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May mesenchymal stem cell transplantation be a solution for COVID-19 induced cytokine storm?

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Abstract

The recently emergent disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), transmitted by droplets and aerosols, was named coronavirus disease 2019 (COVID-19) by World Health Organization. Predominantly, the disease progress is asymptomatic or mild, but one-fifth of the patients advance to severe or critical illness. In severe COVID-19 patients, type-2 T helper cells release numerous cytokines; this excessive immune response is named as cytokine storm. The cytokine storm, which is the hallmark of the COVID-19 induced by the disease and aggravates due to lack of proper immune response, similar to SARS and Middle East respiratory syndrome (MERS), and the disease status may progress forward to acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, multi-organ dysfunction syndrome, and death. Mesenchymal stromal cell transplantation is up-and-coming in treating many diseases such as HIV, hepatitis B, influenza, coronavirus diseases (SARS, MERS), lung injuries, and ARDS. Upon closer inspection on respiratory diseases, COVID-19, influenza, SARS, and MERS have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for the treatment of COVID-19.

Key Words: Mesenchymal stem cell; Mesenchymal stromal cell; COVID-19; Cytokine storm; Immunosuppression; Transplantation

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respiratory syndrome have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for the treatment of COVID-19. Transplantation of mesenchymal stromal cells provides tissue regeneration and rejuvenation with immunotolerant and immunomodulant properties on damaged tissues by exerting their effects through immune cells.

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INTRODUCTION

The substantial clues of a novel severe acute respiratory syndrome (SARS)-like coronavirus and possible outbreak were predicted with highlighting pandemic preparedness by Ge *et al*[1] from Wuhan in 2013. Two years after this study, Menachery *et al*[2] had been likewise drawing attention to a potential risk of SARS coronavirus (SARS-CoV) re-emergence from viruses circulating in bat populations. In late 2019, a few patients related to a seafood market in Wuhan province from China with the symptoms of fever, myalgia, dry cough, dyspnea, headache, sore throat, diarrhea, nausea, vomiting, and SARS-like viral pneumonia were reported[3,4]. Further analyses have shown a novel single-stranded enveloped RNA virus from the Coronaviridae family, and the genome sequence of the virus had 96.2% similarity with other bat betacoronaviruses causing previous diseases [79.6% with SARS, approximately 50% with Middle East respiratory syndrome (MERS)]. The recently emergent disease caused by the SARS-CoV-2 virus, transmitted by droplets and aerosols, was named coronavirus disease 2019 (COVID-19) by World Health Organization (WHO)[5-8]. As a consequence of increasing cases, WHO has announced that the outbreak would be assessed as a pandemic from March 11st, 2020, onward[9]. The disease differs from influenza-related pneumonia in that it is able to progress very seriously, even in young people without comorbidity. To date, mainly being in the first place thousands of bravely health workers like Li Wenliang, more than 4 million deaths and 200 million cases were confirmed, and the outbreak still has destructible impacts on economic and social circumstances[10-12]. The disease currently does not have any curable therapy. Recently discovered vaccines are being commenced to use in many countries with emergency use authorization[13,14]. Several new variants were reported, which are thought to be more infectious from the United Kingdom and numerous countries[15,16]. Due to this manner, the need for new and effective treatments continues.

Predominantly, the disease progress is asymptomatic or mild, but one-fifth of the patients advance to severe or critical illness[17]. In severe COVID-19 patients, type-2 T helper (Th) cells release numerous cytokines; this excessive immune response is named as 'cytokine storm', which is the leading cause of lung injury, acute respiratory distress syndrome (ARDS), multi-organ dysfunction syndrome (MODS), and death[18, 19]. In this review, we aim to outline the usage of mesenchymal stem cells (MSCs) or, in other words, mesenchymal stromal cells, which have immunosuppressant and immunomodulatory benefits in countless diseases such as graft-*vs*-host disease, Crohn's disease, and some type of lung injuries, on severe or critically ill COVID-19 patients[20-24].

