Mesenchymal stem cells as a potential therapy for COVID-19

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Abstract
The outbreak of 2019 novel coronavirus disease (COVID-19) worldwide is becoming rapidly a major concern. The number of severe cases has increased dramatically worldwide, while specific treatment options are scarce. The main pathologic features of severe or critical COVID-19 were consistent with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), characterized by cellular fibromyxoid exudates, extensive pulmonary inflammation, pulmonary edema, and hyaline membrane formation. Mesenchymal stem cells (MSCs) can balance the inflammatory response and has been mentioned to be effective on ALI/ARDS from both infectious and noninfectious causes previously, presenting an important opportunity to be applied to COVID-19. In this commentary, we summarize the clinical trials of MSCs treatments on ALI/ARDS and raise MSCs as a hopefully alternative therapy for severe or critical COVID-19.

Keywords: COVID-19, ALI, ARDS, MSCs

Background
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) is a newly-recognized infectious disease. It has rapidly transmitted and become a major concern all over the world. As of April 3, 2020, the total number of patients has risen sharply to 1,033,060 worldwide, with 54,677 (5.29%) deaths [1]. Apart from supportive care, oxygen supply in mild cases, and extracorporeal membrane oxygenation and low-dose corticosteroids in critical cases, intravenous remdesivir and convalescent plasma might be the effective potential therapy for SARS-CoV-2 infection. However, randomized clinical trials are needed to further evaluate the safety and efficacy of them in COVID-19 treatment. The specific and novel therapeutic methods for this disease are still being explored.

Main text
The main pathologic features of severe or critical COVID-19 contain hypoxemia, diffuse alveolar damage with cellular fibromyxoid exudates, extensive pulmonary inflammation, pulmonary edema, and hyaline membrane formation. The pathologic changes are similar with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [2], also observed in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection. However, more serious inflammatory exudation, pulmonary edema and inflammatory cytokine storm, and milder pulmonary fibrosis and consolidation were observed in severe or critical COVID-19 than those in SARS. Mesenchymal stem cells (MSCs), which originate from bone marrow, fat, umbilical cord, placenta, and other tissues, have abundant supply, differentiation potential, powerful immunoregulation, and endogenous repair mechanisms. As one of the most widely studied adult stem cells in regenerative medicine, MSCs produce...
meaningful therapeutic outcomes for the treatment of pulmonary, cardiovascular, neurological, liver, and kidney diseases. The immune-regulation of MSCs depends mainly on modulating activation and effector function of immune cells, suppressing lung-infiltrated cells, and enhancing the resolution of pulmonary edema [3]. The incomplete revealed mechanisms but critical roles of MSCs on anti-inflammatory effects imply that MSCs is a potential therapy for severe and critical COVID-19.

MSCs have been identified to efficiently cure ALI/ARDS from both infectious and noninfectious causes, mediated primarily by paracrine mechanisms based on the released extracellular vesicles (EVs), such as microvesicles and exosomes [4]. In the cargo of the EVs, more than 850 unique gene products and more than 150 miRNAs have been identified by mass spectrometry analysis. Either the miRNAs or the transcripts are enriched in the regulators of the immune system [5, 6].

Detailed, MSCs can alter the behavior of both adaptive and innate immune cells. They can release keratinocyte growth factor, prostaglandin E2, granulocyte-macrophage colony-stimulating factor, and IL-6 and IL-13 to facilitate the phagocytosis and alternative activation of alveolar macrophage, alter the cytokine secretion profile of immune cells, suppressing lung-infiltrated cells, and enhancing the resolution of pulmonary edema [3]. The in- complete revealed mechanisms but critical roles of MSCs on anti-inflammatory effects imply that MSCs is a potential therapy for severe and critical COVID-19.

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Table 1 The clinical trials of MSCs on ALI/ARDS

