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Review article

Mesenchymal stem cells: a new front emerges in coronavirus disease 2019 treatment

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ABSTRACT

Currently, treating coronavirus disease 2019 (COVID-19) patients, particularly those afflicted with severe pneumonia, is challenging, as no effective pharmacotherapy for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exists. Severe pneumonia is recognized as a clinical syndrome characterized by hyper-induction of pro-inflammatory cytokine production, which can induce organ damage, followed by edema, dysfunction of air exchange, acute respiratory distress syndrome, acute cardiac injury, secondary infection and increased mortality. Owing to the immunoregulatory and differentiation potential of mesenchymal stem cells (MSCs), we aimed to outline current insights into the clinical application of MSCs in COVID-19 patients. Based on results from preliminary clinical investigations, it can be predicted that MSC therapy for patients infected with SARS-CoV-2 is safe and effective, although multiple clinical trials with a protracted follow-up will be necessary to determine the long-term effects of the treatment on COVID-19 patients.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has garnered global attention as the causative agent for the coronavirus disease 2019 (COVID-19) pandemic and its associated morbidity and mortality worldwide. As of today, approximately 6.9 million confirmed cases of COVID-19 have been reported in more than 213 countries and territories, with an estimated 53,000 critically ill and 402,000 dead https://www.worldometers.info/coronavirus/ [1]. First detected in a cluster of patients with pneumonia of unknown cause in the city of Wuhan, China, in December 2019, within 2 months the outbreak was declared a public health emergency of international concern by the World Health Organization. Clinical data suggest that the elderly and people with chronic underlying health issues are more prone to SARS-CoV-2-associated illness and death than young individuals. Currently, there is no specific antiviral treatment or effective vaccines available for COVID-19. The available therapies include non-specific antivirals, antibiotics to treat bacterial infections and sepsis and corticosteroids to lower inflammation. However, these measures fail in patients with severe disease, which is characterized by a cytokine storm.

The clinical manifestations of viral infections, especially SARS, include mild prodrome of fever and myalgias lasting 3-7 days, during which viral replication occurs. Cough, respiratory symptoms, dyspnea and hypoxemia are common during the second week of the illness. Finally, dyspnea may progress to respiratory failure, progressive pneumonia and acute respiratory distress syndrome (ARDS). Interestingly, clinical worsening occurs during the time of decreasing viral load [2], and in several cases the cause seems to be immunopathologic injury rather than direct injury from the virus [3]. Identifying the SARS-CoV-2 virus receptor recognition mechanism, which regulates its virulence and pathogenesis, holds the key to tackling the COVID-19 pandemic [4]. The pathogenesis of SARS-CoV-2 depends on the recognition and engagement of the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) as an entry receptor and transmembrane protease serine 2 for S protein priming [5]. The efficiency of ACE2 usage has been found to be a vital factor for SARS-CoV-2 transmissibility [6]. The ACE2 receptor is extensively distributed on the human cell surface, especially alveolar type II cells of the lungs and capillary endothelial cells [7]. It has been reported that the over-activated immune system of infected patients usually kills the virus, thereby releasing inflammatory mediators, resulting in a cytokine storm, with elevated levels of multiple pro-inflammatory cytokines that cause edema, persistent pain and pressure in the chest, shortness of breath, acute respiratory distress, secondary bacterial infection and increased mortality [8]. Interestingly, the consistent absence of ACE2 in immune cells, such as T and B lymphocytes, and macrophages in bone marrow, lymph nodes, thymus and spleen [9] suggests that immunological therapy could be a potential therapeutic option for infected patients.

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Considering the seriousness of this deadly pandemic and its impact on the global economy, there is an urgent need to develop effective therapies against COVID-19. Here we propose mesenchymal stem cells (MSCs) as a possible therapeutic candidate for SARS-CoV-2 infection. MSCs are an attractive approach for treating both acute and chronic lung pathological conditions like COVID-19, mainly because these cells offer multiple protective mechanisms to defend against and repair pulmonary damage. Moreover, MSCs exhibit broad immune regulatory function, which makes them suitable for antiviral therapy, as the safety and effectiveness of these cells have been documented in clinical trials of severe lung infections [10–12]. Results of preliminary investigations on SARS-CoV-2-infected patients treated with MSCs have revealed a noteworthy reversal of pathological symptoms, further indicating the potential of MSCs in lung infections [8,13].

Methods and Results

MSCs and COVID-19 patients

To date, one clinical case study and a single-center open-label pilot investigation have been published on COVID-19 patients employing MSCs as a therapy [8,13]. Apart from these preliminary studies, 41 clinical trials that employ MSC-based therapies have been approved (including seven that were withdrawn) and are summarized in Table 1. Results from these trials are expected to shed light on the pathophysiology of the disease and the interventions offered by MSCs post-treatment. Here, briefly, we summarize the outcomes of the two published studies from China.

The first study is a case report [13] in which a critically ill 65-year-old female with severe pneumonia, respiratory failure, moderate anemia, hypertension and multiple organ failure received 3 infusions of umbilical cord MSCs (UCMSCs), 5×10^7 cells per infusion, 3 days apart. Before receiving UCMSCs, the clinical laboratory examination showed an abnormal percentage of white blood cells, neutrophils and lymphocytes in the peripheral blood, and the patient received antiviral therapy. During cell therapy, antibiotics were given to manage the bacterial infection, and to modulate the immune system, thymosin $\alpha 1$ was injected. Twenty-four hours after the second UCMSC administration, serum bilirubin, C-reactive protein (CRP), aspartate aminotransferase, alanine transaminase and vital signs began to stabilize, and the patient no longer required mechanical ventilation. After receiving the second cell infusion, white blood cell, neutrophil and lymphocyte counts, together with T subsets, returned to normal levels. Two days after the third injection, the patient tested negative for SARS-CoV-2. Consecutive computed tomography scanning pre- and post-cell administration revealed that pneumonia had resolved. Moreover, no side effects were observed from the first day of UCMSC infusion to the third day, signifying the cells were well tolerated.

Another study by Leng *et al.* [8] reported that the intravenous administration of clinical-grade human MSCs in patients infected with SARS-CoV-2 resulted in improved clinical outcomes. In this study, 7 patients (one critically ill, four severely ill and two with common symptoms of pneumonia) were enrolled in the treatment group, and 3 patients served as placebo controls (all displaying severe symptoms). All treated patients received a single dose of 1×10^6 MSCs/kg, and all seven remarkably showed improvement over a period of 2 weeks, with no noticeable adverse effects. However, within the control group, only one showed improvement, while one exhibited ARDS symptoms and the other died. The overall improvement in the MSC-infused group was striking, as pulmonary function and symptoms in all 7 patients significantly improved within 2 days after treatment, and most tested negative on the SARS-CoV-2 nucleic acid test over 2 weeks after MSC infusion. After 6 days of treatment, cellular immune response showed an elevated peripheral lymphocyte count, decline in CRP and the disappearance of activated $CXCR3^+CD4^+$ T cells, $CXCR3^+CD8^+$ T cells and $CXCR3^+$ natural killer cells. As expected, the number of $CD14^+CD11c^+CD11b^{mid}$ regulatory dendritic cells (DCs) also returned to normal, levels of the pro-inflammatory cytokine tumor necrosis factor alpha (TNF-α) were decreased and the ratio of chemokine IL-10 increased significantly in the MSC treatment group compared with the placebo control group. Furthermore, the gene expression profile showed that MSCs did not express ACE2 or transmembrane protease serine 2, indicating they were free from COVID-19 infection. Finally, the RNA sequencing and gene expression analysis showed that MSCs were closely involved in antiviral pathways and had anti-inflammatory trophic activities.

Although both of these studies provided new insights into the protective mechanism of MSCs during viral infection, a few shortcomings in these treatments can be noticed. For example, severity and mortality largely correspond to age, and it therefore seems curious to have older patients in the placebo group in the study by Leng *et al.* [8]. Moreover, there is a lack of information on the MSC processing and screening before infusion, and long-term follow-up of patients is missing in both of these studies. For a protocol to be implicated in a larger cohort, optimal information regarding MSCs as well as patients needs to be investigated in a rationally designed controlled setting.

