


The critical role of mesenchymal stromal/stem cell therapy in COVID-19 patients: An updated review

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New coronavirus disease 2019 (COVID-19), as a pandemic disaster, has drawn the attention of researchers in various fields to discover suitable therapeutic approaches for the management of COVID-19 patients. Currently, there are many worries about the rapid spread of COVID-19; there is no approved treatment for this infectious disease, despite many efforts to develop therapeutic procedures for COVID-19. Emerging evidence shows that mesenchymal stromal/stem cell (MSC) therapy can be a suitable option for the management of COVID-19. These cells have many biological features (including the potential of differentiation, high safety and effectiveness, secretion of trophic factors and immunoregulatory features) that make them suitable for the treatment of various diseases. However, some studies have questioned the positive role of MSC therapy in the treatment of COVID-19. Accordingly, in this paper, we will focus on the therapeutic impacts of MSCs and their critical role in cytokine storm of COVID-19 patients.

KEYWORDS

cytokine storm, immunoregulatory, mesenchymal stem cell, new coronavirus disease 2019, pneumonia

1 | INTRODUCTION

New coronavirus disease 2019 (COVID-19) is regarded as a pandemic disaster.¹ As of 1 August 2021, the outbreak of COVID-19 generated 171 474 925 confirmed cases, including 3 565 330 deaths worldwide. There is accumulating evidence that shows this virus identifies the angiotensin I converting enzyme 2 (ACE2) receptor via its spike protein, fusing with host cells. Furthermore, this virus enters the host cell and spreads to other body parts by priming the spike protein via cellular transmembrane protease serine 2 (TMPRSS2).^{2,3} In lung alveolar type II cells and capillary endothelial cells, the expression level of the ACE2 receptor and TMPRSS2 is high.^{3,4} Thus, severe respiratory failure is considered the main symptom of COVID-19.

After infection and the occurrence of cytokine storm, the level of several proinflammatory cytokines, such as macrophage inflammatory

protein-1 alpha (MIP1A), interleukin 2 (IL-2), IL-6, IL-1 β , IL-7, monocyte chemoattractant protein 1 (MCP-1), interferon-inducible protein 10 (IP-10) and tumour necrosis factor α (TNF- α), increases. By increasing these proinflammatory cytokines, acute respiratory distress, edema and other infections occur.^{5,6} Currently, for the diagnosis of COVID-19, some methods, such as reverse transcriptase-polymerase chain reaction (RT-PCR), real-time RT-PCR and reverse transcription loop-mediated isothermal amplification (RT-LAMP), are employed.^{7,8}

Currently, there are many worries about the rapid spread of COVID-19; there is no approved treatment for this infectious disease, despite many efforts to develop therapeutic procedures. Several studies have suggested various therapeutic options for the management of this pandemic; in this regard, choosing the most effective option is necessary to end this pandemic. Among these investigated options, mesenchymal stromal/stem cell (MSC) therapy has been suggested to be an appropriate choice to manage COVID-19.⁹⁻¹¹ Besides, several vaccines have been developed to protect against this virus, including

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Pfizer, Covishield, AstraZeneca, Sputnik V, Janssen, Moderna, Sinopharm and Sinovac-CoronaVac.¹²

MSCs, as multipotent stem cells, can be isolated and expanded from a range of tissue sources, such as bone marrow (BM), amniotic membrane, fat tissue, umbilical cord and perinatal tissues (PTs).^{13,14} Therapeutic MSCs were initially isolated from BM in 1994. With growing interest in MSCs in clinical trials, the contribution of adipose tissue (AT) and PT became evident.¹⁵ In a preclinical setting, MSCs demonstrate several biological properties (including the potential of differentiation, high safety and effectiveness, secretion of trophic factors and immunoregulatory features) that make them suitable for the treatment of various diseases.¹⁶⁻¹⁸ Regarding the potential of MSCs in the modulation of the immune system, these cells could be used as an appropriate treatment for patients with COVID-19.¹⁹⁻²¹ However, based on clinical trials and *in vivo* studies, MSCs have been widely used to treat a variety of diseases, but translation into clinical practice has proven to be far more challenging.