INTRODUCTION TO COVID-19 PATHOGENESIS AND PRESENT THERAPIES

In the eighty percent of the people who have been exposed to the SARS-CoV-2 *via* droplets and aerosols from an infected person, the disease remains limited in the upper respiratory tract. However, in the rest of the patients, the virus proceeds to the lower respiratory tract, and with pulmonary involvement, it causes more severe

illness. Disease mortality was reported between 0.5 and 2 percent in different studies and changes with obesity, older age, hypertension, and underlying chronic medical conditions[25-27]. The infectious process might occur progressively in a wide range of manifestations with life-threatening cardiovascular, thromboembolic, neurological, and respiratory complications[4,19,28,29]. As compatible with virus-cell invasion pathophysiology, organ involvement is correlated with the expression of host cells' angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease, serine 2 (TMPRSS2) enzyme[30,31]. Unfortunately, the ACE2 receptor is widely distributed on the human cell surface, like lung, intestine, liver, kidney, brain, especially the alveolar type II (AT2) cells, capillary endothelium, and the AT2 cells highly express TMPRSS2[32-34]. On the grounds of that, the primary target of the virus is the lung. Moreover, the maladaptive immune response in severely ill patients damages the airways and causes a terrible cytokine storm characterized by elevated blood cytokine levels as a consequence of hyperactivation of the immune cells and impaired feedback mechanism. However, it leads to excessive infiltration of monocytes, macrophages, and T cells in the lungs. Therefore, disease severity in patients is due to not only the viral infection but also the host response. A notable example of this condition might be multisystem inflammatory syndrome in children and multisystem inflammatory syndrome in adults[35,36]. This uncontrolled hyperinflammatory response catalyzes multi-organ damage leading to multi-organ failure, especially of the cardiac, hepatic, and renal systems[18,29]. These organ failures raise the mortality rate, such as most patients with SARS-CoV-2 infection who developed acute kidney injury or have existing chronic kidney disease eventually died[37]. At present, no curative and effective COVID-19 treatment available, and the primary approach to patients is supportive care such as oxygen therapy (such as high flow nasal cannula oxygen therapy, mechanic ventilation), antipyretics, or venous thromboembolism prophylaxis[38,39]. Various drugs and supplementary therapies like antivirals (remdesivir, lopinavir/ritonavir, oseltamivir, favipiravir), antibiotics (azithromycin), immunomodulatory drugs (tocilizumab, hydroxychloroquine, convalescent plasma, anakinra, *etc.*) are being still investigated, but none of the therapies have reliable evidence[17]. To date, the only drug which is evidenced to decrease the mortality rate in severe and critically ill patients is corticosteroids[40]. Also, a specific agent to alleviate the SARS-CoV-2 induced cytokine storm is not developed as yet, and drugs that are aimed at this phenomenon are non-specific. Suppressing the excessive immune response is the key difficulty of the therapy options [41]. It is thought that people who overcome COVID-19 might have long-term sequels and different organ damages, notably lung and heart[42,43]. Multipotent MSC transplantation could promote lung and other damaged tissue repairs with its differentiation and paracrine secretory properties (exosomes/extracellular vesicles) and may prevent morbidities[44-47].

IMMUNO-PATHOGENESIS OF THE DISEASE AND PATIENT SELECTION FOR MSC TRANSPLANTATION

The virus that reaches the lungs from the upper respiratory tract *via* the ACE2 receptor infects AT2 cells here. After intracellular replication, it spreads to the parenchyma by exocytosis and causes epithelial and endothelial damage. The alveolar macrophages recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) that arise from infected both AT-1 and AT-2 type dead cells, and the initiation of the inflammation is triggered (Figure 1). Thus, numerous chemokines and cytokines are started to secret excessively by lung and peripheral immune cells[18]. The cytokine storm, which is the hallmark of the COVID-19 induced by the disease and aggravates due to lack of proper immune response, similar to SARS and MERS, and the clinical status may progress forward ARDS, systemic inflammatory response syndrome, MODS, and death[48,49].

When the severe patients' laboratory results were analyzed, decreased lymphocyte count, elevated leukocyte count, neutrophils-lymphocytes ratio, a low percentage of monocyte, eosinophils, and basophils have been observed. Besides, Th, T suppressor (Ts), and regulatory T (Treg) cell count were determined as more obviously decreased in severe cases[50]. While studies on the pathophysiology of the disease are continuing, the following substances were found high in patients who suffer from cytokine storm: interleukin (IL)-1 β , IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, and IL-17; granulocyte-macrophage colony-stimulating factor (GM-CSF); TNF- α , IFN- γ , and IFN- γ inducible protein 10 (IP10); monocyte chemoattractant protein 1 (MCP-1);

