Mesenchymal stem cell treatment for COVID-19

Ruonan Xu,[a,1]* Zhiqian Feng,[b,1] and Fu-Sheng Wang [a]*

[a]Senior Department of Infectious Diseases, The Fifth Medical Center of PLA General Hospital, National Clinical Research Center for Infectious Diseases, Beijing, China
[b]The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China

Summary

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has caused a global pandemic since late 2019 that resulted in more than 360 million population infection. Among them, less than 7% of infected individuals develop severe or critical illness. Mass vaccination has been carried out, but reinfection and vaccine breakthrough cases still occur. Besides supportive and antiviral medications, much attention has been paid in immunotherapies that aim at reducing pathological changes in the lungs. Mesenchymal stem cells (MSCs) is used as an option because of their immunomodulatory, anti-inflammatory, and regenerative properties. As of January 16, 2022, when ClinicalTrials.gov was searched for "Mesenchymal stem cells and COVID-19," over 80 clinical trials were registered. MSC therapy was found to be safe and some effective in preclinical and clinical studies. Here, we summarize the major pathological characteristics of COVID-19 and provide scientific and rational evidence for the safety and possible effectiveness of MSCs in COVID-19 treatment.

Keywords: COVID-19; Mesenchymal stem cell; Immune therapy; Lung injury

Introduction

Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has developed into a global pandemic that began in late 2019. As of January 16, 2022, a total of 5,551,970 deaths have occurred out of a total of 328,675,785 COVID-19 cases.[1] Owing to the emergence of novel viral variants, including omicron, the risks of new infections, reinfections, and vaccine breakthrough infections has increased considerably worldwide, leading to a situation where the current epidemic is not yet well controlled. Similar to SARS-CoV-1 and MERS-CoV, SARS-CoV-2 belongs to the beta coronavirus family.[2] Individuals infected by the virus are frequently classified based on the clinical severity of their cases and designated as asymptomatic, mild, moderate, severe, or critical.[3] Severe and critical patients, particularly older adults and those with co-existing illnesses, have a high risk of mortality[4] and characterizied by over-activated immune disorders. These include inflammatory hyper-responses and cytokine storms, which contribute to pulmonary tissue damage, air exchange dysfunction, acute respiratory distress syndrome (ARDS), multiple organ failure, and even death. To resolve the immune dysfunction arising from COVID-19, besides symptomatic treatment and supplemental oxygen therapy, certain immunotherapy-related clinical trials have been conducted, including treatments based on the use of glucocorticoids,[5] interleukin (IL)-1 family blockers,[6,7] anti-IL-6 antibodies,[8] convalescent plasma,[9] and antiviral specific neutralizing antibodies.[10] Published data have demonstrated that immune-modulation regimens are well tolerated and show some effectiveness in clinical trial; however, further investigation is needed to confirm their efficacy in large-cohort randomized, controlled studies.

Mesenchymal stem cells (MSCs) possess immunomodulatory, anti-inflammatory, and regenerative properties.[11] The safety and some effectiveness of MSCs have been investigated in various clinical trials for the treatment of several disorders, including graft-versus-host disease, inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, and multiple sclerosis.[12] The therapeutic roles of MSCs in preclinical models and clinical trials of acute lung injury, ARDS, and lung fibrosis suggest the feasibility of MSC treatment for COVID-19. For these reasons, MSC therapy can be considered as an optional interventional method for improving clinical outcomes in severe and critical patients. By January 16, 2022, when ClinicalTrials.gov was searched using the terms "Mesenchymal stem cells and COVID-19," there were over 80 clinical trials registered (Figure 1). This review summarizes the pathological features of COVID-19 patients, along with the current progress and

*Corresponding authors.

E-mail addresses: xuruonan2004@aliyun.com (R. Xu), fswang302@163.com (F.-S. Wang).