| No. | Study name (NCT number) | Starting date | Phase | MSCs type and dose | The origin of ALI/ARDS | Key findings/study status |
|-----|-------------------------|---------------|-------|--------------------|------------------------|--------------------------|
| 1   | Adipose-derived MSCs in ARDS (NCT 01902082) | Nov 2012 | Phase 1b | Intravenous infusion of human adipose MSCs, with 1 × 10^6/kg | Unknown | Low dose of 1 × 10^6 adipose-derived MSCs/kg was well tolerated |
| 2   | MSCs for ARDS (NCT 01775774) | Jul 2013 | Phase 1b dose-escalation tolerated | Intravenous infusion of hBM MSCs, with 1, 5, or 10 × 10^6/kg | Pneumonia or sepsis or aspiration or pre eclampsia | All MSCs doses well tolerated. No adverse effects detected |
| 3   | MSCs for treatment of ARDS in stem cell transplant patients (NCT 02804945) | Feb 2017 | Phase 2 | By vein with a maximum dose of 3 × 10^6 cell/kg one time at day 1 | Unknown | Completed |
| 4   | Clinical study to assess the safety and preliminary efficacy of hUC-MSCs in ARDS (NCT 04289194) | Dec 2019 | Phase 1–2 | Intravenous administration of allogeneic adipose-derived adult MSCs expanded and pulsed with H_2O_2, the maximum tolerated dose (1 or 2 × 10^6 cells/kg) | Unknown | Active, not recruiting |
| 5   | Repair of ARDS by stromal cell administration (NCT 03042143) | Jan 2019 | Phase 1–2 | Human UC-derived CD362-enriched MSCs, the maximum tolerated dose from phase 1 trial | Unknown | Recruiting |
| 6   | UC-MSCs therapy in ARDS (NCT 02608592) | Jun 2018 | Not applicable | Intravenous infusion of UC-MSCs, dose 1 × 10^6/kg | Unknown | Recruiting |
| 7   | UC-MSCs therapy in ALI (NCT 02444455) | May 2015 | Phase 1–2 | Intravenous infusion of hUB-MSCs, 5 × 10^6 cell/kg once a day, three times | Unknown | Recruiting |
| 8   | MSCs in patients with ARDS (NCT 02112500) | Feb 2014 | Phase 2 | Intravenously infusion of MSCs | Unknown | Recruiting |
| 9   | UC-MSCs in the treatment of novel coronavirus severe pneumonia (NCT 04273646) | Feb 2020 | Not applicable | Intravenous 4 times of UC-MSCs (0.5 × 10^6 UC-MSCs/kg BW) at day 1, 3, 5, 7 | Unknown | 2019-COVID Not yet recruiting |
| 10  | A pilot clinical study on inhalation of MSCs exosomes treating severe novel coronavirus pneumonia (NCT 04276987) | Feb 2020 | Phase 1 | 5 times aerosol inhalation of MSCs-derived exosomes (2.0 × 10^7 nano vesicles/3 ml) at day 1, 2, 3, 4, 5 | Unknown | 2019-COVID Not yet recruiting |
| 11  | UC-MSCs treatment for the 2019-novel coronavirus pneumonia (NCT 04269525) | Feb 2020 | Phase 2 | Intravenous infusion of UC-MSCs at day 1, 3, 5, 7 | Unknown | 2019-COVID Recruiting |
| 12  | Treatment with MSCs for severe corona virus disease 2019 (NCT 04288102) | Feb 2020 | Phase 1–2 | Intravenous 3 times of MSCs (BW ≥ 70 kg, 4.0 × 10^7 cells/time; BW < 70 kg, 3.0 × 10^7 cells/time) at day 0, 3, 6 | Unknown | 2019-COVID Not yet recruiting |
| 13  | MSCs treatment for pneumonia patients infected with 2019 novel coronavirus (NCT 04252118) | Jan 2020 | Phase 1 | Intravenous 3 times of MSCs 3.0 × 10^6 at day 0, 3, 6 | Unknown | 2019-COVID Recruiting |
| 14  | Efficacy and safety of UC-MSCs for the treatment of severe viral pneumonia (NCT 04282928) | Feb 2020 | Phase 1 | Intravenous infusion of definitive HUC-MSCs (1 × 10^6 cell/kg × BW) | Unknown | Influenza infection viremia pneumonia Not yet recruiting |

Abbreviations: MSCs mesenchymal stem cells, UC umbilical cord, UC-MSCs umbilical-cord-derived mesenchymal stem cells, hBM MSCs human bone marrow-derived mesenchymal stem cells, BW body weight, NCT National Clinical Trial, ALI acute lung injury, ARDS acute severe respiratory failure, COVID nCoV infection severe pneumonia.
dendritic cell subsets, and decrease the release of interferon γ from natural killer cells. IL-10, transforming growth factor β, and tryptophan catabolizing enzyme indoleamine 2,3-dioxygenase secreted from them can also suppress the proliferation of T cells and change the cytokine secretion profile of T cell subsets [7]. Moreover, the proliferation, differentiation, and chemotactic properties of B cells were impaired by MSCs as well [8]. Except for the immune regulatory effects, MSCs can enhance restoration of capillary barrier [9], inhibit bacterial growth [10], and restore alveolar ATP [11]. All the functions mentioned above might also be effective on ARDS induced by COVID-19 infection.