SARS-CoV-2 infection and immune response

To understand lung pathophysiology associated with SARS-CoV-2 infection, it is important to recognize the behavior of the virus within the host (humans). Clinically, the immune reaction induced by SARS-CoV-2 infection has 2 stages: (i) the immune protective phase (incubation phase) and (ii) the inflammation-driven damage phase (severe phase) [14]. During non-severe stages, a particular adaptive immune response is required to remove the virus and to prevent progression of the disease to severe stages. However, when the protective immune response is impaired, the virus spreads; thus, enormous destruction of not only lung but also all ACE2-expressing tissue is imminent. The damaged cells induce innate inflammation that is largely mediated by pro-inflammatory macrophages and granulocytes [14]. As MSCs can immunomodulate cells from the innate and adaptive immune system [15–18], they could offer a new therapeutic approach to COVID-19 patients. However, a major concern is when to initiate MSC treatment. An argument can be made for stratifying patients based on disease severity and focusing specifically on those who present with a cytokine storm and require ventilation [19]. Interestingly, in a recent study displaying results from responders versus non-responders to MSC treatment in graft-versus-host disease (GVHD), the authors argued, based on the results, that the severity of the disease could help stratify patients for MSC treatment [20]. In any event, existing pre-clinical data [21] as well as data from clinical trials in non-viral ARDS patients support the use of MSCs in moderate or mild disease, although this remains disputable . However, because of limited understanding of the pathogenesis of COVID-19, an optimal approach for administration of MSC-based therapies has yet to be established.

Cytokine storm

The cytokine storm is a systematic inflammatory response associated with a variety of infectious and non-infectious diseases. This exuberant immune response is clinically related to excessive inflammatory parameters and widespread lung damage, resulting in acute respiratory distress and multi-organ failure [22–27]. Reports from SARS-CoV-2-infected individuals with critical illness have depicted a complex picture of cytokine networks and their contributions to pathological outcomes (Figure 1). Thus, preventing and reversing the cytokine storm may be a primary factor in determining the outcome of patients with severe COVID-19 pneumonia. However, very limited information regarding cytokine storm is available in coronavirus

Table 1
Summary of MSC-based clinical trials recorded up to April 21, 2020.

Clinical trial number	Study title	Phase	Status	Sample size, n	Cellular intervention	Primary outcome measure	Location	References
NCT04315987	NestCell mesenchymal stem cell to treat patients with severe COVID-19 pneumonia	I	Not recruiting	66	NestCell	Change in clinical condition	Sao Paulo, Brazil	https://clinicaltrials.gov/ct2/show/NCT04315987?term=mesenchymal
NCT04313322	Treatment of COVID-19 patients using Wharton's jelly- mesenchymal stem cells	I	Recruiting	5	Wharton's jelly mesenchymal stem cells	Clinical outcome CT scan RT-PCR	Saudi Arabia, Amman, Jordan	https://clinicaltrials.gov/ct2/show/NCT04313322?term=mesenchymal
NCT04288102	Treatment with mesenchymal stem cells for severe corona virus diseases 2019 (COVID-19)	II	Recruiting	90	Mesenchymal stem cells	Size of lesion area and severity of pulmonary fibrosis	Maternal and Child Hospital of Hubei Province, Wuhan, Hubei, China; and Wuhan Huoshenshan Hospital, Wuhan, Hubei, China	https://clinicaltrials.gov/ct2/show/NCT04288102?term=mesenchymal
NCT04302519	Novel coronavirus-induced severe pneumonia treated by dental pulp mesenchymal stem cells	Early phase	Not recruiting	24	Dental pulp mesenchymal stem cells	Time to disappearance of ground-glass shadow in the lungs	–	https://clinicaltrials.gov/ct2/show/NCT04302519?term=mesenchymal
NCT04252118	Mesenchymal stem cell treatment for pneumonia patients infected with 2019 novel coronavirus	I	Recruiting	20	Mesenchymal stem cells	Size of lesion area Side effects in MSC treatment group	Beijing 302 Military Hospital of China, Beijing, China	https://clinicaltrials.gov/ct2/show/NCT04252118?term=mesenchymal
NCT04273646	Study of human umbilical cord mesenchymal stem cells in the treatment of novel coronavirus severe pneumonia	–	Not recruiting	48	Umbilical cord mesenchymal stem cells	Pneumonia severity index Oxygenation index (P_{AO_2}/F_{IO_2})	Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China	https://clinicaltrials.gov/ct2/show/NCT04273646?term=mesenchymal
NCT04269525	Umbilical cord (UC)-derived mesenchymal stem cells (MSCs) treatment for the 2019-novel coronavirus (nCOV) pneumonia	II	Recruiting	10	Umbilical cord mesenchymal stem cells	Oxygenation index	Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China	https://clinicaltrials.gov/ct2/show/NCT04269525?term=mesenchymal
NCT04333368	Cell therapy using umbilical cord-derived mesenchymal stromal cells in SARS-cov-2-related ARDS	I and II	Not recruiting	60	Umbilical cord Wharton's jelly-derived human mesenchymal stromal cells	Respiratory efficacy	Hopital Pitie-Salpetriere, APHP, Paris, France; and Hopital European Georges Pompidou, APHP, Paris, France	https://clinicaltrials.gov/ct2/show/NCT04333368?term=mesenchymal
NCT04276987	A pilot clinical study on inhalation of mesenchymal stem cells exosomes creating severe novel coronavirus pneumonia	I	Not recruiting	30	Mesenchymal stem cell-derived exosomes	Adverse reaction and severe adverse reaction Time to clinical improvement	–	https://clinicaltrials.gov/ct2/show/NCT04276987?term=mesenchymal
NCT04299152	Stem Cell Educator therapy treat the viral inflammation caused by severe acute respiratory syndrome coronavirus 2	II	Not recruiting	20	Stem Cell Educator-treated mononuclear cell apheresis	Determination of number of COVID-19 patients who were unable to complete SCE therapy.	–	https://clinicaltrials.gov/ct2/show/NCT04299152?term=mesenchymal

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Table 1 (*Continued*)

Clinical trial number	Study title	Phase	Status	Sample size, n	Cellular intervention	Primary outcome measure	Location	References
NCT04336254	Safety and efficacy study of allogeneic human dental pulp mesenchymal stem cells to treat severe COVID-19 patients	I and II	Recruiting	20	Allogeneic human dental pulp stem cells	Time to clinical improvement	Renmin Hospital of Wuhan University (East Campus), Wuhan, Hubei, China	https://clinicaltrials.gov/ct2/show/NCT04336254?term=stem
NCT04331613	Safety and efficacy of CAStem for severe COVID-19-associated with/without ARDS	I and II	Recruiting	9	CAStem	Adverse reaction and severe adverse reaction Changes in lung imaging examinations	Beijing Youan Hospital, Capital Medical University, Beijing, China	https://clinicaltrials.gov/ct2/show/NCT04331613?term=stem
NCT04339660	Clinical research of human mesenchymal stem cells in the treatment of COVID-19 pneumonia	I and II	Recruiting	30	Umbilical cord mesenchymal stem cells	Immune function (TNF-α, IL-1β, IL-6, TGF-β, IL-8, PCT, CRP) Blood oxygen saturation Evaluation of pneumonia change	Puren Hospital, Wuhan University of Science and Technology, Wuhan, Hubei, China	https://clinicaltrials.gov/ct2/show/NCT04339660?term=COVID19&cond=Mesenchymal
NCT04346368	Bone marrow-derived mesenchymal stem cell treatment for severe patients with coronavirus disease 2019 (COVID-19)	I and II	Not recruiting	20	Bone marrow mesenchymal stem cells	Changes in oxygenation index (PaO_2/FiO_2) Evaluation of pneumonia improvement	Guangzhou Institute of Respiratory Health, Guangzhou Medical University, Guangzhou, Guangdong, China	https://clinicaltrials.gov/ct2/show/NCT04346368?term=COVID19&cond=Mesenchymal
NCT04352803	Adipose mesenchymal cells for abatement of SARS cov-2 respiratory compromise in COVID-19 disease 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	I	Not recruiting	20	Autologous adipose mesenchymal stem cells	Side effects in the BM-MSC treatment group Incidence of unexpected adverse events Changes in mortality rate		https://clinicaltrials.gov/ct2/show/NCT04352803?term=COVID19&cond=Mesenchymal
NCT04349631	Repair of acute respiratory distress syndrome by stromal cell administration (REALIST) (COVID-19) (REALIST) Study of allogeneic HB-adMSCs to provide immune support against COVID-19	II	Enrolling by invitation	56	Hope Biosciences-adipose-derived mesenchymal stem cells	Incidence of hospitalization for COVID-19 Number of subjects requiring hospitalization for COVID-19 Incidence of COVID-19 symptoms Number of subjects developing symptoms associated with COVID-19	-Hope Biosciences Stem Cell Research Foundation, Texas, USA	https://clinicaltrials.gov/ct2/show/NCT04349631?term=COVID19&cond=Mesenchymal
NCT03042143		I and II	Recruiting	75	Human umbilical cord-derived, CD362-enriched mesenchymal stem cells	Oxygenation index Incidence of serious adverse events		https://clinicaltrials.gov/ct2/show/NCT03042143?term=COVID19&cond=Mesenchymal
NCT04348435		II	Enrolling by invitation	100	Hope Biosciences-adipose-derived mesenchymal stem sells	Incidence of hospitalization for COVID-19 Number of subjects hospitalized for COVID-19 Incidence of symptoms associated with COVID-19 during conduction of study Number of subjects who experience symptoms deemed to be associated with COVID-19	Belfast Health and Social Care Trust, Royal Hospitals, Northern Ireland, United Kingdom Hope Biosciences Stem Cell Research Foundation Sugar Land, Texas, USA	https://clinicaltrials.gov/ct2/show/NCT04348435?term=COVID19&cond=Mesenchymal