Despite the fact that in the past 5 years, MSCs from BM, AT and PT with almost equal frequency have been used in clinical trials due to a great diversity in MSC products, the tissue source from which MSCs are derived is very important.²² Thus, due to variable levels of highly procoagulant tissue factor (TF/CD142), which are expressed by MSC products, the safety and effectiveness of cell therapy in COVID-19 are not clear.²³ In other words, some studies have questioned the beneficial effects of MSCs therapy on COVID-19 and focused on its complications. Hence, in the present review, we will highlight the critical roles of MSCs in cytokine storm of COVID-19 and discuss the different therapeutic effects of MSCs on COVID-19.

2 | COVID-19: ORIGIN, EVOLUTION, TRANSMISSION AND CLINICAL MANIFESTS

COVID-19 is generally known as a coronavirus and, as a member of the subfamily Orthocoronavirinae, belongs to the family of Coronaviridae.^{24,25} This big virus family is severely pathogenic and often considered infectious, as caused the epidemic of severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome (MERS) in 2012.^{26,27} In late December 2019, the outbreak of a new coronavirus that caused a respiratory-associated disease was reported in Wuhan, Hubei, China; it was then announced as a global health disaster by the World Health Organization (WHO); nowadays, the disease is widely called COVID-19.²⁸

A great number of studies first concentrated on raccoon dogs and palm civets as an important reservoir of infection in the case of SARS-CoV. At the beginning of 2020, they were misdiagnosed as seasonal flu; also, the pathogenesis and aetiology of such pneumonia-like symptoms remained unidentified. Based on some studies, epidemiologists discovered that the cluster was related to the human seafood market in Wuhan, which led to the hypothesis of zoonotic disease transmission. According to the phylogenomic analysis of COVID-19, it has been demonstrated that the novel coronavirus is most closely linked to two SARS-like-CoV sequences, which were obtained in bats

between 2015 and 2017, proposing that the bats' coronavirus and COVID-19 share similar ancestry. As a result, COVID-19 is known as SARS-CoV-2, a SARS-like virus.

Moreover, the two bat viruses were isolated in Zhoushan, China; in this regard, it was thought that COVID-19 might have first appeared close to Zhoushan.^{29,30} Coronaviruses consist of alpha-, beta-, gamma- and delta-coronavirus subfamilies. Alpha- and beta-coronaviruses can cause infection in mammals, whereas the other two types are more likely to infect birds.³¹ COVID-19 shares about 80%, 50% and 96% sequence likeness with SARS-CoV, MERS and bat coronavirus, respectively.³²

Unlike other coronaviruses, this emerging virus is a positive-sense single-stranded RNA (ssRNA) virus. Moreover, its genome size ranges between about 27 000 and 32 000 base pairs (bp). This novel virus is spherical with a diameter of about 125 nm, which is translated into structural proteins (eg, spike, envelope, membrane and nucleocapsid) and nonstructural proteins (eg, replicas [orf1a/b]), nsp2, nsp3 and accessory proteins (orf3a and orf7a/b).³³⁻³⁵ The virus can be transmitted through the environment, droplets or aerosols, coughing and sneezing, and direct contact with infected individuals.

The disease quickly spread not just throughout China but also throughout the ancient continent. It did not take long for the disease to spread throughout the globe and become a global pandemic.³⁶ Less than 3 months after the outbreak began, >100 000 cases and about 4500 deaths were reported worldwide.³⁷ When dozens of countries were witnessing a growing number of new cases, the pattern of disease spread in China was declining. At the beginning of the public spread of the disease, some countries, such as Iran and Italy, became significantly more affected by the disease.³⁸

Early clinical manifestations of COVID-19 patients are dry cough, fever, myalgia, sore throat, diarrhoea and difficulty breathing,³⁹ and the prognosis of infected people was correlated with host features.⁴⁰ It was reported that during hospitalization, respiratory failure occurred in approximately 90% of patients.³⁹ A number of biochemical parameters change during the disease course, including decreased white blood cells (WBC) and lymphocytes, as well as increased aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and C-reactive protein (CRP).⁴¹ After about 2 to 5 days, the symptoms manifest.⁴²