Some clinical trials for evaluating the efficacy and safety of MSC treatment on ALI/ARDS have begun. The inclusion criteria are according to the Berlin definition of ARDS [12] in common, while the START trial [13] had a more strict definition of moderate-to-severe ARDS with 4 categories: (1) positive pressure ventilation by an endotracheal or tracheal tube with a PaO2/FiO2 ratio of < 200 with at least 8 cm H2O positive end-expiratory airway pressure, (2) bilateral infiltrates consistent with pulmonary edema on the frontal chest radiograph, (3) without clinical evidence of left atrial hypertension or a pulmonary arterial occlusion pressure ≤ 18 mmHg, and (4) categories 1–3 must be present within a 24-h time period and at the time of enrolment. Exclusion criteria included patients younger than 18 years, pre-existing severe disease of any major organs, pregnancy, malignant disease, severe chronic respiratory disease, recent deep vein thrombosis or pulmonary embolism, human immunodeficiency virus infection, or if informed consent could not be obtained. In addition, the patients in whom more than 96 h since first meeting the Berlin definition for ARDS had also been excluded in the START trial to avoid enrolling patients with late ARDS. The completed clinical trials demonstrate that MSCs are well tolerated without adverse effects in ALI/ARDS (Table 1) [14, 15]. Additionally, acute graft-versus-host-disease (GVHD) is a life-threatening complication of allogeneic hematopoietic stem cell transplantation due to its inflammatory storm. A meta-analysis revealed that infused MSCs could reduce acute GVHD grade and increase overall survival [16]. The therapeutic effects of MSCs on ALI/ARDS and GVHD with powerful inflammatory balance are solid proofs for the application of MSCs on other originated ALI/ARDS.

Furthermore, MSC treatment significantly ameliorates ALI/ARDS induced by H9N2 avian influenza virus [17] and H5N1 [18] in mice, and even influenza virus in pig [19], indicating the possible efficacy of MSCs on viral ALI/ARDS. Importantly, MSCs can cure the patients with severe refractory ARDS [20], who failed to improve after both standard life support measures including mechanical ventilation and additional measures including extracorporeal ventilation, pointing that MSC could be used for serious viral ALI/ARDS. Some Chinese research groups triggered the clinical studies on MSCs treating critical COVID-19 (Table 1). In the trigged clinical trials, the inclusion criteria for severe or critical COVID-19 include respiratory rate (RR) ≥ 30 times/min, pulse oxygen saturation (SpO2) at rest ≤ 93%, partial pressure of PaO2/FiO2 ≤ 300 mmHg, requirement for mechanical ventilation, shock, etc. As of February 21, 2020, four patients with severe COVID-19 were recovered and discharged by MSCs therapy in China [21]. Therefore, we believe that MSCs would be a new effective therapeutic method for severe or critical COVID-19.

According to World Health Organization [22], the management of COVID-19 has mainly focused on infection prevention, case detection and monitoring, and supportive care. However, no specific anti-SARS-CoV-2 treatment is recommended because of the absence of evidence. Most importantly, the current guidelines emphasize that systematic corticosteroids should not be given routinely for COVID-19 treatment, which was also the recommendation in a Comment in The Lancet [23]. Evidence shows that MSCs can be used as a treatment without the occurrence of severe adverse events. In conclusion, it might be noteworthy to test the safety and efficacy of MSC transfusion in COVID-19 patients, especially for the severe or critical cases.

**Abbreviations**

COVID-19: 2019 novel coronavirus disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; MSCs: Mesenchymal stem cells; MERS: Middle Eastern respiratory syndrome; GVHD: Graft-versus-host-disease; EVs: Extracellular vesicles

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**Authors’ contributions**

SL and DP contributed to the study design, data analysis and interpretation, and writing of the manuscript. HQ collected the data mentioned in the article. KY revised the manuscript. ZF and LZ contributed to the study design, financial support, data analysis and interpretation, and writing, editing and revising and final approval of the manuscript. The author(s) read and approved the final manuscript.

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**Availability of data and materials**

Please contact us for the detailed data.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.
Competing interests
The authors have no conflicts of interest to declare.

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