[1] These authors contributed equally to this work.
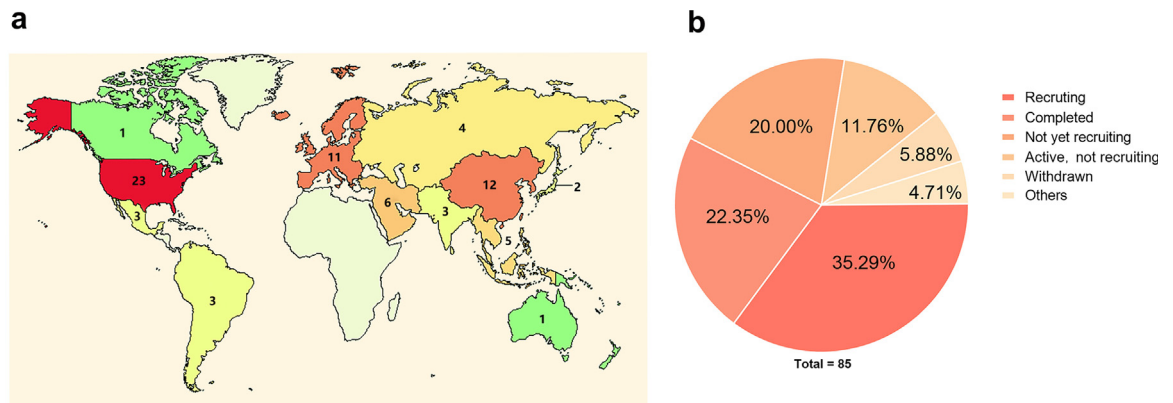
Figure 1. A summary of clinical trials registered in ClinicalTrials.gov by searching "Mesenchymal stem cells and COVID-19". (a) A map for all registered clinical trials. (b) The chart for the recruitment status of clinical trials.

challenges of using MSCs to treat COVID-19, and also establishes the rationality of using MSCs in the treatment of the disease.

Pathological features of COVID-19

During acute infection with SARS-CoV-2, viral replication and attack may directly result in injury to the respiratory tract and pulmonary tissues, which can trigger a series of over-active immune responses that not only play an antiviral role but also induce tissue inflammation and damage. Autopsies of dead patients with critical illness showed that the histological characteristics of lesions in the lungs were virus-induced and led to diffuse alveolar epithelial damage and inflammatory cell infiltration. This resulted in alveolar destruction with alveolar lining cell necrosis, protein-rich exudates, hyaline membrane formation, and endothelial cell membrane destruction. All of these eventually led to an increase in alveolar-capillary membrane permeability and loss of aerated lung tissue. Moreover, certain patients had fibrous deposition, mural fibrosis, and microcystic honeycombing in the lungs.[13−16] In contrast to other types of pneumonia, SARS-CoV-2 appears more likely to cause severe thrombotic disorders and widespread thrombosis with microangiopathy.[14,17,18] In mild and moderate cases, innate and adaptive immune responses are well coordinated, which contributes to viral symptom resolution and convalesence.[19] However, in severe cases, over-activation and massive infiltration of immunocytes such as macrophages, natural killer cells, and CD4+ and CD8+ T cells into the lungs result in high levels of cytokine and chemokine production.[20] Uncontrolled pro-inflammatory feedback triggers a cytokine storm and accelerates local tissue damage and systemic injuries.[21] Severe patients showed a significant increase in plasma levels of cytokines, including IL-2, IL-6, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-inducible protein 10, monocyte chemoattractant protein-1, macrophage inflammatory protein (MIP)-1α, and tumor necrosis factor (TNF)-α.[22−25] The antiviral immune-related interferon (IFN) type I response was also highly impaired in the majority of patients with severe symptoms. Furthermore, the total numbers of peripheral CD4+ T cells and CD8+ T cells were significantly lower in severe and critical cases,[26,27] particularly in patients with lymphocytopenia, impaired type I IFN production, and excessive activation of Th1 and inflammatory monocytes.[28] A high viral load may further aggravate the ongoing inflammatory cascades.[29]