The average interval from the onset of symptoms to death has been considered 14 days,⁴³ depending on the patient's immune system and age. This average interval is shorter in people >70 years of age than in people <70 years of age.⁴⁴ A chest computed tomography (CT) scan can confirm pneumonia, but there are some aberrant characteristics, such as RNAemia, acute respiratory distress syndrome (ARDS), acute heart damage and incidence of ground-glass opacities, all of which culminated in death.⁴⁵ Cytokine storm in the lungs is a hallmark of SARS-CoV-2 pathogenesis. Acute cytokine release of GCSF, IL-2, IL-6, IL-7, IP-10, MCP-1, MIP1A and TNF caused by a virus causes pulmonary edema, airway dysfunction and ARDS.

In the vast majority of cases, SARS-CoV-2 infections vary from asymptomatic to symptoms similar to seasonal flu, and about 14%, 6% and 3% of patients showed severe, critical and fatal outcomes, respectively.⁴⁶ Due to lung and multiorgan failure, tissue destruction and

virus-induced cytokine storm with a unique pattern, severe patients necessitate intensive care unit (ICU).⁴⁷ Secondary clinical manifestations, including cardiomyopathy, acute cardiac damage, acute renal infection, bacterial infection, organ failure and sepsis, occur in about 5% of all cases.⁴⁸

Patients with severe COVID-19 are more likely to experience complications such as ARDS, acute lung injury (ALI) and sepsis.⁴⁹⁻⁵¹ ARDS is the most severe type of ALI⁵² with neutrophil, monocyte and lymphocyte infiltration in the bloodstream.⁵³ It is generally divided into categories depending on the clinical circumstances, such as sepsis, transfusion or trauma.⁵⁴ Based on evidence, sepsis-induced ARDS is the most prevalent cause.⁵⁵ All three ARDS, ALI and sepsis are defined by the release of abnormally high levels of cytokines, which can cause systemic problems.⁵⁶ The frequency and severity of ALI is a key determinant of the prognosis of COVID-19 patients.

In the ICU, over 30% of COVID-19 patients have significant pulmonary edema, dyspnea, hypoxemia or possibly ARDS.⁵⁷ A large number of critically ill COVID-19 patients (who have a poor prognosis) are in a systemic procoagulant condition, which puts them at risk for disseminated intravascular coagulation (DIC), thrombosis and thrombotic multiorgan failure (which is one of the major reasons for mortality in these patients). Because of the risk of damage to these patients, systemic intravenous (IV) MSC therapy would be a contraindication.²³ The Chinese Center for Disease Control and Prevention conducted the largest study on COVID-19 patients in China; they analysed data from 72 314 COVID-19 patients and found that 81% of cases were mild with an overall case fatality rate of 2.3%, and 5% of them presented with respiratory failure, septic shock and multiorgan dysfunction with 50% of fatality.⁵⁸

3 | MESENCHYMAL STROMAL/STEM CELLS

MSCs were reported by Friedenstein et al as fibroblast-colony forming cells derived from rat BM.^{59,60} Besides BM, MSCs can be obtained from AT,⁶¹ dental pulp,⁶² umbilical cord blood,⁶³ fetal lung⁶⁴ and placenta.⁶⁵ Based on growing evidence, MSCs, as a heterogeneous population of cells, have the capability of differentiation into mesodermal lineages. These cells have several biological properties (including the potential of differentiation, tissue remodelling, secretion growth factors and immune protective cytokines, safety and easy isolation) that make them suitable for stem cell-based therapy.⁶⁶

MSCs can home to injured sites and release various factors (such as vascular endothelial growth factor [VEGF], insulin-like growth factor 1 [IGF-1], IL-6, stromal-derived factor 1 [SDF-1], hepatocyte and nerve growth factors), which can promote cell survival.^{67,68} However, due to the occurrence of instant blood mediated inflammatory response (IBMR), which poses a serious threat to graft survival and function, this is not a very efficient process. In addition, the expression of TF (CD142) has been identified as a key trigger of IBMR.^{18,22,23,58} On the other hand, MSCs' therapeutic effects on lung injury are due to their ability to secrete some factors such as nitric

oxide (NO), transforming growth factor β (TGF- β), prostaglandin E2, indoleamine 2, 3 dioxygenase (IDO) and keratinocyte growth factor (KGF).^{69,70} Prostaglandin E2 stimulates the conversion of alveolar macrophages from the proinflammatory M1-macrophages to the anti-inflammatory phenotype, which can release IL-10 and decrease the severity of inflammation.⁷¹ Besides, prostaglandin E2, NO, IDO and KGF can also suppress T-cell-dependent inflammation.⁷²⁻⁷⁴