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Table 1 (*Continued*)

Clinical trial number	Study title	Phase	Status	Sample size, n	Cellular intervention	Primary outcome measure	Location	References
ChiCTR2000029606	Clinical study for human menstrual blood-derived stem cells (COVID-19)	0	Recruiting	63	Human menstrual blood-derived stem cells	Mortality rate	Hangzhou, Zhejiang, China	http://www.chictr.org.cn/showprojen.aspx?proj=49146
ChiCTR2000029580	Severe novel coronavirus pneumonia (COVID-19) patients treated with ruxolitinib in combination with mesenchymal stem cells: a prospective, single blind, randomized controlled clinical trial	0	Recruiting	70	Mesenchymal stem cells	Safety	Qiaokou District, Wuhan, Hubei, China	http://www.chictr.org.cn/showprojen.aspx?proj=49088
ChiCTR2000030300	Umbilical cord mesenchymal stem cells (hUCMSCs) in the treatment of high-risk novel coronavirus pneumonia (COVID-19) patients	I	Recruiting	9	Mesenchymal stem cells	Time to disease recovery Time for coronavirus to become negative Exacerbation time	Gulou District, Nanjingy, Jiangsu, China	http://www.chictr.org.cn/showprojen.aspx?proj=50022
ChiCTR2000030173	Key techniques of umbilical cord mesenchymal stem cells for the treatment of novel coronavirus pneumonia (COVID-19) and clinical application demonstration	0	Not recruiting	60	Umbilical cord mesenchymal stem cells	Pulmonary function Novel coronavirus pneumonic nucleic acid test	Changsha Economic and Technological Development Zone, Changsha, Hunan, China	http://www.chictr.org.cn/showprojen.aspx?proj=49229
ChiCTR2000030138	Clinical trial for human mesenchymal stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19)	II	Not recruiting	60	Human umbilical cord mesenchymal stem cells	Clinical index	Haidian District, Beijing, China	http://www.chictr.org.cn/showprojen.aspx?proj=50004
ChiCTR2000030116	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)	–	Recruiting	16	Umbilical cord mesenchymal stem cells	Time to getting off ventilator after MSC infusion	Donghu District, Nanchang, Jiangxi, China	http://www.chictr.org.cn/showprojen.aspx?proj=49901
ChiCTR2000030088	Umbilical cord Wharton's jelly-derived mesenchymal stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19)	0	Not recruiting	40	Wharton's jelly mesenchymal stem cells	Time for nucleic acid to turn negative Ground-glass shadow disappearance	Haidian District, Beijing, China	http://www.chictr.org.cn/showprojen.aspx?proj=49902
ChiCTR2000030020	The clinical application and basic research related to mesenchymal stem cells to treat novel coronavirus pneumonia (COVID-19)	–	Recruiting	20	Mesenchymal stem cells	Time for nucleic acid to turn negative Inflammation index	Zhengxiang District, Hengyang, Hunan, China	http://www.chictr.org.cn/showprojen.aspx?proj=49812
ChiCTR2000029990	Clinical trials of mesenchymal stem cells for the treatment of pneumonitis caused by novel coronavirus pneumonia (COVID-19)	I and II	Recruiting	120	Mesenchymal stem cells	Improved respiratory system function (blood oxygen saturation)	Dongdan, Dongcheng District, Beijing, China	http://www.chictr.org.cn/showprojen.aspx?proj=49674
ChiCTR2000029569	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	0	Not recruiting	30	Umbilical cord mesenchymal stem cells	Pneumonia severity index	Fancheng District, Xiangyang, Hubei, China	http://www.chictr.org.cn/showprojen.aspx?proj=49062
ChiCTR2000030261	A study for the key technology of mesenchymal stem cells exosomes atomization in the treatment of novel coronavirus pneumonia (COVID-19)	0	Not recruiting	26	Mesenchymal stem cell-derived exosomes	Lung CT	Jiangsu, China	http://www.chictr.org.cn/showprojen.aspx?proj=49963
ChiCTR2000030484	HUMSCs and exosomes treating patients with lung injury following novel coronavirus pneumonia (COVID-19)	–	Not recruiting	90	Human umbilical cord mesenchymal stem cells	P_{AO_2}/F_{IO_2} Frequency of respiratory exacerbation Number and range of lesions Time for dyspnea to become mild or disappear Inflammatory cytokines (CRP, PCT, SAA, etc.) Frequency of serious adverse events	Chaoyang District, Beijing, China	http://www.chictr.org.cn/showprojen.aspx?proj=50263

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Table 1 (*Continued*)

Clinical trial number	Study title	Phase	Status	Sample size, n	Cellular intervention	Primary outcome measure	Location	References
ChiCTR2000031139	Safety and effectiveness of human embryonic stem cell-derived M cells (CAStem) for pulmonary fibrosis correlated with novel coronavirus pneumonia (COVID-19)	0	Recruiting	20	The cell dose was 3*10^6 cells/kg, intravenously infused twice in a row, and the interval between each infusion was 1 week (± 2 days). If the investigator considered it necessary, an additional infusion could be performed. Infusion interval was 1 week (± 2 days) from the last infusion.	Pulmonary function evaluation Changes in blood gas analysis Evaluation of activity Evaluation of dyspnea	Dongxihu District, Wuhan, Hubei, China	http://www.chictr.org.cn/showprojen.aspx?proj=51404
ChiCTR2000030944	Clinical study of human NK cells and MSCs transplantation for severe novel coronavirus pneumonia (COVID-19)	I	Not recruiting	20	On the basis of the current clinical treatment of SNCP, NK cells and MSCs were increased	Changes in serum inflammatory factors Patient death risk Drug-related adverse reactions and events	Jiangxi, China	http://www.chictr.org.cn/showprojen.aspx?proj=50199
ChiCTR2000030866	Open-label, observational study of human umbilical cord-derived mesenchymal stem cells in the treatment of severe and critical patients with novel coronavirus pneumonia (COVID-19)	0	Recruiting	30	Mesenchymal stem cells	Oxygenation index Patient conversion rate from serious to critical Patient conversion rate and conversion time from critical to serious Mortality in serious and critically ill patients	Hunan, China	http://www.chictr.org.cn/showprojen.aspx?proj=50299
ChiCTR2000030835	Clinical study for the efficacy of mesenchymal stem cells (MSC) in the treatment of severe novel coronavirus pneumonia (COVID-19)	–	Recruiting	20	Routine treatment plus MSCs (2 × 10^6/kg each time)	–	Henan, China	http://www.chictr.org.cn/showprojen.aspx?proj=51050

BM-MSC, bone marrow-derived MSC; CT, computed tomography; NK, natural killer; PCT, procalcitonin; RT-PCR, real-time polymerase chain reaction; SAA, severe aplastic anemia; SCE, Stem Cell Educator; SNCP, severe novel coronavirus pneumonia.

The studies withdrawn, post-registration are as:

1- NCT04293692 (https://clinicaltrials.gov/ct2/show/NCT04293692?term=stem±cell&cond=COVID19&draw=2&rank=11)
2- ChiCTR2000029816 (http://www.chictr.org.cn/showprojen.aspx?proj=49389)
3- ChiCTR2000029817 (http://www.chictr.org.cn/showprojen.aspx?proj=49384)
4- ChiCTR2000030224 (http://www.chictr.org.cn/showprojen.aspx?proj=49968)
5- ChiCTR2000030509 (http://www.chictr.org.cn/showprojen.aspx?proj=49956)
6- ChiCTR2000030329 (http://www.chictr.org.cn/showprojen.aspx?proj=49779)
7- ChiCTR2000029812 (http://www.chictr.org.cn/showprojen.aspx?proj=49374)

studies, and existing knowledge of the mechanism underlying the cytokine storm is predicated on pre-clinical data in influenza infection models [,]. It has been suggested that when a virus infects the epithelial, endothelial and alveolar macrophage, the immune system initiates a rapid antiviral response for virus clearance and tissue homeostasis. In the process of virus clearance, the immune system activates the signaling cascade, resulting in production of several cytokines. The number of cytokines produced by direct contact with the virus and immune effector cells is estimated to be greater than 15, excluding chemokines [28]. The activated cytokines can stimulate the expression of a secondary wave of cytokines. For instance, influenza infection in epithelial cells activates type I interferons that upregulate the expression of a variety of interferon-stimulated genes [29]. In turn, the high expression of interferon-stimulated genes activates downstream antiviral responses and subsequent inflammatory cytokine production by innate immune cells like DCs, macrophages, neutrophils and monocytes. In the adaptive phase, diverse subsets of T cells and group 2 innate lymphoid cells regulate the discharge of secondary cytokines [29].