Generally, pulmonary inflammatory lesions were primarily resolved in the convalescence stage, while > 80% of severe/critical patients and 60% of mild/moderate patients still exhibited residual computed tomography (CT) abnormalities three months after discharge. These predominantly included ground-glass opacity followed by strip-like fibrosis.[30] A recent result of a one-year follow-up study showed that 25% of individuals discharged from hospitalization still had chest CT abnormalities, including residual linear opacities and multifocal reticular/cystic lesions, and older patients with severe pneumonia, ARDS, and lymphopenia were more likely to develop CT abnormalities for over a year.[31] Pulmonary fibrosis is seen as an important factor affecting long-term clinical outcomes.[32,33] In an extended study of SARS-CoV-1-infected patients, lung fibrosis persisted for over seven years, suggesting that lung fibrosis could be a persistent sequela of pulmonary inflammatory injury.[34] The increased expression of angiotensin-converting enzyme 2, transforming growth factor beta, connective tissue growth factor, and fibronectin[35] and endothelial/epithelial-to-mesenchymal transition have all been believed to account for pulmonary fibrosis and vascular destruction post-COVID-19.[36]

Extrapulmonary manifestations, including thrombotic complications, myocardial dysfunction and arrhythmia, acute coronary syndromes, hepatocellular

injury, gastrointestinal symptoms, acute kidney injury, and hyperglycemia, may further complicate the natural course of COVID-19 in severe and critical cases.[37–39] A broad distribution of SARS-CoV-2 in the respiratory, cardiovascular, genitourinary, digestive, and immune systems and in endo/exocrine glands and the skin was identified in autopsy specimens.[38,40] Renal autopsy revealed coronavirus-like particles in the cytoplasm of the renal proximal tubular epithelium, accompanied by prominent acute renal tubular injury.[41] Human islet autopsy showed selective SARS-CoV-2 infection in β cells, followed by attenuated pancreatic insulin secretion and increased β cell apoptosis.[42] In the heart, both compositional and gene expression changes were recorded during acute SARS-CoV-2 infection.[43]

Rationality of MSC treatment for COVID-19

MSCs may exert immunomodulation via autocrine, paracrine, and endocrine pathways (Figure 2).[44–46] MSCs can modulate host innate and adaptive immune responses, thus reducing proinflammatory cytokine production.[45,46] Given the previously described