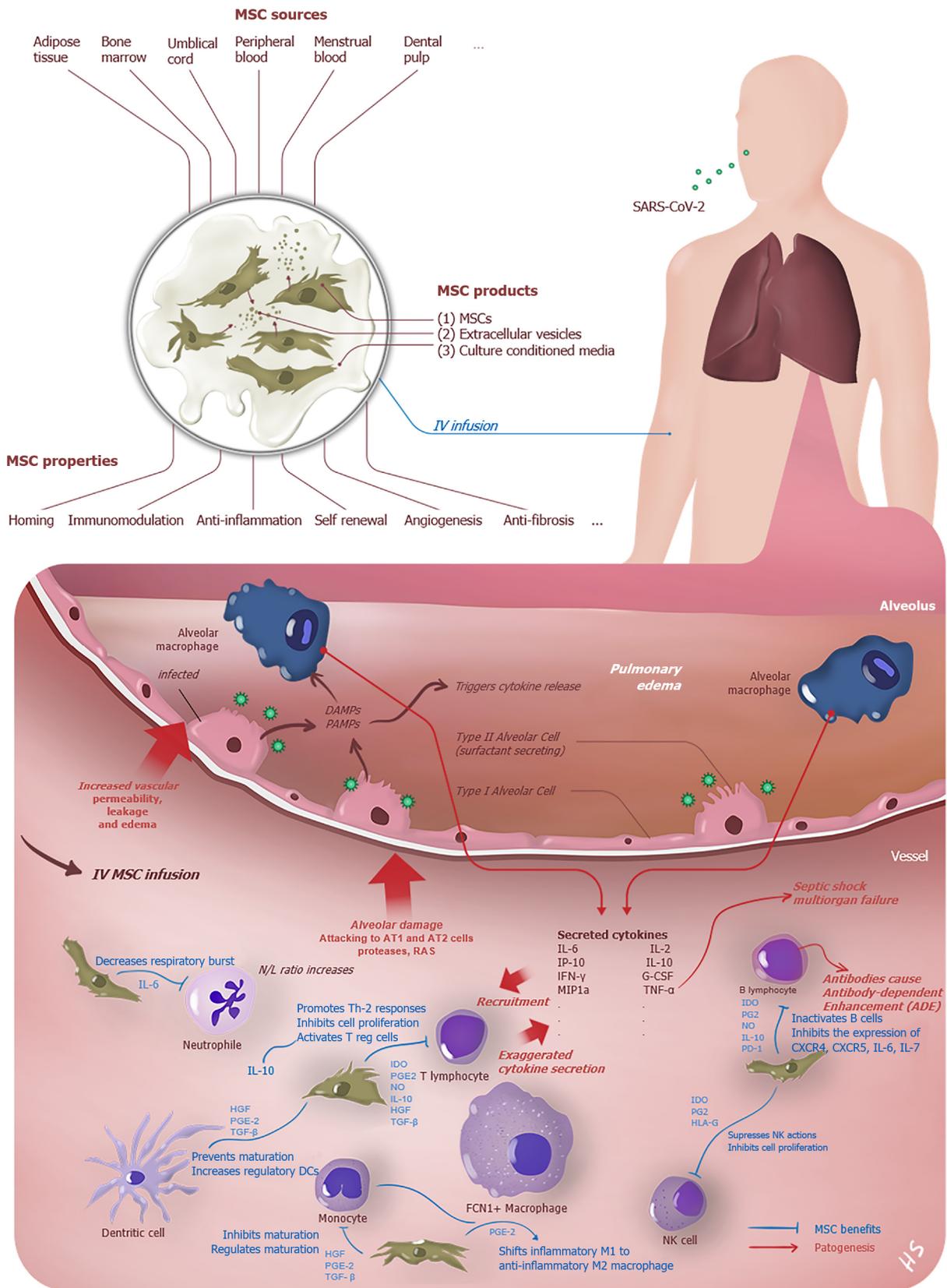


Figure 1 Summary of coronavirus disease 2019 pathogenesis and mesenchymal stem cells benefits. IL: Interleukin; PAMP: Pathogen-associated molecular patterns; DAMP: Damage-associated molecular patterns; IP-10: Interferon gamma-induced protein 10; IFN: Interferon; MIP1a: Macrophage inflammatory protein-1a; TNF- α : Tumor necrosis factor α ; IDO: Indoleamine 2,3-dioxygenase; G-CSF: Granulocyte colony-stimulating factor; PG: Prostaglandin; PD-1: Programmed cell death protein 1; HGF: Hepatocyte growth factor; TGF- β : Transforming growth factor- β ; FCN1+: Ficolin-1 (highly inflammatory monocyte-derived macrophage); AT: Adipose tissue; DC: Dendritic cell; T reg: regulatory T lymphocytes; NK cells: Natural killer cells; CXCR: CXC motif chemokine receptors; IV: Intravenous; RAS: Renin-angiotensin system; N/L: Neutrophil/lymphocyte; MSC: Mesenchymal stem cells.

