recruiting; From 2020-02-01 to 2020-08-31	N/A
32.	Canceled by the investigator Clinical study of mesenchymal stem cells in treating severe novel coronavirus pneumonia (COVID-19) Sponsor: The First Affiliated Hospital of Nanchang University	ChiCTR2000030224	Hubei, China	Clinical study, open label Severe or critical COVID-19 patients; N = 32 stratified severity and randomized to stem cells or injection with saline	• Several primary endpoints—not specified	Not yet recruiting; From 2020-02-14 to 2020-05-31	N/A
33.	Umbilical cord mesenchymal stem cells (hUC-MSCs) in the treatment of high risk novel coronavirus pneumonia (COVID-19) patients Sponsor: Nanjing Second Hospital	ChiCTR2000030300	Jiangsu, China	A single-center, single-arm, prospective, open clinical study N = 9. UC-MSCs will be injected to COVID-19 patients.	• Time to disease recovery; • Exacerbation (transfer to RICU) time	Recruiting; From 2020-02-19 to 2021-02-20	Phase 1
34.	Stem Cell Educator Therapy Treat the Viral Inflammation Caused by Severe Acute Respiratory Syndrome Coronavirus 2 Sponsor: Tianhe Stem Cell Biotechnologies Inc.	NCT04299152	?	This is a prospective, two-arm, partially masked, single-center clinical study. N = 20 patients with SARS-CoV-2 undergoing either stem cell therapy or conventional treatment	• Determine the number of COVID-19 patients who were unable to complete SCE therapy • The feasibility will be evaluated by the number of COVID-19 patients who were unable to complete SCE therapy	Not yet recruiting; Nov 2020	Phase 2
35.	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells Sponsor: CAR-T (Shanghai) Biotechnology Co., Ltd.	NCT04302519	?	Single-arm study N = 24. Patients with severe COVID-19 assigned to stem cell therapy.	• Disappear time of ground-glass shadow in the lungs [time frame: 14 days]	Not yet recruiting; July 2021	phase 1

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
36.	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells Sponsor: Stem Cells Arabia	NCT04313322	Jordan	Single-arm study N = 5 with COVID-19	<ul style="list-style-type: none"> <li>Improvement of clinical symptoms;</li> <li>Adverse events;</li> <li>Viral RNA</li> </ul>	Recruiting. Sept 2020	Phase 1
37.	NestCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE) Sponsor: Azidus Brazil	NCT04315987	Not stated	N = 24 patients	<ul style="list-style-type: none"> <li>Disappear time of ground-glass shadow in the lungs</li> </ul>	Not yet recruiting. June 2020	Phase 1–2
38.	Study the effect of intravenous injection of dental pulp mesenchymal stem cells in treatment of patients with COVID-19 pneumonia Sponsor: Kerman University of Medical Sciences	IRCT20140911019125N6	Iran, Kerman	Clinical trial without control group, community based, not blinded, non-randomized controlled study. Dental pulp mesenchymal stem cells will be injected intravenously at one time.	<ul style="list-style-type: none"> <li>Pulmonary condition</li> <li>Expression of nucleic acid of virus</li> <li>Lymphocyte count</li> <li>Patients clinical signs</li> </ul>	Recruiting, 2020-04-04,	Phase 2
39.	Evaluation of the efficacy and safety of cord-derived mesenchymal stem cell transplantation in the treatment of COVID-19 Sponsor: MOM research and innovation center	IRCT20140528017891N8	Iran, Tehran	This study was a parallel randomized controlled clinical trial study design. The sample size of the study is 10 corona virus patients that will be assigned to intervention and control groups using simple randomization method.	<ul style="list-style-type: none"> <li>Death</li> <li>Evaluation of Pneumonia Severity Index</li> <li>Evaluation of oxygen supply index</li> <li>C- Reactive protein</li> <li>Pro-calcitonin</li> <li>Lymphocyte count</li> <li>Counting of CD3 +, CD4 + and CD8 + T cells</li> <li>CD4 + / CD8 ratio</li> <li>Improve pneumonia evaluated by CT scan</li> </ul>	Recruitment complete, 2020-03-24	Phase 3
40.	Mesenchymal stem cell utilization in reducing complications and enhancing pneumonia healing in patients infected with 2019-nCoV (phase I clinical trial) Sponsor: Bagheiatallah University of Medical Sciences	IRCT20200325046860N2	Iran, Tehran	Experimental: mesenchymal stem cell (MSC) treatment group conventional treatment plus MSC participants will receive conventional treatment plus 3 times of MSCs (7.0 × 10E7 MSCs intravenously at day 0, day 3, day 6), 5	<ul style="list-style-type: none"> <li>Respiratory function of patients</li> </ul>	Recruitment complete, 2020-04-01	Phase 1