Several anti-cytokine approaches have proven effective in reversing cytokine storm syndromes, including those triggered by viruses [30]. These approaches include drugs targeting interleukins, such as IL-1, IL-6 and IL-18, and interferon gamma (IFN-γ). With respect to MSCs, Leng *et al.* [8] suggested using the cells specifically to combat the cytokine storm in COVID-19 patients. This approach is supported by data from non-viral acute lung injury animal studies. However, since existing animal models cannot replicate the natural course of acute lung injury [31], the aforementioned approach awaits further validation, especially in ARDS patients. A recent study by Park *et al.* [32] demonstrated that nanovesicles derived from MSCs had the ability to ameliorate the signs of cytokine storm, including weight and temperature changes, as well as excessive inflammatory response in a mouse model of sepsis provoked by bacterial outer membrane vesicles. Similarly, Khatri *et al.* [33] demonstrated that MSC-derived extracellular vesicles had the ability to attenuate inflammation in an influenza virus-induced swine lung injury model. Likewise, MSCs isolated from human orbital fat tissues have been found to be effective in modulating lipopolysaccharide (LPS)-induced acute lung inflammation through paracrine regulation of macrophage-mediated cytokine storm [34,35].

Improving MSC therapy for COVID-19 patients

There is mounting interest in the development of protocols for the generation of optimized immunomodulatory MSCs, which could be customized to target specific viral diseases. Since most intravenously infused MSCs get trapped in the lungs, cells can exert anti-inflammatory, anti-microbial and tissue repair functions while residing within damaged lungs via cell-to-cell contact without engrafting into the tissue [36]. However, the retention time of MSCs within the lungs is extremely short [36] and may or may not be increased during injury or infection. Galleu *et al.* [20] demonstrated that MSCs, when given as treatment for GVHD, show therapeutic efficacy without engrafting into the tissue. The mechanism underpinning recovery was found to be immunosuppression exerted by apoptotic MSCs. The study showed that *in vivo*MSCs undergo extensive apoptosis in response to paracrine secretion by cytotoxic cells. It is worth mentioning that, aside from MSC holding time in the tissue, identification of the most clinically effective MSC subpopulation is of great importance for ensuring homogeneous clinical outcomes. In this context, as suggested elsewhere in this article, the present findings could be used as a biomarker to predict clinical responses to MSCs. Nevertheless, stem cells transplanted in the infected or diseased lung usually encounter massive cell death within a few days of therapy. To enhance engraftment, preconditioning of MSCs could be beneficial [37]. For example, exposure to hypoxia prolongs survival of engrafted MSCs and increases their effectiveness in treating bleomycin-induced lung injury in rodents [38]. Moreover, hypoxic preconditioning induces the expression of pro-survival and pro-angiogenic markers in MSCs [39].

A similar study reported that hypoxia preconditioning of MSCs efficiently enhances cell survival, engraftment and engrafted cell survival, improves pulmonary respiratory function and downregulates inflammatory and fibrotic factor expression in a bleomycin-induced pulmonary fibrosis mouse model [38]. Another important strategy is genetic modification of MSCs to enhance their intrinsic ability to migrate and survive. For example, overexpression of *CXCR4* facilitates MSC homing and colonization within injured pulmonary tissues in acute lung injury [40], and MSCs engineered to overexpress *HO-1* [41] or *MnSOD* [42] show an improved survival rate in models of lung injury. Keratinocyte growth factor gene transfected to MSCs has been shown to improve lung infection and promote type II lung epithelial cell proliferation, thus facilitating survival after LPS-induced acute lung injury in a mouse model [43].

Other possible approaches to enhance the therapeutic effect of MSCs include overexpression of pro-reparative molecules, including platelet-derived growth factor [44] and angiopoietin 1 [45], or cytokines, such as IFN-γ [46] and IL-10 [47], to increase their immunosuppressive activity. Additionally, MSCs protect lung tissue from bleomycin-induced injury [48] via expression of interleukin 1 receptor antagonist (IL1RN), as IL1RN can block the production or activity of TNF-α and IL-1 [49]. Thus, identification of IL1RN-expressing human MSC subpopulations may provide a novel cellular vector for treating pulmonary infections in humans. Stimulation of MSCs via pre-treatment with pro-inflammatory signaling molecules (such as IL-1β) might also enhance the immunomodulatory properties of MSC-secreted exosomes [50]. The latter represent a viable cell-free approach that can be used to treat infected individuals. MSCs also express high levels of toll-like receptor (TLR) 3 and 4 [51]. The activation of TLR proteins represents an efficient mechanism for reinstating immune responses in the event of infection by enhancing the immunosuppressive effect of MSCs [51]. Similarly, the activation of toll-like receptor on MSCs by pathogen-associated molecules like LPS is also effective [52]. Selections of MSCs based on expressed levels of immunomodulatory proteins may enhance efficacy. As an example, a subset of Stro-1$^+$ MSCs show enhanced support for human hematopoietic stem cell engraftment and greater immunosuppressive capacity, while Stro-1$^-$MSCs manifest a broad distribution after infusion into tissues [53,54]. ACE2 has broader allocations in humans , which may possibly explain why some COVID-19 patients present with multiple complications. In these cases, MSCs with the potential for broad *in vivo* distribution may be applied. Additionally, combination therapies may be explored to enhance the effect of MSCs *in vivo*. For example, the combination of the sphingosine 1 phosphate analog FTY720 and UCMSCs attenuates acute lung injury and affords better survival in mice than either monotherapy [55]. Similarly, combining adipose-derived MSCs with pre-activated and disaggregated shape-changed platelets provides more protection to the rat lung from ARDS complicated by sepsis [56]. Nebulized heparin along with MSCs inhibits coagulation and inflammatory pathways and modulates alveolar macrophages [57]. All the aforementioned approaches seem advantageous, but whether they apply to COVID-19 has yet to be determined.

Discussion

The COVID-19 pandemic is rapidly spreading all over the world, posing great health and economic challenges. Thus far, available data suggest that the most vulnerable to infection are people aged 65 or older and those with existing serious health issues [58]. In severely affected patients, lung inflammation is characterized by invasion of neutrophils and macrophages into the alveolar space, which, together with overactivated pro-inflammatory cytokines, results in