Furthermore, numerous studies have indicated the immunomodulatory properties of MSCs. The immunomodulatory potential of these cells occurs by altering the function of T cells, B cells, natural killer (NK) cells and monocytes/macrophages.^{71,75-77} In addition, these cells can decrease interferon- γ (IFN- γ), TNF- α and IL-17 production while increasing IL-10 production, resulting in a modulation of the host immune response.⁷⁰ There is no effective therapy for COVID-19, but MSC therapies have shown promising outcomes in treating inflammation, sepsis and ARDS (these are the leading mortality cause of COVID-19 patients). Thus, immunomodulatory and regenerative characteristics suggest that MSCs could be used as a cellular therapy for COVID-19 patients with lung injury.⁷⁸

4 | CROSS TALK BETWEEN MSCs AND CYTOKINE STORM IN COVID-19

MSCs can release different cytokines by paracrine secretion or interacting directly with immune cells, resulting in immunomodulation.⁷⁹ The activation of toll-like receptors (TLRs) in MSCs is induced by pathogen-associated molecules (including double-stranded RNA from viruses); this activation enhances the immunomodulatory actions of MSCs.^{80,81} Self-renewal, multidirectional differentiation and immunosuppression are the advantages of MSCs.⁸² These cells can play a vital role in COVID-19 treatment due to their anti-inflammatory and immunomodulatory effects.⁸³ MSCs control a wide range of effectors (including T cells, B cells, macrophages, neutrophils, NK cells and dendritic cells [DCs]) to affect innate and adaptive immunity (Figure 1).

SARS-CoV-2 interacts with TLRs, causing the production and release of proinflammatory IL-1, IL-6 and TNF, which are key mediators in the inflammatory cascade.^{84,85} TIR domain-containing adapter-inducing interferon- β (TRIF) or myeloid differentiation primary response 88 (MyD88) promotes the activation of tumour necrosis factor receptor-associated factor 6 (TRAF6). TRAF6 promotes caspase 1, causing pro-IL-1 cleavage and inflammasome activation, as well as tumour growth factor-activated kinase and I kappa B kinase (IKK). Then, proinflammatory cytokines (such as TNF, IL-6 and IL-1) initiate inflammatory processes in the lungs.^{86,87}

SARS-CoV-2 may generate cytokine storm as a result of defective acquired immune responses and uncontrolled inflammatory innate responses.⁵ During the cytokine storm associated with COVID-19, increased serum levels of IP-10, MCP-1, granulocyte colony-stimulating factor (G-CSF), MIP1A, IL-2, IL-7, IL-6 and TNF cause pulmonary edema, respiratory tract dysfunction and ARDS in patients.^{88,89}

MSCs have many unique immunomodulatory functions, which control the cytokine storm or balance immune responses via restoring