macrophage inflammatory protein 1 α (MIP-1 α) and MIP-1 β ; chemokines like CC

chemokine ligand 2 (CCL2), CCL3, and CCL5; and C-X-C motif chemokine ligand 8 (CXCL8), CXCL9, and CXCL10[4,51]. In the detailed clustering analyses of the patients, higher C-reactive-protein (CRP), D-Dimer, ferritin, IP-10 (CXCL10), IL-10, IL-6 were founded to strongly correlated with poor clinical prognosis[52,53].

Together with these results, it is thought immunosuppression might be harmful in the early stages but helpful late stages of the disease. For this reason, the timing of the immunomodulatory therapies is essential[19]. Mortality rate reductive effects of the corticosteroids in patients who are intubated or only taken oxygen support can be explained with their potent anti-inflammatory effects[54]. Immunosuppression is a two-sided sword, and selective application is fundamental. Nevertheless, the ideal candidates for the immunomodulatory therapy in COVID-19 are still unspecified. Even only cytokine-specific therapies like IL-6 inhibitor tocilizumab might cause increasing the risk of sepsis, bacterial pneumonia, gastrointestinal perforation, and hepatotoxicity as a possible consequence of profound immunosuppression[55]. Additionally, indiscriminate and long-lasting immunosuppression has some disadvantages as SARS-CoV-2 progression and secondary infections. Therefore, administration of the short half-live immunosuppressant drugs will be more appropriate management.

There is still no consensus about the biomarkers that can be used for patient selection. However, besides the being need for further studies, it is thought that severe and critically ill patients might benefit from immunomodulatory options including MSC transplantation. Focusing on potential cytokine storm predictors, cytokine level measurement, especially IL-6, is not routine and usually is a "send-out" test. Instead of that, there are more accessible tests such as CRP, D-Dimer, and Ferritin, but their cut-off values vary in different studies. Another disease, hemophagocytic lymphohistiocytosis (HLH), which is induced cytokine storm, has a diagnostic score H score, (it assets temperature, organomegaly, number of cytopenias, triglycerides, fibrinogen, ferritin, aspartate aminotransferase, hemophagocytes on bone marrow aspirate, and known immunosuppression), and modified or a redesigned version of the score will be helpful not only in the management of MSC transplantation but, including other immunomodulatory therapies[56]. Further studies, which take these variables into account, need to be undertaken.

BENEFITS AND MECHANISMS OF MSC TRANSPLANTATION AND LIMITATIONS OF THE STUDIES

MSCs were firstly described in 1968 by Friedenstein *et al*[58] with a cluster of cells from bone marrow as colony-forming unit-fibroblasts[57]. Multipotent MSCs were defined by the International Society for Gene & Gene Therapy with three minimal criteria; being plastic adherent, specific surface antigen expression (expressing CD73, CD90, and CD105, lacking the expression of hematopoietic and endothelial markers CD11b, CD14, CD19, CD34, CD45, CD79 α , and HLA-DR) and multipotent differentiation potential (capable of *in vitro* differentiation into adipocyte, chondrocyte and osteoblast lineages)[59]. Recently, The International Society for Cell & Gene Therapy (ISCT) Mesenchymal Stromal Cell (ISCT MSC) committee has advised naming these extraordinary cells as "Mesenchymal Stromal Cells" instead of "Mesenchymal Stem Cells" to clarify nomenclature[60]. In this review, we use the terms as synonyms. These cells derived from limited tissues like adipose, umbilical cord, placenta, synovium, and menstrual blood has such properties as priming, self-renewal, differentiation, immunomodulation & immunoprivilege, angiogenesis & repair, homing mechanism, anti-apoptosis, anti-inflammation & anti-fibrosis, and clinical trials about the benefits on COVID-19 patients continue[61].

MSC transplantation is up-and-coming in treating many diseases such as HIV, Hepatitis B, Influenza, coronaviruses (SARS, MERS), lung injuries, and ARDS. The only treatment of the HLH disease that causes the cytokine storm is stem cell transplantation[62]. Upon closer inspection on respiratory diseases, COVID-19, influenza, SARS, and MERS have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for COVID-19 treatment[56,63]. In influenza A (H5N1) infection-induced lung injury, which acts similar to COVID-19 pro-inflammatory cytokine release, the significant benefits of MSCs in both cytokine profile and alveolar clearance are evidenced[23,64]. Menstrual-blood-derived MSC transplantation has significantly reduced mortality in influenza A (H7N9)-induced ARDS[22]. Mahendiratta *et al*[65] recently published a systematic review and reported pooled evidence on MSC therapy

benefits in SARS-CoV-2, SARS-CoV, MERS-CoV, and ARDS.