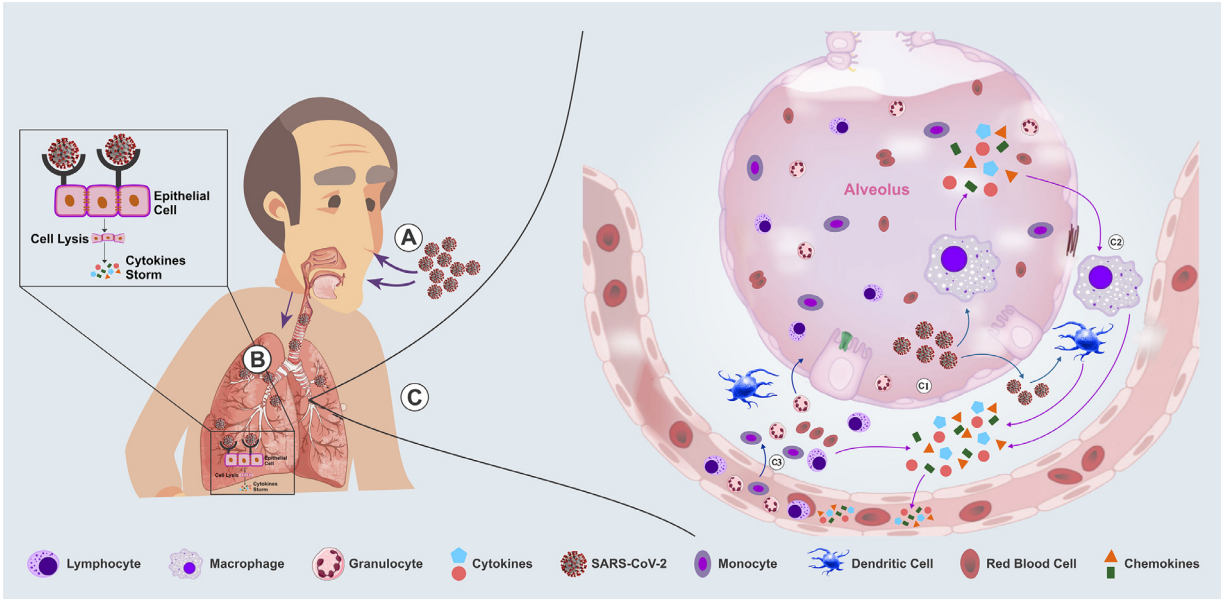

Figure 1. Representation of cytokine storm in the lungs following severe SARS-CoV-2 infection. (A) SARS-CoV-2 lands in the nose and mouth and reaches the lungs. (B) Schematic of SARS-CoV-2 infecting lung epithelial cells. (C) Enlarged picture of the events involved in the production of a cytokine storm. Viruses infect lung epithelial cells and alveolar macrophages, produce viral progeny and release cytokines and chemokines. Cytokine- and/or chemokine-activated macrophages and virally infected dendritic cells lead to a more intense immune response and thus initiate a cytokine storm. Discharged chemokines draw additional inflammatory cells from blood vessels into the site of inflammation. These cells discharge additional chemokines or cytokines to amplify the cytokine storm. (Color version of figure is available online).

impairment of lung endothelial and epithelial cells . Currently, in the absence of any specific therapies, the best way to manage COVID-19 is to reduce infection and mortality rates. Thus, there's a pressing need to find treatments that are effective in addressing infection-induced cytokine storm, which is associated with increased mortality, and also to prevent damage that may cause long-lasting impairment of lung function. Studies have shown that MSC-based therapies are effective in preventing steroid-resistant acute GVHD and viral diseases [59]. The antiviral [60] and antibacterial [61] action of MSCs, combined with their hypoimmunogenic nature due to low major histocompatibility complex class I expression and lack of major histocompatibility complex class II expression, is well documented. As shown in previous studies [59,60], ARDS develops most commonly in the setting of pneumonia (bacterial and viral; rarely fungal) [62].

In brief, respiratory pathogens, such as respiratory viruses and bacteria, induce inflammation in pathologic lesions and spread to lower respiratory cells along the respiratory tract [63]. Interestingly, intact pathogens (e.g., influenza virus) have not been detected in patients with fatal outcomes or experimental animals with extensive pathologic lesions of ARDS [64,65], indicating that pathogens, rather than acting directly, secrete toxins into the host cells. Nearly all infectious diseases, including pneumonia, have a primary infection site where pathogens replicate and where toxic substances are produced and released into nearby local lesions or the systemic circulation. MSCs have shown the ability to control virus replication and the inflammatory response of the host in a relevant pre-clinical large animal model of influenza virus [33]. Similarly, in bacterial infections, the focus of a replication site may produce many substances, including bacteria and fragments of bacterial components, such as polysaccharide capsules and bacterial exotoxins like pneumolysin and bacteriocin, which can be detected by blood cultures and microscopic examinations. In this context, MSC therapy has been found in a sepsis murine model to modulate transcription of up to 13% of the genome, with immune response-related effects, including a decrease in genes involved in antigen presentation and cell-to-cell interactions that regulate endothelial integrity and increase phagocytosis and bacterial killing [66], suggesting the antibacterial potential of MSCs. MSCs can also transfer mitochondria and microvesicles that modulate immunity and epithelial response to injury [67]. These data, coupled with the fact that MSCs can be readily procured in large numbers from various tissues, including adipose, liver and placental tissue as well as cord blood and dental pulp [68], make them an excellent candidate for cell therapy.

Accumulating evidence suggests that a subgroup of patients with severe COVID-19 show signs of cytokine storm syndrome . The virally induced cytokine storm has been linked to uncontrolled pro-inflammatory responses that encourage significant pulmonary immunopathology. Thus, understanding the relationships between events that occur from incubation to the onset of severe phases of disease progression holds the key for therapeutic interventions. The plasma of COVID-19 patients shows a higher level of IL-2, IL-6, IL-7, IL-10, TNF-α, granulocyte colony-stimulating factor, monocyte chemoattractant protein 1 and macrophage inflammatory protein 1α [], an indication of uncontrolled systemic cytokine storm, which may be attenuated using treatment with MSCs [8], although the mechanism remains unclear. As in hyper-inflammation, immunosuppressive measures are likely to be beneficial; thus, MSCs may exert an effect through inhibiting pro-inflammatory cytokines via their immunosuppressive potential [8]. Moreover, by making direct cell-to-cell contact with immune cells or secreting a range of anti-inflammatory factors, MSCs can target immune cells and affect their function. In addition, MSCs express several cell adhesion molecules, including intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, that attract activated immune cells [69], thereby increasing their exposure to anti-inflammatory signals from MSCs.

IL-6 is also a vital initiator of an uncontrolled cytokine storm [70] and is significantly correlated with severe cases of COVID-19 [71]. Previous studies have indicated that MSCs significantly inhibit cytokine storm by impeding the overproduction of IL-6 [72]. Thus, it is reasonable to assume that MSCs may, to some extent, suppress activated cytokines by suppressing the activation of IL-6 production. In any case, blocking IL-6 could be an effective strategy. The licensing approach is another robust technique to enhance the effectiveness of MSCs. Patients infected with SARS-CoV-2 have increased concentrations of IFN-γ , and the activation of IFN-γ prompts MSCs to exert their anti-inflammatory effect, which may be absent in severely

affected COVID-19 patients, as T cells are not activated well by SARS-CoV-2 infection [14]. In a recent clinical trial, the Abu Dhabi Stem Cell Center employed "activated" MSCs in 73 COVID-19 patients and claimed that inhaling MSCs nebulized into a fine mist helped patients overcome the symptoms caused by the virus, though it did not kill the virus (https://www.khaleejtimes.com/coronavirus-pandemic/coronavirus-uaes-stem-cell-treatment-fights-symptoms-of-covid-19-not-cure-it–) [73]. Based on the results, the authors of the study suggested that licensing/priming/activating MSCs could be a potential therapeutic strategy against COVID-19.

MSCs have been shown to improve lung function and endurance in chronic inflammatory lung diseases, including pulmonary hypertension, asthma, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis and silicosis [74]. For instance, COPD patients receiving bone marrow-derived MSCs have shown improved forced expiratory volume (NCT01306513) [75], lung mechanics and survival indicators (e.g., low CRP and body mass, airflow obstruction, dyspnea and exercise capacity index) (NCT01872624) [76]. Likewise, patients suffering from silicosis have shown increased lung perfusion, suggesting that the cells were well tolerated (NCT01239862) [77]. These data support the effectiveness and safety of MSCs in chronic lung diseases. Nevertheless, several studies have documented a lack of benefit or even potential negative impact of MSC transplantation in chronic pulmonary disease patients. For example, the multi-center, double-blind, placebo-controlled phase 2 clinical study by Weiss *et al.* [78], employing non-human leukocyte antigen-matched allogeneic bone marrow-derived MSCs, showed no significant differences in the overall number or frequency of COPD exacerbations or disease severity (NCT00683722). However, no adverse reactions or deaths were noticed in patients undergoing treatment.