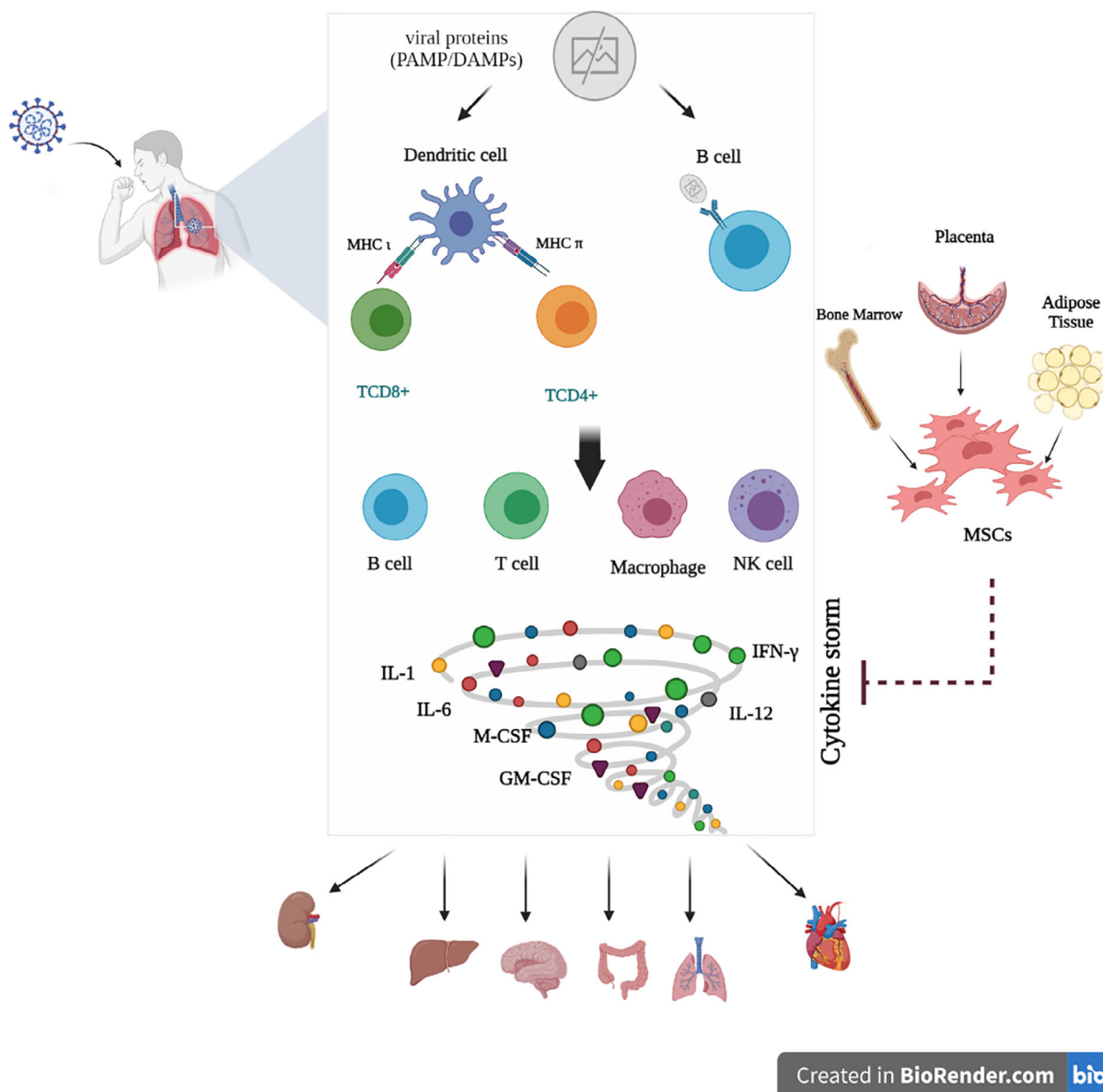


FIGURE 1 Crosstalk between MSCs and COVID-19

the pulmonary microenvironment, preserving alveolar epithelial cells and treating COVID-19 pneumonia.⁹⁰ In a clinical trial conducted by Leng et al, seven patients with COVID-19 were given only one IV infusion of MSCs. After 3 to 6 days, the patients' health improved significantly, inflammatory cytokine levels declined, anti-inflammatory IL-10 levels increased and overactivated cytokine-secreting T cells and NK cells vanished.⁹¹

Despite several efforts to comprehend the therapeutic effects of MSCs in ARDS, their mechanism has not yet been fully defined.⁹² On the other hand, most COVID-19 patients are at high risk for DIC, thromboembolism and thrombotic multiorgan failure.²³ MSC-based products can express variable levels of TF (CD142), leading to blood clotting and thrombotic multiorgan dysfunction.²³

5 | THERAPEUTIC PROPERTIES OF MSCs IN COVID-19

MSCs have been widely used in cell-based therapies, from basic research to clinical trials.⁹³ The efficacy and safety of MSCs have been shown in clinical studies.^{94,95} Although the International Society for Stem Cell Research (ISSCR) has recently announced that there is no approved stem cell-based strategy for COVID-19 prevention and treatment, MSCs are currently proposed as one of the therapeutic techniques for treating COVID-19.^{9,96}