While MHC-1 expression of the MSCs provides the escape from Natural killer cells response, minimal MHC-2 expression or absence of this surface protein hampers the CD4⁺ T cell response. For this reason, they are assumed as hypoimmunogenic[66]. MSCs, provide tissue regeneration and rejuvenation with immunotolerant and immunomodulant properties on damaged tissues by exerting their effects through immune cells[67]. Also, young MSCs might be useful in older adults because aged MSCs contribute to inflammaging and immunosenescence, which may explain the high mortality rate in this population due to COVID-19[68,69]. As well as numerous mechanisms are continuing to be investigated, some of them can be summarized as follows: (1) Inhibition of T cell (significantly cytotoxic CD8⁺ T cells, Th 1, Th 17)[61,70-72], B cell proliferation to plasma cell (thus MSCs can reduce the secretion of immunoglobulin), Dendritic cell activation, and apoptosis of T cells; (2) Differentiation of the cytokine profile and cell type of T cells and B cells into anti-inflammatory cytokines such as induces the production of IL-10 and regulatory T cell, regulatory B cell[61,67]; (3) Reduction of production in cytokine storm-related inflammatory factors, such as IL-1 α , IL-6, IFN- γ , IL-17, TNF- α (Figure 1)[73]; (4) Promoting the transformation of inflammation-related M1 macrophages to regeneration-related M2 macrophages[74, 75]; and (5) MSC products like exosomes and extracellular vesicles that do not contain any cell are thought to have similar effects to MSC transplantation, owing to the soluble mediator profiles they secrete[67,76].

Besides being encouraging and promising, the previous studies had some limitations, and one crucial of them is the small sample size. Also, the outcomes of the studies were not standardized, and most of the outcomes are observatory. Commonly evaluated parameters are CRP, D-dimer, IL-6, IL-10, TNF- α , blood lymphocyte, neutrophil counts, pulmonary involvements in thorax computed tomography, and radiography imaging. Another point is that some studies were assumed as successful, despite having already an ameliorative trend in parameters before transplantation[77, 78]. In almost all of the studies, patients had received antibiotics, antivirals, antipyretics, corticosteroids, and supportive treatments (Table 1).

ISSUES OF THE MSC TRANSPLANTATION

Although clinical research is still ongoing, strict 'Good Manufacturing' rules are applied in the preparation of MSCs for clinical use[79]. It is seen that these rules are rigorously followed in the studies. The frequently preferred IV MSC dose is 10⁶ cells per kilogram, and the infusion rate is 60 min, but the total dose calculation (*e.g.*, 15 × 10⁷ cells) and multiple injection choices varied in different studies (Table 1). MSCs reach the lungs about venous vascular anatomy through IV administration and have been shown clearance from injured and inflamed lung tissue within 24-48 h[80]. Most of the studies to date have not contained any information about the ACE2 expression of administered MSCs or supposed as lack of ACE2 expression. Nevertheless, Derkeste *et al*[81] reported that adult bone marrow, adipose tissue, and umbilical-cord derived MSCs highly express ACE2. The same study has shown that placenta-derived MSCs and human-induced pluripotent stem cells are the best sources for COVID-19 treatment because of very low or absence ACE2 expression. Another significant aspect of MSC products is the contained pro-inflammatory cytokine amount. There are concerns regarding the possibility of worsened the cytokine storm by this situation. Moreover, the inflammatory response within the first two hours was reported due to IV MSC infusion[82]. About that, it has been seen a single shot corticosteroid application before the MSC infusion in previous studies. A recent systematic review from Thompson *et al*[83] has indicated intravascular (IV) MSC transplantation safety. The study has shown an association with fever but not non-fever acute infusional toxicity, infection, thrombotic/embolic events, or malignancy. However, Moll *et al*[84] have drawn attention to that MSCs highly express the procoagulant tissue factor and could trigger blood clotting in COVID-19 patients already in a hypercoagulable state. Finally, while cell-based strategies have tremendous benefits, it should be kept in mind that treatment costs are still very high, and the developing countries will have difficulties meeting these therapies[85].