MSCs have also been shown to improve acute pulmonary anomalies [79], and several positive outcomes of MSC transplantation in acute lung diseases are well documented [80–82]. For instance, the randomized phase 2 START trial showed that allogeneic MSC treatment for moderate to severe ARDS resulted in no toxic side effects, as the study noted only 1 death out of the 60 patients who received

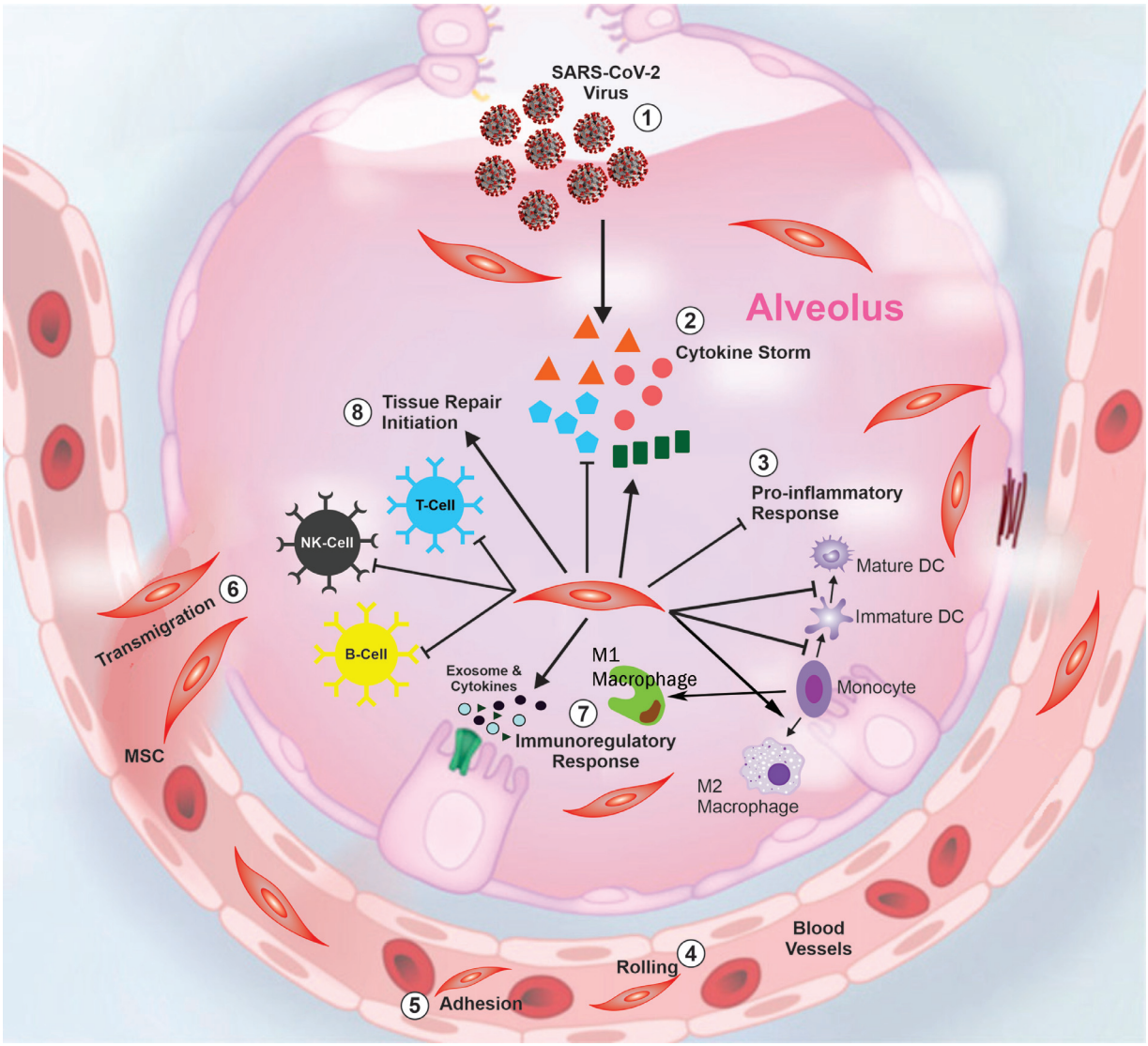

Figure 2. Hypothetical sketch of the immune response of MSCs in the SARS-CoV-2-infected lung. SARS-CoV-2 infection in the alveolus leads to uncontrolled production of growth factors. Depending on the cytokine signals, MSCs initiate the immunoregulatory response and repair the pulmonary tissue. In brief, the virus enters the alveolus (1), thereby activating the cytokine storm (2); the supplementation of exogenous MSCs in the alveolus though its anti-inflammatory potential (3), immunomodulatory reponses (7), paracrine secretion, cytokine storm modulation (2), tissue protection, tissue repair (8) and, possibly, viral resistance reverses the detrimental outcome of the pulmonary microenvironment. The number 4,5,6 shows the transmigration and adhesive abilities of the MSCs. Abbreviation: DC: Dendritic Cells, SARS-CoV2: Severe acute respiratory syndrome coronavirus 2; MSC: Mesenchymal Stem Cell; NK-cells: Natural Killer cells. (Color version of figure is available online).

MSC treatment, and the death was judged to be unrelated [83]. However, the multi-center, open-label, dose-escalation phase 1 START trial showed adverse events in 3 of the 9 patients who received MSCs. Two patients developed worsening multi-organ failure and shock on study day 6 and expired on study day 9, after the MSC infusion, and one showed multiple embolic infarcts of the spleen, kidneys and brain. Nevertheless, based on the MRI results, the observed embolic infarcts were believed to have occurred prior to the MSC infusion [84]. Although the safety of MSCs is well documented in lung pathologies, larger trials are needed to prove their effectiveness and to investigate any associated adverse events before MSCs can be employed in acute or chronic inflammatory lung diseases.

In addition, MSCs have been shown to inhibit the differentiation of monocytes into DCs and alter the cytokine profiles of DCs by upregulating regulatory cytokines and downregulating pro-inflammatory cytokines as well as induce tolerant phenotypes of naive and effector T cells and suppress T and natural killer cell differentiation and proliferation [16–19] (Figure 2). Interestingly, MSCs may also promote regulatory T-cell expansion and suppress proliferation of effector T cells [85]. Moreover, the immunomodulatory properties of MSCs are linked to the expression of TLR receptors in MSCs, which is stimulated by pathogen-associated molecules like LPS or double-stranded RNA from viruses [86] such as SARS-CoV-2. Therefore, the role of TLR signaling in the abrogation of the disease by MSC treatment cannot be ruled out. Altogether, these findings are consistent with evidence indicating that MSCs enhance COVID-19 resolution by inhibiting inflammatory responses.

One of the important factors in COVID-19 treatment is the time window with regard to anti-inflammatory treatment, as patients with severe cases of the disease usually experience abrupt deterioration within 1–2 weeks of onset. Thus, prompt initiation of anti-inflammatory measures is likely to be of significant benefit. Identifying the correct timing and dose of MSCs—in addition to MSC passage number—as well as route of delivery is therefore important for achieving favorable outcomes. Equally important may be determining the optimal MSC tissue source [87]. It is also important to take into account the fitness of the MSCs, as freshly harvested cells may tend to show more robustness post-transplantation. It is worth mentioning that freshly harvested cells are the prime choice for infusion in clinics, although cryopreserved cells are certainly becoming the norm nowadays. Since clinical experience with regard to MSCs and SARS-CoV-2 viral infection in the lungs is incredibly limited, further studies addressing the efficacy of MSCs in pulmonary damage are needed to reveal the true potential of MSC-based therapies for this viral infection.

Conclusions

MSC therapy can overcome the present clinical challenges in COVID-19 patients, especially those who are critically ill and not responsive to conventional therapies. Preliminary clinical data suggest that MSCs possess the capacity to lessen systemic inflammatory responses and protect against SARS-CoV-2 virus-induced injury. Though preliminary results from clinical investigations are encouraging, it is too early to predict the therapeutic potential of MSCs in COVID-19. Additional studies in a larger cohort of patients are needed to validate their potential efficacy.

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Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: Acquisition of data: Analysis and interpretation of data: Drafting or revising the manuscript: SSR. MAK writtent the introduction of the current manuscript. Both authors have approved the final article.