The important anti-inflammatory activities of MSCs suggest that they could be used as a treatment for serious and life-threatening COVID-19 complications.¹¹ Cell contact-dependent and paracrine activities, such as the release of IL-10, TNF-stimulated gene 6, IDO,

adenosine and extracellular vesicles (EVs), are among the immunomodulatory mechanisms of MSCs.⁹⁷ This modulation is based on modifying immune cell activation and effector function, inhibiting lung-infiltrated cells and improving pulmonary edema resolution.⁹⁸

MSCs convert inflammation from a proinflammatory state with a massive release of proinflammatory cytokines (such as IL-6, IL-1, TNF, MCP-1, MIP-2, chemokine [CXC motif] ligand 1 [CXCL1] CXCL2, IL-12, IL-17 or type II IFN) and proteases (such as MMP-2, MMP-9 and MMP-12) to an anti-inflammatory state by releasing cytokines such as IL-10, IL-4, CC chemokine ligand 18 (CCL18), TGF- α and prostaglandin E2. As a result of this transition, inflammation decreases, and tissue repair occurs.^{99,100} IV infused MSCs are considered to aggregate in the lungs, producing several paracrine substances that can preserve or rejuvenate the epithelial cells of the alveoli, combat fibrosis and improve lung function.¹⁰¹ However, it is not yet clear whether IV infusion of MSCs is a safe and effective process to deliver COVID-19 patients. The reason is that they induce the expression of highly procoagulant TF (CD142) by MSC-based products. A significant increase in complement C3 activation fragment a (C3a) and coagulation activation marker thrombin-antithrombin complex (TAT), as well as a decrease in platelet count and a significant increase in fibrinolysis marker D-dimer, was observed after ex vivo expanded MSCs administered in patients. In this way, certain cell formulations, such as MSCs, with low-dose heparin can suppress complement activity and tend to provide better clinical outcomes.²³

The interactions of MSCs with B lymphocytes, NK cells, DCs, neutrophils and macrophages have been the focus of MSC-regulated immunomodulation.^{71,102} These interaction mechanisms are dependent on cell-cell contact and the release of soluble immune components.¹⁰³ Immunosuppressive ligands on the surface of MSCs, such as programmed death-ligand 1 (PD-L1) and Fas ligand (Fas-L), attach to receptors on the surface of immune cells, causing immune cells to lose function.^{104,105}

In the context of neutrophils and macrophages, MSCs can control these immune cell responses.⁷¹ Macrophages are classified into M1 (which is a classically activated macrophage) and M2 (which is an alternatively activated macrophage).¹⁰⁶ Pathogen phagocytosis and antigen epitope presentation to DCs, as well as promoting T_H1 responses, are performed by M1 macrophages. However, M2 macrophages are considered immunosuppressive cells as they stimulate T_H2 responses.¹⁰⁷ By activating M2 macrophages, inflammatory cytokines are expressed at low levels, while anti-inflammatory IL-10 is produced at high levels. MSCs can promote M2 macrophage activation through paracrine or cell-to-cell connections.^{79,106}

Another immunomodulatory function of MSCs is the inhibition of DC maturation via soluble factor production.^{106,108,109} MSCs can limit DC maturation by inactivating signalling cascades mediated by mitogen-activated protein kinase (MAPK) and nuclear factor- κ B (NF- κ B) via producing TNF-stimulated gene 6 (TSG-6).¹¹⁰ It has been reported that prostaglandin E2 (PGE2) released by activated MSCs plays a key function in DC maturation inhibition.¹⁰⁶

Furthermore, it has been discovered that NK cells and MSCs have a highly complicated interaction.¹¹¹ NK cells are lymphocytes in the innate immune system.¹¹² They have several receptors that can transmit by either activating or inhibiting signals.¹¹³ The production of

soluble substances by MSCs suppresses the immune response of NK cells.¹⁰⁶ IL-2-induced NK-cell responses can be inhibited by IDO and PGE2.^{106,114} Additionally, MSCs have TLRs, which appear to play an important function. The TLR3 activation in MSCs results in enhanced immunosuppression of NK cells.¹¹⁵