pathological characteristics of COVID-19,[47,48] MSCs are considered an optional candidate for the treatment of COVID-19. In preclinical models of acute lung injury, the benefit of MSCs was associated with the alleviation of local and systemic inflammation,[49] the amelioration of immune cell activation,[50] and mitigated lung injury.[45] MSCs have been shown to reduce the infiltration of macrophages, neutrophils, and DCs into the lungs and to decrease the levels of MIP-2, TNF-α, IL-6, IL-1β, and IL-12p70 in bronchoalveolar lavage fluid.[45,46,49,51,52] Stanniocalcin-2 was found to mediate the effect of MSCs through modulating macrophage polarization from the M1 to M2 phenotype.[53] In addition, MSCs induce mature DCs to become tolerogenic DCs, maintain immune tolerance, and negatively regulate the immune response.[54] Furthermore, MSCs can attenuate pulmonary inflammation by regulating different T cell subsets; for example, MSCs can inhibit the activation and proliferation of T cells and induce the polarization of CCR2+CD4+ T cell subsets enriched with forkhead box P3 and IL-10.[55] They can also inhibit the production of proinflammatory IL-17 and IFN-γ in T cells[49] and alleviate the infiltration of proinflammatory
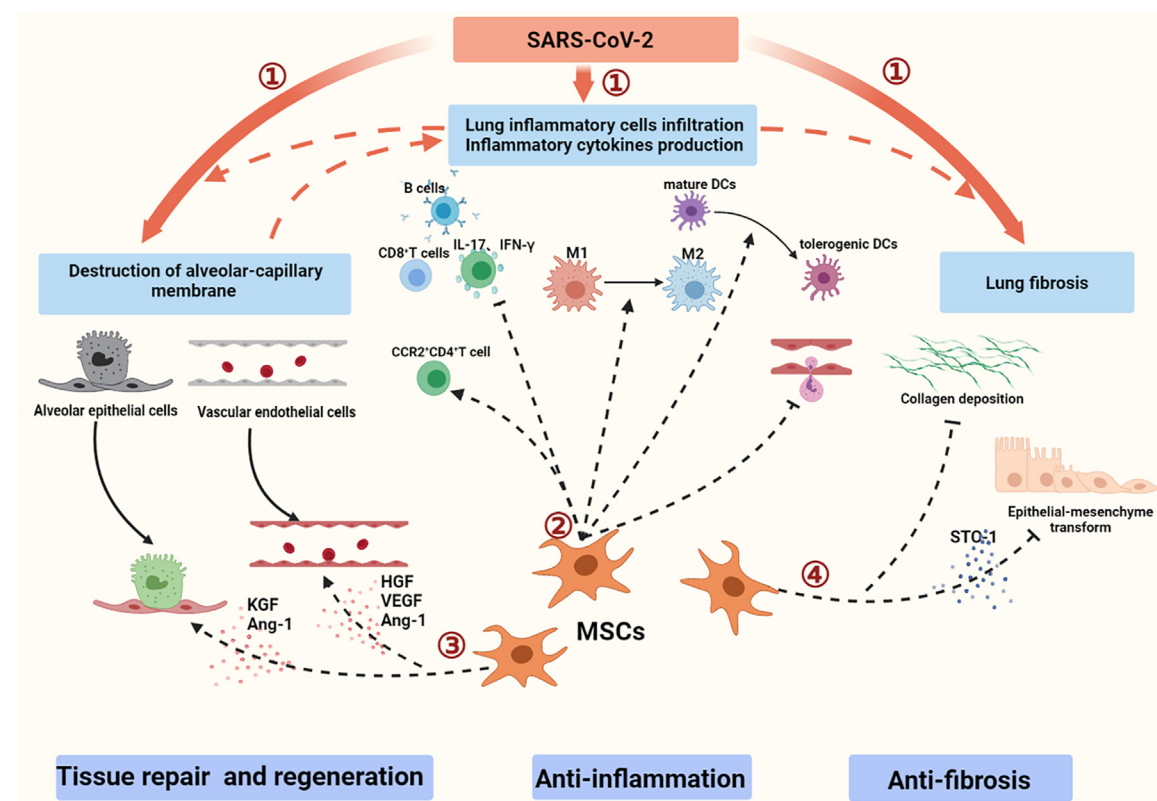
Figure 2. A schematic overview of the pathological characteristics and potential of MSCs for treating COVID-19. (1) During the acute phase, SARS-CoV-2 infection induces an inflammatory hyper-response and pulmonary tissue damage, which may lead to the partial fibrosis of lung tissues. (2) Immunomodulatory effects of MSCs contribute to reducing inflammation. (3) MSCs promote proliferation of alveolar epithelial cells and vascular endothelial cells and reduce their apoptosis. (4) MSCs contribute to decreasing collagen deposition and inhibiting epithelial−mesenchymal transformation.

CD8+ T cells[56] and B cells expressing chemokines for neutrophil recruitment and immunoglobulin production.[57] Additionally, MSC-derived extracellular vesicles could also participate in immunoregulation by decreasing the absolute count of neutrophils and TNF-α levels in an *ex vivo* lung injury model[58] and by transferring functional mitochondria to macrophages to reduce proinflammatory cytokine production and increase their phagocytic capacity.[59]

MSCs possess regenerative and differentiation properties that contribute to the repair of injured tissues. MSCs have been shown to improve alveolar fluid clearance and lung function by secreting paracrine factors that regulate membrane transport, restore the alveolar epithelial and pulmonary microvascular endothelial lining, reduce pulmonary edema, and ultimately promote the restoration of lung structure. Different cytokines are released through paracrine pathways, including keratinocyte growth factor (KGF), angiopoietin (Ang)-1, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF).[60−62] KGF produced by MSCs may rapidly and specifically contribute to the proliferation and differentiation of alveolar epithelial type II cells.[60] KGF is also related to surfactant production,[61] alveolar epithelial cell apoptosis relief,[63] and sodium-dependent alveolar fluid transport recovery.[64] Furthermore, HGF and VEGF may have synergistic effects on the restoration of endothelial intercellular junctions, reduction of caveolin-1 protein expression, and endothelial apoptosis.[65] Additionally, Ang-1 produced by MSCs has the capacity to increase endothelial cell proliferation during vascular remodeling, promote vascular stabilization during inflammation, and improve human alveolar epithelial type II cell permeability through directly affecting cytoskeletal remodeling.[62,66,67]