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References

[1] Worldometer: https://www.worldometers.info/coronavirus/
[2] Shah RD, Wunderink RG. Viral Pneumonia and Acute Respiratory Distress Syndrome. Clin Chest Med 2017;38(1):113–25.
[3] Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y, Yuen KY. KU/UCH SARS Study Group. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361 (9371):1767–72.
[4] Shang J, Ye G, Shi K, Wan Y, Luo C, Aihara H, Geng Q, Auerbach A, Li F. Structural basis of receptor recognition by SARS-CoV-2. Nature 2020;30.
[5] Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;4.
[6] Li F, Li W, Farzan M, Harrison SC. Structure of SARS coronavirus spike receptor-binding domain complexed with receptor. Science 2005;309:1864–8.
[7] Jia HP, Look DC, Hickey M, Shi L, Pewe L, Netland J, Farzan M, Wohlford-Lenane C, Perlman S, McCray Jr PB. Infection of human airway epithelia by SARS coronavirus is associated with ACE2 expression and localization. Adv Exp Med Biol 2006;581:479–84.
[8] Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 neumonia. Aging Dis 2020;11:216–28.
[9] Cano RLE, Lopera DHE. Introduction to T and B lymphocytes. Bogota (Colombia), 18. El Rosario University Press; 2013.
[10] Wilson JG, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. Lancet Respir Med 2015;3:24–32.
[11] Chen J, Hu C, Chen L, Tang L, Zhu Y, Xu X, Lu Chen, Gao H, Lu X, Yu L, Dai X, Xiang C, Li L. Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. Engineering (Beijing) 2020;28.
[12] Zheng G, Huang L, Tong H, Shu Q, Hu Y, Ge M. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. Resp Res 2014;15:39.
[13] Liang B, Chen J, Li T, Wu H, Yang, Li WY, Li Y, Li J, Yu C, Nie F, Ma Z, Yang M, Nie P, Goa Y, Qian C, Hu M. Clinical remission of a critically ill COVID19 patient treated by human umbilical cord mesenchymal stem cells. 2020. http://chinaxiv.org/abs/202002.00084.
[14] Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G. COVID-19 infection: the perspectives on immune responses. Cell Death Diff 2020.
[15] Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105(4):1815–22.
[16] Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine pro- duction: role of indoleamine 2,3-dioxygenase and prostaglan- din E2. Blood 2008;111(3):1327–33.
[17] Luz-Crawford P, Kurte M, Bravo-Alegria J. Mesenchymal stem cells generate a CD4 +CD25+Foxp3+ regulatory T cell population during the differentiation process of Th1 and Th17 cells. Stem Cell Res Ther 2013;4(3):65.
[18] Luz-Crawford P, Djouad F, Toupet K. Mesenchymal stem cell-derived interleukin 1 receptor antagonist promotes macrophage polarization and inhibits B cell differentiation. Stem Cells 2016;34(2):483–92.
[19] Khoury M, Cuenca J, Cruz FF, Figueroa FE, Rocco PRM, Weiss DJ. Current Status of Cell-Based Therapies for Respiratory Virus Infections: Applicability to COVID-19. Eur Respir J 2020;7:2000858.
[20] Galleu A, Riffo-Vasquez Y, Trento C, Lomas C, Dolcetti L, Cheung TS, von Bonin M, Barbieri L, Halai K, Ward S, Weng L, Chakraverty R, Lombardi G, Watt FM, Orchard K, Marks DI, Apperley J, Bornhauser M, Walczak H, Bennett C, Dazzi F. Apoptosis in mesenchymal stromal cells induces in vivo recipient-mediated immunomodulation. Sci Transl Med 2017;9(416). eaam7828.
[21] Hayes M, Masterson C, Devaney J, Barry F, Elliman S, O'Brien T, O' Toole D, Curley GF, Laffey JG. Therapeutic Efficacy of Human Mesenchymal Stromal Cells in the

Repair of Established Ventilator-Induced Lung Injury in the Rat. Anesthesiology 2015;122(2):363–73.
[22] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semi Immunopathol 2017;39(5):529–39.
[23] Liu Q, Zhou YH, Yang ZQ. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell Mol Immunol 2016;13(1):3–10.
[24] Behrens EM, Koretzky GA. Review: Cytokine Storm Syndrome: Looking Toward the Precision Medicine Era. Arthritis Rheumatol 2017;69(6):1135–43.
[25] Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy 2016;8(8):959–70.
[26] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China. The Lancet. 2020;395:497–506.
[27] Liu Q, Zhou Y, Yang Z. The cytokine storm of severe influenza and development of immunomodulatory therapy. Cell Mol Immunol 2016;13:3–10.
[28] Guo XJ, Thomas PG. New fronts emerge in the influenza cytokine storm. Semin Immunopathol 2017;39(5):541–50.
[29] Kato H, Sato S, Yoneyama M, et al. Cell Type-Specific Involvement of RIG-I in Antiviral Response. Immunity 2005;23:19–28.
[30] Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID19): The Perspectives of clinical immunologists from China. Clin Immunol 2020;214:108393.
[31] Matute-Bello G, Frevert CW, Martin TR. Animal models of acute lung injury. Am J Physiol Lung Cell Mol Physiol 2008;295(3):L379–99.
[32] Park KS, Svennerholm K, Shelke GV, Bandeira E, Lässer C, Jang SC, Chandode R, Gribonika I, Lötvall J. Mesenchymal stromal cell-derived nanovesicles ameliorate bacterial outer membrane vesicle-induced sepsis via IL-10. Stem Cell Res Ther 2019;10(1):231.
[33] Khatri M, Richardson LA, Meulia T. Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model. Stem Cell Res Ther 2018 Jan 29;9(1):17.
[34] Lien GS, Liu JF, Chien MH, Hsu WT, Chang TH, Ku CC, Ji AT, Tan P, Hsieh TL, Lee LM, Ho JH. The ability to suppress macrophage-mediated inflammation in orbital fat stem cells is controlled by miR-671-5p. Stem Cell Res Ther 2014;5(4):97.
[35] Chien MH, Bien MY, Ku CC, Chang YC, Pao HY, Yang YL, Hsiao M, Chen CL, Ho JH. Systemic human orbital fat-derived stem/stromal cell transplantation ameliorates acute inflammation in lipopolysaccharide-induced acute lung injury. Crit Care Med 2012;40:1245–53.
[36] Armitage J, Tan DBA, Troedson R, Young P, Lam KV, Shaw K, Sturm M, Weiss DJ, Moodley YP. Mesenchymal stromal cell infusion modulates systemic immunological responses in stable COPD patients: A phase I pilot study. Eur Respir J 2018;51(3).
[37] Meng SS, Xu XP, Chang W, Lu ZH, Huang LL, Xu JY, Liu L, Qiu HB, Yang Y, Guo FM. LincRNA-p21 promotes mesenchymal stem cell migration capacity and survival through hypoxic preconditioning. Stem Cell Res Ther 2018;9(1):280.
[38] Lan YW, Choo KB, Chen CM, Hung TH, Chen YB, Hsieh CH, Kuo HP, Chong KY. Hypoxia-preconditioned mesenchymal stem cells attenuate bleomycin-induced pulmonary fibrosis. Stem Cell Res Ther 2015;6(1):97.
[39] Chacko SM, Ahmed S, Selvendiran K, Kuppusamy ML, Khan M, Kuppusamy P. Hypoxic preconditioning induces the expression of prosurvival and proangiogenic markers in mesenchymal stem cells. Am J Physiol Cell Physiol 2010;299:C1562–70.
[40] Yang JX, Zhang N, Wang HW, Gao P, Yang QP, Wen QP. CXCR4 receptor overexpression in mesenchymal stem cells facilitates treatment of acute lung injury in rats. J Biol Chem 2015;290(4):1994–2006.
[41] Chen X, Wu S, Tang L, et al. Mesenchymal stem cells overexpressing heme oxygenase-1 ameliorate lipopolysaccharideinduced acute lung injury in rats. J Cell Physiol 2019;234(5):7301–19.
[42] Chen HX, Xiang H, Xu WH, et al. Manganese superoxide dismutase gene-modified mesenchymal stem cells attenuate acute radiation-induced lung injury. Human Gene Therapy 2017;28(6):523–32.
[43] Chen J, Li C, Gao X, et al. "Keratinocyte growth factor gene delivery via mesenchymal stem cells protects against lipopolysaccharide-induced acute lung injury in mice. PLoS One 2013;8(12):e83303.
[44] Wang S, Mo M, Wang J, et al. Platelet-derived growth factor receptor beta identifies mesenchymal stem cells with enhanced engraftment to tissue injury and proangiogenic property. Cell Mol Life Sci 2018;75:547–61.
[45] Mei SH, McCarter SD, Deng Y, et al. Prevention of LPS-induced acute lung injury inmice by mesenchymal stem cells overexpressing angiopoietin 1. PLoS Med 2007;4:e269.
[46] Krampera M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A, et al. Role for interferon-gamma in the immunomodulatory activity of human bone marrow mesenchymal stem cells. Stem Cells 2006;24(2):386–98.
[47] Wang C, Lv D, Zhang X, et al. Interleukin-10- Overexpressing Mesenchymal Stromal Cells Induce a Series of Regulatory Effects in the Inflammatory System and Promote the Survival of Endotoxin-Induced Acute Lung Injury in Mice Model. DNA Cell Biol 2018;37:53–61.
[48] Ortiz LA, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N, Phinney DG. Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. Proc Natl Acad Sci U S A 2003;100(14):8407–11.
[49] Ortiz LA, Dutreil M, Fattman C, Pandey AC, Torres G, Go K, Phinney DG. Interleukin 1 receptor antagonist mediates the antiinflammatory and antifibrotic effect of mesenchymal stem cells during lung injury. Version 2. Proc Natl Acad Sci U S A 2007;104(26):11002–7.
[50] Song Y, Dou H, Li X, et al. Exosomal miR-146a Contributes to the Enhanced Therapeutic Efficacy of Interleukin-1beta-Primed Mesenchymal Stem Cells Against Sepsis. Stem Cells 2017;35:1208–21.
[51] de Witte SF, Franquesa M, Baan CC, Hoogduijn MJ. Toward Development of iMesenchymal Stem Cells for Immunomodulatory Therapy. Front Immunol 2016;6:648.
[52] Liotta F, Angeli R, Cosmi L, Fili L, Manuelli C, Frosali F, et al. Toll-like receptors 3 and 4 are expressed by human bone marrow-derived mesenchymal stem cells and can inhibit their T-cell modulatory activity by impairing notch signaling. Stem Cells 2008;26(1):279–89.
[53] Bensidhoum M, Chapel A, Francois S, Demarquay C, Mazurier C, Fouillard L, et al. Homing of in vitro expanded Stro-1- or Stro-1+ human mesenchymal stem cells into the NOD/SCID mouse and their role in supporting human CD34 cell engraftment. Blood 2004;103(9):3313–9.
[54] Nasef A, Zhang YZ, Mazurier C, Bouchet S, Bensidhoum M, Francois S, et al. Selected Stro-1-enriched bone marrow stromal cells display a major suppressive effect on lymphocyte proliferation. Int J Lab Hematol 2009;31(1):9–19.
[55] Zhang Z, Li W, Heng Z, et al. Combination therapy of human umbilical cord mesenchymal stem cells and FTY720 attenuates acute lung injury induced by copolysaccharide in a murine model. Oncotarget 2017;8:77407–14.
[56] Chen CH, Chen YL, Sung PH, et al. Effective protection against acute respiratory distress syndrome/sepsis injury by combined adipose-derived mesenchymal stem cells and preactivated disaggregated platelets. Oncotarget 2017;8:82415–29.
[57] Chimenti L, Camprubi-Rimblas M, Guillamat-Prats R, et al. Nebulized Heparin Attenuates Pulmonary Coagulopathy and Inflammation through Alveolar Macrophages in a Rat Model of Acute Lung Injury. Thromb Haemost 2017;117:2125.
[58] Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395(10229):1014–5.
[59] Thanunchai M, Hongeng S, Thitithanyanont A. Mesenchymal Stromal Cells and Viral Infection. Stem Cells Int 2015;2015:860950.
[60] Chan MC, Kuok DI, Leung CY, Hui KP, Valkenburg SA, Lau EH, Nicholls JM, Fang X, Guan Y, Lee JW, Chan RW, Webster RG, Matthay MA, Peiris JS. Human mesenchymal stromal cells reduce influenza A H5N1-associated acute lung injury in vitro and in vivo. Proc Natl Acad Sci U S A 2016;113(13):3621–6.
[61] Walter J, Ware LB, Matthay MA. Mesenchymal stem cells: Mechanisms of potential therapeutic benefit in ARDS and sepsis. Lancet Respir Med 2014;2(12):1016–26.
[62] Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG, Calfee CS. Acute respiratory distress syndrome. Version 2. Nat Rev Dis Primers 2019;5(1):18.
[63] Lee KY. Pneumonia, Acute Respiratory Distress Syndrome, and Early Immune-Modulator Therapy. Int J Mol Sci 2017;18(2):388.
[64] Lee KY, Rhim JW, Kang JH. Hyperactive immune cells (T cells) may be responsible for acute lung injury in influenza virus infections: A need for early immunemodulators for severe cases. Med Hypotheses 2011;76:64–9.
[65] Hers JF, Goslings WR, Masurel N, Mulder J. Death from Asiatic influenza in the Netherlands. Lancet 1957;273:1164–5.
[66] dos Santos CC, Murthy S, Hu P, Shan Y, Haitsma JJ, Mei SH, Stewart DJ, Liles WC. Network analysis of transcriptional responses induced by mesenchymal stem cell treatment of experimental sepsis. Am J Pathol 2012;181(5):1681–92.
[67] Monsel A, et al. Therapeutic effects of human mesenchymal stem cell-derived microvesicles in severe pneumonia in mice. Am J Respir Crit Care Med 2015;192(3):324–36.
[68] Raza SS, Wagner AP, Hussain YS, Khan MA. Mechanisms underlying dentalderived stem cell-mediated neurorestoration in neurodegenerative disorders. Stem Cell Res Ther 2018 Sep 26;9(1):245.
[69] Ren GW, Zhao X, Zhang LY, Zhang JM, L'Huillier A, Ling WF, et al. Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in mesenchymal stem cells are critical for immunosuppression. J Immunol 2010;184(5):2321–8.
[70] Kong LX, Zhou YJ, Bu H, Lv T, Shi Y, Yang J. Deletion of interleukin-6 in monocytes/macrophages suppresses the initiation of hepatocellular carcinoma in mice. J ExpClin Cancer Res 2016;35:131.
[71] Pedersen SF, Ho YC. SARS-CoV-2: A Storm is Raging. J Clin Invest 2020;27:137647.
[72] Guo G, Zhuang X, Xu Q, Wu Z, Zhu Y, Zhou Y, Li Y, Lu Y, Zhang B, Talbot P, et al. Peripheral infusion of human umbilical cord mesenchymal stem cells rescues acute liver failure lethality in monkeys. Stem Cell Res Ther 2019;10:84.
[73] https://www.khaleejtimes.com/coronavirus-pandemic/coronavirus-uaes-stem-cell-treatment-fights-symptoms-of-covid-19-not-cure-it–
[74] Cruz FF, Rocco PRM. The potential of mesenchymal stem cell therapy for chronic lung disease. Expert Rev Respir Med 2020;14(1):31–9.
[75] Stolk J, Broekman W, Mauad T, et al. A phase I study for intravenous autologous mesenchymal stromal cell administration to patients with severe emphysema. QJM 2016;109:331–6.
[76] de Oliveira HG, Cruz FF, Antunes MA, et al. Combined bone marrow-derived mesenchymal stromal cell therapy and one-way endobronchial valve placement in patients with pulmonary emphysema: a phase i clinical trial. Stem Cells Transl Med 2017;6(3):962–9.
[77] Morales MM, Souza SA, Loivos LP, et al. Pilot safety study of intrabronchial instillation of bone marrow-derived mononuclear cells in patients with silicosis. BMC Pulm Med 2015;15:66.