These types of stem cells release some chemicals that can influence B-cell and T-cell responses positively or negatively.¹¹⁶ Through the production of PGE2, IDO, TGF and hepatocyte growth factor (HGF), MSCs can effectively limit T-cell proliferation.^{106,117} Direct cell-to-cell contacts, mostly involving the Fas/Fas-L, TNF-related apoptosis-inducing ligand/death receptor (TRAIL/DR), death signalling and PD-L1/PD-1 pathways, can cause B cell apoptosis.^{118,119} Besides, cell cycle arrest of B cells can be caused by IDO and PGE2, as well as the synthesis of TGF-1 and HGF.¹²⁰

MSCs inhibit viral reproduction, shedding and lung epithelial cell (LEC) damage caused by viruses. Through transferring RNAs from EVs to LECs, MSC-derived extracellular vesicles (MSC-EVs) enhance both anti-inflammatory and antiviral characteristics.¹²¹ Exosomes and ectosomes are examples of EVs, which can be thought of as miniature maps of their origin cells and can make any of the therapeutic benefits of MSCs.¹²²⁻¹²⁵ MSC-EVs may offer various advantages over MSCs as a COVID-19 treatment. For example, although MSCs are most commonly delivered via IV infusion,¹²⁶ systemic administration of EVs is not required and can be administered intranasally or through inhalation. Furthermore, since EVs do not self-replicate, they do not pose the risk of uncontrolled cell division that has been raised in the past regarding cell-based treatments.^{83,127}

MSCs were found in greater abundance in lung tissue from patients with fibrotic lung disorders.¹²⁸ Early application of MSCs to alleviate inflammation and lung tissue remodelling with mild fibrosis was established in animal models.¹²⁸ The lung osmotic gradient created by active ion transport across the alveolar epithelium causes alveolar fluid clearance (AFC).¹²⁹ AFC decreases in COVID-19 patients with ARDS, linked to increased morbidity and death.¹³⁰ Patients who die of ARDS had much decreased fluid clearance.¹³¹ MSC interaction with chloride and sodium ion channels improves AFC and facilitates the clearance of pulmonary edema.^{132,133}

Based on Tang et al's findings, following MSC treatment, oxygenation and immunological indicators improved, and inflammatory indicators were reduced. They indicated that clinical data on the therapy of COVID-19 were provided via MSC transplantation.¹⁹ A case-report study was conducted on a COVID-19 patient with worsening conditions and signs of liver injury despite rigorous treatment. After human umbilical cord MSC (hUCMSC) therapy, most laboratory tests and CT scans revealed that the inflammatory symptoms waned. The patient was taken off the ventilator and able to walk 4 days after her second cell injection without any critical side effects.¹³⁴

In another study, Leng et al assessed MSC transplantation in seven COVID-19 pneumonia patients. They discovered that 4 days after MSC injection, the functional outcomes of the patients considerably improved with no adverse effects.⁹¹ Similar to these results, in China, a study on the treatment of a severe COVID-19 patient with human umbilical cord Wharton's jelly-derived MSCs (hWJCs) showed that intravascular transplantation of hWJCs for the treatment of COVID-19 pneumonia was found to be safe and effective.¹³⁵