Table 1 Promising mesenchymal stem cells studies

Ref.	MSC type	Sample size	Dose	Outcome
Leng <i>et al</i> [86]	ACE2 ⁺ MSC	10 patients (7 MSC + 3 Placebo)	Single infusion 10 ⁶ cells/kg cells IV, 40 min	A decrease of TNF- α and an increase of anti-inflammatory IL-10 were significant ($P < 0.05$). Other outcome data consisted of one critically ill patient. Three of the 7 patients who taken MSC discharged in the follow-up period
Zhang <i>et al</i> [77]	Human umbilical cord Wharton's jelly-derived MSCs (hWJCs)	One critically ill patient	Single infusion 10 ⁶ cells/kg cells IV, 40 min	The patient was discharged 6 d after the administration. They suggested that remarkable amelioration in imaging, laboratory, and clinical test outcomes
Sánchez-Guijo <i>et al</i> [87]	Adipose tissue-derived MSC (AT-MSC)	13 severe ill patients	More than 1 infusion approximately 10 ⁶ cells/kg cells IV	Two patients died during the follow-up period. They detected a decrease in inflammatory parameters and an increase in total lymphocyte counts 5 d after administration
Sengupta <i>et al</i> [88]	Bone marrow MSCs derived exosomes	24 patients	Single infusion 15 ml ExoFlo™ IV	The study's survival rate is 83%, and 71% of the patients were recovered in the study interval. The outcome of the study is a clinical improvement with an average PaO ₂ /FiO ₂ rate increase of 192% ($P < 0.001$)
Peng <i>et al</i> [89]	UC-MSCs and CP	1 severe ill patient	Two times infusion plasma volume 400 mL (Total) (1:160 titer SARS-CoV-2 specific IgG); 3 times infusion 10 ⁶ cells/kg (Total) IV 30-40 min	Lack of response to CP treatment, MSCs were administrated to the patient. After the clinical improvement, the patient was discharged
Liang <i>et al</i> [78]	UC-MSCs	1 critically ill patient	3 times infusion 5 × 10 ⁷ cell (each time) with thymosin- α 1 IV	Clinical and laboratory improvement had been seen; The patient was discharged 17 d after the first MSC infusion
Tang <i>et al</i> [90]	Menstrual blood-derived MSCs	2 patients	3 times infusion 10 ⁶ /kg cells	Imaging and laboratory improvement had been seen
Shu <i>et al</i> [91]	UC-MSCs	41 severe ill patients (12 MSC treatment + 29 Placebo)	Single infusion 2 × 10 ⁶ cells/kg IV 60 min	In treatment arm progression from severe to critical illness and 28-d mortality rate were 0, while 4 patients deteriorated to critical condition and 3 of them died, 28 d mortality rate was 10.34%. The treatment arm's clinical and laboratory improvements were significantly faster than the placebo group
Tao <i>et al</i> [92]	Human umbilical cord blood-derived MSCs	1 critically ill patient	5-times infusion 1.5 × 10 ⁶ cells/kg (each time) IV 60-80 min	After the MSC treatment, related to the clinical condition, the patient had undergone lung transplantation. The patient died 6 d after the transplantation because of the rejection
Feng <i>et al</i> [93]	UC-MSCs	16 severe and critically ill patients	4 times with one-day intervals 1 × 10 ⁸ cells once 90 min	The primary outcome was oxygenation index on day 14, and it has improved after UC-MSCs transplantation. On day 28, there is no significant difference between severe and critical types' mortality rates (6.25%)
Guo <i>et al</i> [94]	UC-MSCs	31 severe and critically ill patients	10 ⁶ /kg cells in 100 mL saline 200 mL (median volume) for each patient	They reported a significant increase in lymphocyte count, PaO ₂ /FiO ₂ , and decrease CRP, D-Dimer, IL-6, procalcitonin

UC: Umbilical cord; MSC: Mesenchymal stem cell; AT: Adipose Tissue; CP: Convalescent plasma; IL: Interleukin; PaO₂: Partial pressure of oxygen; FiO₂: Fraction of inspired oxygen; CRP: C reactive protein.

CONCLUSION

Despite to be seen the benefits of MSC and its products in COVID-19, the mechanisms still need to be elucidated. Therefore, the need for the results of ongoing clinical trials and meta-analyses of randomized controlled trials continues. We think that if the costs, ethical, and storage problems of treatments are resolved over time, they might prevent COVID-19 related morbidity and mortality. We foresee that most of these problems will get over with advanced researches on MSC products. However, it should not be overlooked that MSC and MSC-based treatments are still experimental and have pros and cons.

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