[78] Weiss DJ, Casaburi R, Flannery R, LeRoux-Williams M, Tashkin DP. A placebocontrolled, randomized trial of mesenchymal stem cells in COPD. Chest 2013;143:1590–8.
[79] Cardenes N, Caceres E, Romagnoli M, Rojas M. Mesenchymal stem cells: a promising therapy for the acute respiratory distress syndrome. Respiration 2013;85:267–78.
[80] Zhang L, Li Q, Liu W, Liu Z, Shen H, Zhao M. Mesenchymal Stem Cells Alleviate Acute Lung Injury and Inflammatory Responses Induced by Paraquat Poisoning. Med Sci Monit 2019;25:2623–32.
[81] Pedrazza L, Cunha AA, Luft C, Nunes NK, Schimitz F, Gassen RB, Breda RV, Donadio MV, de Souza Wyse AT, Pitrez PMC, Rosa JL, de Oliveira JR. Mesenchymal stem cells improves survival in LPS-induced acute lung injury acting through inhibition of NETs formation. J Cell Physiol 2017;232(12):3552–64.
[82] Zanoni M, Cortesi M, Zamagni A, Tesei A. The Role of Mesenchymal Stem Cells in Radiation-Induced Lung Fibrosis. Int J Mol Sci 2019;20(16):3876.
[83] Matthay MA, Calfee CS, Zhuo H, Thompson BT, Wilson JG, Levitt JE, Rogers AJ, Gotts JE, Wiener-Kronish JP, Bajwa EK, Donahoe MP, McVerry BJ, Ortiz LA, Exline M, Christman JW, Abbott J, Delucchi KL, Caballero L, McMillan M, McKenna DH, Liu KD. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. Lancet Respir Med 2019;7(2):154–62.
[84] Wilson JG, Liu KD, Zhuo H, et al. "Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. The Lancet Respiratory Medicine 2015;3(1):24–32.
[85] Belkaid Y, Tarbell K. Regulatory T cells in the control of host-microorganism interactions (*). Annu Rev Immunol 2009;27:551.
[86] Li W, Ren G, Huang Y, Su J, Han Y, Li J, et al. Mesenchymal stem cells: a double-edged sword in regulating immune responses. Cell Death Differ 2012;19:1505–13.
[87] Ahmad A, Fauzia E, Kumar M, Mishra RK, Kumar A, Khan MA, Raza SS, Khan R. Gelatin-coated Polycaprolactone Nanoparticle-mediated Naringenin delivery rescue human Mesenchymal Stem Cells from Oxygen-glucose Deprivation induced Inflammatory Stress. ACS Biomater Sci Eng 2019;5(2):683–95.