TABLE 1 Ongoing clinical studies exploring the contribution of MSCs

Conditions	Treatment Source	Enrolment	Phase	Clinical trial number
Covid19 Pneumonia Multiple organ failure Corona virus infection	MSCs	30	Phase 1/2	NCT04392778
Acute respiratory distress syndrome due for COVID-19	MSCs	10	Phase 2	NCT04416139
COVID-19 patients	Wharton's Jelly-MSCs	5	Phase 1	NCT04313322
COVID-19 patients	MSCs	20	Phase 1	NCT04252118
COVID-19 pneumonia	UC-MSC	30	Phase 1/2	NCT04339660
Severe COVID-19 patients	Allogeneic human dental pulp mesenchymal stem cells	20	Phase 1/2	NCT04336254
Severe corona virus disease 2019	MSCs	90	Phase 2	NCT04288102
SARS-CoV-2-related acute respiratory distress syndrome	MSCs	60	Phase 2/3	NCT04366063
COVID-19 patients	MSCs	106	Phase 2	NCT04366271
Acute respiratory distress syndrome due for COVID-19	MSCs	300	Phase 3	NCT04371393
Acute respiratory distress syndrome due for COVID-19	MSCs	30	Phase 1/2	NCT04390139
COVID-19 patients	UC-MSC	24	Phase 1/2	NCT04355728
COVID-19 pneumonia	UC-MSCs	10	Phase 2	NCT04269525
Acute respiratory distress syndrome	UC-MSC derived CD362 enriched MSCs	75	Phase 1/2	NCT03042143
COVID-19 patients	UC-MSCs	48	NA	NCT04293692
Severe COVID-19 patients	AT-MSC exosomes	30	1	NCT04276987
Acute respiratory distress syndrome induced by epidemic influenza A (H7N9)	Menstrual-blood-derived MSCs	17		NTC02095444
COVID-19 pneumonia	UC-MSCs	48	NA	NCT04273646
COVID-19 pneumonia	cord blood mesenchymal stem cells	60	0	ChiCTR2000029816
Acute COVID-19 pneumonia	NK cells and UCB-MSCs	60	0	ChiCTR2000029817
Acute COVID-19 pneumonia	MSCs	63	0	ChiCTR2000029606
Acute COVID-19 pneumonia	MSCs	70	0	ChiCTR2000029580
High-risk COVID-19 pneumonia	UC-MSCs	9	1	ChiCTR2000030300
Severe COVID-19 pneumonia	MSCs	32	NA	ChiCTR2000030224
Novel COVID-19 pneumonia	UC-MSCs	60	0	ChiCTR2000030173
Severe COVID-19 pneumonia	UC-MSCs	60	2	ChiCTR2000030138
Acute respiratory distress syndrome of COVID-19 pneumonia	UC-MSCs	16	NA	ChiCTR2000030116
Severe COVID-19 pneumonia	UC-Wharton's jelly MSCs	40	0	ChiCTR2000030088
COVID-19 pneumonia	MSCs	20	NA	ChiCTR2000030020
COVID-19 pneumonia	MSCs	120	Phase1/2	ChiCTR2000029990
Severe and critically COVID-19 pneumonia	UC-MSCs CM	30	0	ChiCTR2000029569
COVID-19 pneumonia	MSC exosomes	26	0	ChiCTR2000030261
COVID-19 pneumonia	UC-MSCs and exosomes	90	NA	ChiCTR2000030484
Acute COVID-19 pneumonia	UCBMCs	60	0	ChiCTR2000029812
COVID-19 pneumonia	UCBMCs	30	0	ChiCTR2000029572

The use of MSCs for COVID-19 has become a hot topic among researchers. MSC therapy improved COVID-19 patients' outcomes; it could be a good option for disease treatment,²¹ but further preclinical

and clinical research is needed to further investigate its mechanism, safety, and efficacy¹³⁶ (Table 1). In addition, it is effectively used in clinical trials for the treatment of various disorders, such as multiple

sclerosis and osteoarthritis. MSCs possess both regenerative and immunomodulatory features, the latter of which can be employed to reduce the severity of SARS-CoV-2 infection.¹³⁷

6 | CONCLUSION

Based on recent studies, MSC-based treatments in COVID-19 patients have become a hot topic among researchers. Regarding the properties of MSCs to combat viruses, immunomodulatory features and their potential for tissue regeneration, this type of therapy has attracted the attention of researchers and could be used more to treat COVID-19 patients. Moreover, MSC therapy has not indicated any negative side effects on patients. However, multiple challenges exist related to cell-based treatment. Nowadays, the safety, efficacy and timing of MSC administration, suitable and effective dose and route preparation for infusion source of MSC delivery are under investigation as well. Hence, MSC-based treatments could be one of the most appropriate therapeutic approaches to treat COVID-19 patients.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are included in the article.

ETHICS STATEMENT

This article does not contain any studies with human participants or animals performed by any of the authors.

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