MSCs have the capacity to reshape the lung cell microenvironment by reducing the levels of profibrogenic factors. MSC infusion contributes to lung structure recovery by restoring lung epithelial cell proliferation and decreasing collagen deposition in a bleomycin-induced idiopathic pulmonary fibrosis model.[68,69] The efficacy of MSCs is also associated with the correction of inappropriate epithelial−mesenchymal transformation.[70]

Clinical trials of MSCs for COVID-19 treatment

The safety of MSC treatment for patients with ARDS has been demonstrated in the studies listed in Table 1.[71−76] In addition, MSCs simultaneously promote the restoration of pathological lung tissues.[77] Therefore, MSC therapy is considered an alternative option for patients with severe COVID-19.

To date, several clinical trials have utilized different sources of MSCs (Table 2).[78] Compared with conventional treatment, MSC add-on therapy may improve clinical symptoms, which are characterized by the relief

Numbers	Trial ID	Sources of MSCs	Phase	Numbers of patients	Doses and administration routes	Primary outcomes	Refs.
1	NCT01902082	AD-MSCs	1	12	A single dose of 1×10^6 cells/ kg; IV	No adverse events or serious adverse events. The clinical effect at this dose is weak.	71
2	Not reported	BM-MSCs	Case report	2	A single dose of 2×10^6 cells/ kg; IV	Oxygenation and pulmonary compliance were improved. Levels of inflammation markers were reduced.	72
3	Not reported	UC-MSCs	1	9	A single dose of 1.0×10^6 cells/kg or 5.0×10^6 cells/kg or 1.0×10^7 cells/kg;IV	Tolerated without serious adverse events.	73
4	NCT01775774	BM-MSCs	1	9	A single dose of 1×10^6 cells/kg or 5×10^6 cells/kg or 10×10^6 cells/kg;IV	Well tolerated and safe.	74
5	NCT02097641	BM-MSCs	2a	60	A single dose of 10×10^6 cells/kg; IV	No MSC-related predefined hemodynamic or respiratory adverse events.	75
6	NCT03042143.	UC-MSCs	1	9	A single dose of 1 or 2 or 4×10^8, IV	Well tolerated. Adverse events included apyrexia, non-sustained ventricular tachycardia, and deranged liver function.	76

Table 1: **Completed clinical studies of MSCs in the treatment of patients with ARDS.**
MSCs, mesenchymal stem cells; AD-MSCs, adipose-derived MSCs; BM-MSCs, bone marrow autologous MSCs; UC-MSCs, umbilical cord-derived MSCs; IV, intravenous injection.