**Table 1** Overview of planned or ongoing studies of cell therapy for the treatment of COVID-19 (Continued)

NO	Title and sponsor	Trial ID	Location	Design	Primary outcome	Recruitment status	Phase
41.	A Comparison Study on Safety & Efficacy of Repeated Intravenous Infusion of Allogeneic Mesenchymal Stem Cell from Different Sources in ARDS Patients: A Randomized, Double Blind, Clinical Trial Phase II Sponsor: Bagheiatallah University of Medical Sciences	IRCT20080901001165N44	Iran, Tehran	patients, clinical trial phase I No intervention: conventional control group without MSC therapy but conventional treatment should be received. A uncontrolled, parallel, double-blind, randomized, clinical trial, phase II 4 groups, 3 patients in each group, totally 12 patients 4 cell interventional groups 12 months follow-up	<ul style="list-style-type: none"> <li>Numbers of patients occurred any unexpected severe adverse events (including all-cause deaths)</li> </ul>	Recruiting, 2020-03-29	Phase 1-2
42.	Mesenchymal Stem Cell Therapy for Acute Respiratory Distress Syndrome in Coronavirus Infection: A Phase 2-3 Clinical Trial Sponsor: Iranian academic center for education culture and research	IRCT20200217046526N2	Iran, Tehran	A controlled randomized clinical trial phase 2-3	<ul style="list-style-type: none"> <li>Adverse events assessment</li> <li>Blood oxygen saturation</li> </ul>	Recruiting, 2020-04-05	Phase 2-3
43.	Cell therapy in patients with coronavirus19 using mesenchymal stem cells Sponsor: Barket Pharmaceutical Group	IRCT20190717044241N2	Iran, Tehran	One group with 10 uncontrolled patients, Phase I clinical trial	<ul style="list-style-type: none"> <li>Clinical response</li> <li>partial arterial oxygen pressure (PaO<sub>2</sub>) &amp; oxygen concentration (FiO<sub>2</sub>)</li> </ul>	Recruiting, 2020-04-20	Phase 1

respiratory distress and mortality because of immunosenescence [112–114]. It is proved that the intravenous infusion of MSCs is a safe and efficient orientation for treating patients infected by COVID-19 pneumonia, including older people with severe pneumonia [115].

Nowadays, several clinical trials using stem cell therapy to treat the coronavirus have been recorded from China, Iran, USA, Columbia, France, Denmark, Jordan, and Saudi Arabia, which are listed at [www.clinicaltrials.gov](http://www.clinicaltrials.gov), [www.chictr.org](http://www.chictr.org), [www.irct.ir](http://www.irct.ir) and summarized in Table 1.

### Conclusion and future perspective

Given the prevalence of COVID-19 and its complications such as cytokine storm, which is followed by ARDS and death of patients, finding a way to treat and improve the patients is of high importance [116]. As mentioned in this paper, there is no specific therapy for this virus and supportive therapies as well as non-specific antiviral drugs are mainly used for this purpose. Today, cell therapy is a modern method for treating a variety of diseases and several studies have been conducted in recent months to treat the SARS-CoV-2 virus using stem cells, suggesting the application of MSCs or immune cells such as NK cells [33, 117, 118]. According to research on MSC-based therapy, the safety and immunomodulatory role of MSCs in ARDS have been approved [82]. MSCs can secrete factors that improve the lung micro-environment, inhibit immune system overactivation, promote tissue repair, rejuvenate alveolar epithelial cells, inhibit pulmonary counteracting fibrosis, or improve function in damaged lung tissue because of SARS-CoV-2 infection [119, 120].

Many issues related to the application of MSCs, including the ideal dose and optimum timing of MSC delivery, should be further explored. In several animal models of human diseases, the use of secretory exosomes from MSCs has been claimed to mimic the beneficial effects of MSCs in antiviral therapy for influenza virus, reducing virus replication in lungs and virus-induced release of pro-inflammatory cytokines [121, 122]. Experimental studies and ongoing randomized trials will play an essential role in the clarification of the therapeutic potential of MSCs, which further our understanding of how MSCs interact with lung tissue infected by SARS-CoV-2.

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### Authors' contributions

MK, JV, and MS contributed to the concept of the review. MK, JV, and MS were responsible for the reference selection and writing of the manuscript. MK and MS contributed to the critical review of the manuscript. All authors read and approved the final manuscript.

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### Consent for publication

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### Competing interests

The authors declare that they have no competing interests.

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