Numbers	Trial ID	Source of MSCs	Phase	Numbers of patients	Doses and administration routes	Primary outcomes	Refs.
1	NCT04252118	UC-MSCs	1	18	Three doses of 3×10^7 cells; IV	Safe and well tolerated.	[79]
2	ChiCTR2000029990	MSC	1	10	A single dose of 1×10^6 cells/ kg; IV	No adverse effects. Pulmonary function and symptoms significantly improved.	[80]
3	Not reported	MB-MSCs	Case report	2	Three doses of 1×10^6 cells/ kg; IV	Values of immune indicators increased, and levels of inflammation indicators decreased. Lung exudate lesions were absorbed.	[81]
4	ChiCTR2000029606	MB-MSCs	1	44	Three doses of 3×10^7 cells; IV	Safe and well tolerated. SpO_2 was significantly improved, and chest imaging results were improved.	[82]
5	ChiCTR2000031494	UC-MSCs	1	41	A single dose of 2×10^6 cells/ kg; IV	Clinical symptoms were relieved and alleviated in a shorter time. Levels of inflammatory factors rapidly decreased, and lymphocyte count returned to normal levels in less time.	[83]
6	Not reported	UC-MSCs	1	31	1×10^6 cells/ kg were suspended in 100 ml normal saline. The volume of infused UC-MSCs was $100-300$ mL; IV	No adverse events were observed. Laboratory parameters tended to improve.	[84]
7	Not reported	Convalescent plasma combination with UC-MSCs	Case report	1	Three doses of 1×10^6 cells/kg; IV	Absolute lymphocyte count increased, bilateral infiltrates were absorbed, and pulmonary function was significantly improved.	[85]
8	Not reported	UC-MSCs or PL-MSCs	Case series	11	Three doses of 2×10^8 cells; IV	No serious adverse events. Levels of inflammatory biomarkers significantly decreased.	[86]
9	Not reported	hESC-IMRCs	1	27	One to three doses of 3×10^6 cells/ kg; IV	No adverse events or abnormal responses related to cell therapy occurred. The area of lung fibrosis lesions decreased.	[87]
10	NCT04269525	UC-MSCs	A pilot study	16	Four doses of 1×10^8 cells; IV	No infusion-related or allergic reactions. Oxygenation index was improved, and CT scan improved. Restoration of lymphocyte count and subsets.	[88]
11	NCT04416139	UC-MSCs	1	5	A single dose of 1×10^6 cells /kg; IV	PaO_2/FiO_2 was improved.	[89]
12	Not reported	hESC-IMRCs	Case report	1	Two doses of 3×10^6 cells/ kg; IV	Levels of proinflammatory cytokines were decreased. SpO2 improved.	[90]
13	NCT04288102	UC-MSCs	2	100	Three doses of 4×10^7 cells; IV	Safe and potentially effective. Lung lesion volume, especially solid component lesion volume, was reduced. The 6-minute walk test result improved.	[91]
14	NCT04457609	UC-MSCs	1	40	A single dose of 1×10^6 cells/ kg; IV	Safe and well tolerated. Survival rate increased.	[92]

Table 2 (Continued)

Review

Numbers	Trial ID	Source of MSCs	Phase	Numbers of patients	Doses and administration routes	Primary outcomes	Refs.
15	NCT04392778	WJ-MSCs	1	30	Three doses of 3×10^6 cells/kg; IV	All the indicators of anti-inflammation, anti-fibrosis signs in the lungs, and levels of immunodulatory markers were dramatically improved.	[93]
16	NCT04355728	UC-MSCs	1/2a	24	Two doses of $100 \pm 20 \times 10^6$ cells; IV	No serious adverse events were observed. Mortality and time to recovery decreased significantly.	[94]
17	Not reported	MSCs	1	23	Two or three doses of 1×10^6 cells/kg; IV	Safe and well tolerated. Pulmonary function and overall outcomes were improved.	[95]
18	Not reported	UC-MSCs	1	210	A single dose of $1\text{-}2 \times 10^6$ cells/kg;IV	No adverse effects. SaO2 improved.	[96]
19	Not reported	AD-MSCs	1	13	One to three doses of 0.98×10^6 cells/kg; IV	No adverse events. Clinical symptoms and values of inflammatory parameters improved.	[97]
20	NCT04339660	UC-MSCs	2	58	A single dose of 1×10^6 cells /kg; IV	MSC-treated patients had fewer adverse events. Clinical symptoms, values of inflammatory parameters, and CT scan improved. MSCs promoted the production of SARS-CoV-2-specific antibodies.	[98]
21	IRCT20190717044241N2	WJ-MSCs	1	5	Three doses of 150×10^6 cells; IV	Safe and well tolerated. Levels of inflammatory biomarkers improved.	[99]
22	Not reported	UC-MSCs	Case report	1	Three doses of 5×10^7 cells/ kg; IV	No obvious side effects. Values of clinical indices and clinical symptoms were improved.	[100]
23	Not reported	UC-MSCs	Case report	1	Five doses of 1.5×10^6 cells/ kg; IV	The number of lymphocytes was increased. Respiratory and renal functions were improved.	[101]
24	Not reported	WJ-MSCs	Case report	1	A single dose of 1×10^6 cells /kg; IV	The percentage and counts of T cells were increased. CT scan was improved.	[102]
25	Not reported	MSCs	A retrospective study	25	One to three doses of 1×10^6 cells/kg; IV	Three cases experienced treatment-related side effects including liver dysfunction, heart failure, and allergic rash.	[103]
26	Not reported	ExoFlo	1	27	15 ml of ExoFlo was added to 100 mL of normal saline; IV	No adverse events. Clinical status, oxygenation, and laboratory values improved, levels of acute phase reactants declined.	[105]

Table 2: **Completed clinical studies of MSCs in the treatment of patients with COVID-19.**

MSCs, mesenchymal stem cells; MB-MSCs, menstrual blood-derived MSCs; PL-MSCs, placenta-derived MSCs; hESC-IMRCs, human embryonic stem cell−derived immunity− and matrix−regulatory cells; WJ-MSCs, Wharton's jelly-derived MSCs; ExoFlo, exosomes derived from allogeneic bone marrow MSCs; SaO2, arterial oxygen saturation; SpO2, oxygen saturation; CT, computed tomography.

of dyspnea and a shorter recovery time.[79−90] CT images of the lungs also showed notable improvements in pulmonary lesions,[81−83,86,91] including a decrease in pathological lobes, ground-glass opacity, and consolidations.[83] Other studies have shown that MSC add-on therapy enhanced the survival of severe/critical patients[82,92] and even those who developed ARDS.[86,93−95] The choice of a time window for MSC-based therapies was considered crucial; MSC transfusion for severe patients prior to intubation could reduce the risk of disease progression and 28-day mortality.[83,96] Furthermore, early initiation of MSC treatment might contribute to a higher extubation rate in patients who received mechanical ventilation.[97]

The underlying mechanisms of MSC-based remedies for the maintenance of homeostasis, immune reconstitution, and tissue repair have been investigated in detail, and the effect of MSCs on hematopoiesis was found to correlate with the activation of a novel subpopulation of VNN2+ hematopoietic stem/progenitor like (HSPC-like) cells, which were mobilized following MSC infusion.[98] Notably, the changes in inflammatory indices following MSC treatment were inconsistent. Partial data from clinical trials showed that MSCs exerted anti-inflammatory and immunoregulatory effects through reducing the levels of inflammatory biomarkers (C-reactive protein, IL-6, IL-2, IL-12, IL-8, TNF-α, and IFN-γ) and increasing the level of anti-inflammatory IL-10 and T cell counts.[80,81,83,84,94,95,98−102] In other trials, significant changes in inflammatory factor levels were not observed.[82,91,103] Therefore, the effect of MSC treatment on inflammation should be further studied in large-cohort randomized controlled trials.

In our double-blind, placebo-controlled phase 2 trial, MSC administration significantly reduced solid component lesion volume within 28 days in patients with severe COVID-19.[91] During the subsequent one-year follow-up period, the patients who received MSC treatment showed reduced solid component lesion volume and improved pulmonary function, indicating that MSC therapy might have long-term benefits.[104] Bone marrow MSC-derived exosomes have also been reported to be safe and effective in reducing acute phase reactant and neutrophil counts, increasing T cell counts, and improving oxygenation in severe cases.[105] These data support the therapeutic potential of MSCs for severe cases with progressive lung damage.

Although most clinical trials showed that MSC treatment is generally safe and well tolerated, some MSC-related adverse events have still been recorded. The major clinical symptoms included facial flushing, fever,[79] shivering,[86] headache,[99] liver dysfunction, heart failure, and allergic rash.[95] However, adverse events were recorded in both MSC-treated patients and controls, indicating that the side effects might be infusion-related.[94] Furthermore, the speed of transfusion and the baseline status of patients with co-existing illnesses may be associated with the occurrence of adverse events.

Challenges and perspective

Large-scale vaccination has provided essential protection by establishing herd immunity, which will further contribute to the control of the SARS-CoV-2 pandemic. However, there are still re-infection and post-vaccination breakthrough cases in COVID-19. Many infected individuals are asymptomatic or show mild/moderate symptoms; however, it is difficult to ensure the full recovery of severe and critical patients using current medications, including symptomatic treatment, antiviral therapy, and respiratory support treatment. MSCs may serve as an alternative immunotherapeutic option for severely affected individuals and contribute to the improvement of COVID-19 outcomes. Notably, clinical application protocols for MSCs are diverse, and optimized standard protocols will be required to maximize their therapeutic effect. Moreover, the choice of a time window for treatment, the identification of COVID-19 patients at suitable phases, and the regimen (including dosage, interval time, and round) all need to be comprehensively optimized.

Most importantly, adverse reactions related to MSC treatment and infusion also require caution. Low-grade fever, facial flushing, headache, and allergic rash after MSC infusion were reported, although these side effects were transient and generally disappeared within 24 h without any treatment. However, treatment of these symptoms may be required in severe cases. In addition, the risks of thromboembolic events associated with intravenous infusions of high doses of MSCs should also be noted. To improve safety, it is best to monitor the electrocardiogram and percutaneous oxygen saturation during MSC infusion, and to test for laboratory parameters, including liver and kidney function, blood routine, CRP, inflammatory cytokines, coagulation, procalcitonin, blood gases, and heart function, before MSC infusion.[106]

Follow-up studies extending over a year in length have reported that severe COVID-19 patients still experienced symptoms and persistent physiological and radiographic abnormalities.[31] These data indicate that some severe COVID-19 patients will still require suitable interventions to improve their long-term prognoses. MSCs have been suggested for post-COVID-19 treatment for their antifibrotic and regeneration/differentiation properties. To determine the fate of the infused cells and to interpret the interactions between the colonized MSCs and immunocytes, MSC tracking *in vivo* is required. Furthermore, specific airspace and plasma biomarkers are required to predict and verify the efficacy of MSCs against COVID-19.

Both fresh and frozen MSCs with proven efficacy in clinical applications are readily available, and it is

noteworthy that dead or apoptotic MSCs found in MSC preparations exert the same immunomodulatory properties as the "living MSCs" by releasing phosphatidylserine.[107] In addition, MSCs derived from different donors and tissues lead to individual heterogeneity, which complicates the progress of consistent and standardized stem cell production.[108,109] Therefore, it is necessary to screen qualified MSCs to avoid uncertain effects.

In summary, MSC therapy appear to serve as an alternative candidate for ameliorating inflammation, repairing lung tissue injury, and preventing long-term pulmonary disability in patients with COVID-19. However, the different groups of enrolled patients, therapeutic regimen and the time window for treatment of MSCs may lead to the disparities of data in the previous clinical trials. Prospective, multicenter, randomized and controlled trials with large sample size are still necessary to further confirm therapeutic efficacy of MSCs for the patients with severe and critical COVID-19.

Outstanding questions

Although available data from preliminary clinical trials have proved the safety and some efficiency of MSC treatment for COVID-19 patients, there are certain disparities caused by the inconsistency of inclusion and exclusion criteria. Therefore, determining the characteristics of patients who may gain more clinical benefits from MSC treatment will require more multicenter, randomized, controlled trials and long-term follow-up studies. Moreover, concomitant treatments may exert a synergistic or antagonistic role with MSCs, and treatment regimens need to be optimized. Further mechanistic studies are also needed to verify the efficacy of MSCs in COVID-19 treatment.

Search strategy and selection criteria

Data for this review were identified by searches of PubMed and Google Scholar and references from relevant articles using the search terms "SARS-CoV-2," "COVID-19," "immunotherapy," "Mesenchymal stem cells," "ARDS," "Clinical trial," "Lung injury," "pulmonary fibrosis," "Cytokine storm," "immune response," "clinical features," "follow-up," and related terms. Only articles published in English between 1994 and 2021 were included in the study. Articles were selected based on their relevance and the authors' best judgments.

Contributors

Ruonan Xu and Fu-Sheng Wang contributed to the conception and design of the review. The draft was written by Ruonan Xu and Zhiqian Feng. Fu-Sheng Wang, Ruonan Xu critically and systemically revised the manuscript. All authors contributed to the article and approved the submitted version.

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