Review

Mesenchymal stem cell transfusion: Possible beneficial effects in COVID-19 patients

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ABSTRACT

SARS-CoV-2 attaches to the angiotensin-converting enzyme 2 (ACE-2) receptor on human cells. The virus causes hypercytokinemia, capillary leak, pulmonary edema, acute respiratory distress syndrome, acute cardiac injury, and leads to death. Mesenchymal stem cells (MSCs) are ACE-2 negative cells; therefore, can escape from SARS-CoV-2. MSCs prevent hypercytokinemia and help the resolution of the pulmonary edema and other damages occurred during the course of COVID-19. In addition, MSCs enhance the regeneration of the lung and other tissues affected by SARS-CoV-2. The case series reported beneficial effect of MSCs in COVID-19 treatment. However, there are some concerns about the safety of MSCs, particularly referring to the increased risk of disseminated intravascular coagulation, and thromboembolism due to the expression of TF/CD142. Prospective, randomized, large scale studies are needed to reveal the optimum dose, administration way, time, efficacy, and safety of MSCs in the COVID-19 treatment.

1. Introduction

Coronaviruses (CoVs) were first identified in the 1930s as the cause of animal bronchitis and gastroenteritis [1]. Human CoVs were first discovered in the 1960s as the cause of the common cold; however, they caused life-threatening acute respiratory distress syndrome (ARDS) in the last two decades [2,3]. In 2002, Severe Acute Respiratory Syndrome CoV (SARS-CoV) started to cause fatal respiratory system infections in China and spread to Southeast Asia and Canada, resulted in 8273 infected cases with a case fatality rate (CFR) of 9.3 % [2]. Ten years later, Middle East Respiratory Syndrome CoV (MERS-CoV) started to cause fatal infections in Saudi Arabia. Two additional MERS outbreaks were reported in 2015 and 2018, affecting 2494 cases in 27 countries, with a CFR of 37 % [4]. At the end of 2019, Novel CoV (2019-nCoV) which was later named as SARS-CoV-2, found to be related with a cluster of pneumonia patients in China [5,6]. The disease caused by SARS-CoV-2 was named as COVID-19, by the World Health Organization (WHO). More than 160 million confirmed cases of COVID-19 have been

registered to the WHO as of 15 May 2021, including more than 3 million deaths [7].

2. Pathophysiology of COVID-19

2.1. Entrance into the host cell

SARS-CoV-2 attaches to the angiotensin-converting enzyme 2 (ACE-2) receptor on human cells. ACE-2 is highly expressed on epithelial cells of lung [8,9]. In addition to the lung, ACE-2 is expressed by a variety of tissues, including heart, liver, and kidney [9]. Therefore, once SARS-CoV-2 enters the bloodstream, it can bind to many tissues in the body. This explains why SARS-CoV-2 mainly affects the respiratory system, but dysfunctions of other organs are also observed during the course of COVID-19 [10].

2.2. Tissue damage

SARS-CoV-2 causes hypercytokinemia and exacerbated systemic inflammation is known to be the leading cause of death [11]. The release of cytokines including interferon gamma (IFN-γ), inducible protein (IP)-10, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1A, interleukin (IL)-2, IL-6, IL-7, and tumor necrosis factor (TNF) results in capillary leak, pulmonary edema, ARDS, and acute cardiac injury, and leads to death [12].

3. Characteristics of mesenchymal stem cells

In stem cell therapy, either differentiated cells or stem cells capable of differentiation are transplanted into an individual with the objective of yielding specific cell types in the damaged tissue and restoring its function [13]. Stem cells can remain undifferentiated for a long period and can differ between one lineage (unipotent), multiple lineages (multipotent), or all 3 germ layers (pluripotent) [14]. Mesenchymal stem cells (MSCs) can differentiate into cells from all 3 germ layers [15].

Mesenchymal stem cells must be plastic-adherent when maintained in standard culture conditions using tissue culture flasks. Expression of CD105, CD73 and CD90 can be demonstrated by flow cytometry on ≥95 % of the MSC population. The cells must be able to differentiate to osteoblasts, adipocytes and chondroblasts under standard in vitro differentiating conditions. Furthermore, these cells must lack expression (≤2% positive) of CD45, CD34, CD14 or CD11b, CD79a or CD19 and major histocompatibility complex (MHC) class II [16]. As they are MHC class II negative cells; allogenic transplantation of MSCs does not require immunosuppressive treatment [17].

Mesenchymal stem cells can be isolated from a variety of tissues, including bone marrow, adipose tissue, intervertebral disc, amniotic fluid, dental tissues, human placenta, and cord blood [18].

They have a role in the regulation of tissue homeostasis and are being used for regenerative purposes such as bone and cartilage repair, skin wound healing, neuronal, and heart tissue regeneration [19]. These cells are important carrier cells in gene therapy, they can also repair damaged endometrium and inhibit graft versus host responses [20]. They may be used as a potential treatment for patients who suffer from infertility caused by intrauterine adhesions. In addition, MSC therapy is an effective treatment for myocardial infarction, osteoporosis, bone cysts, lupus nephritis, diabetes, liver cirrhosis, liver failure, spinal cord injury and Parkinson's disease [21–24].

Allogenic MSC products are cryopreserved, allowing them to be off-the-shelf products in order to use in acute tissue injury syndromes such as stroke, sepsis, or myocardial infarction, because it is not feasible to supply sufficient quantities of autologous MSCs in these patients. However, cryopreservation and thawing can effect the potency of MSCs. Fresh MSCs are more potent than frozen cells [25].

MSCs can secrete a variety of cytokines and enhance the resolution of pulmonary edema [26–28]. Mesenchymal stem cells have

immunomodulatory effects on both innate and adaptive immune cells. To ensure activation and phagocytosis of alveolar macrophages, MSCs secrete keratinocyte growth factor, prostaglandin E2, IL-6 and IL-13, they can alter cytokine release of dendritic cell subsets and reduce the release of INF-γ from natural killer cells. IL-10, transforming growth factor (TGF)-β, and tryptophan catabolizing enzyme indolamine 2, 3-dioxygenase secreted from MSCs may suppress proliferation of T cells and change the cytokine secretion profile of T cell subsets as well [29].

Mesenchymal stem cells can produce both the membrane bound and soluble human leukocyte antigen –G (HLA-G) isoforms. HLA-G can inhibit the proliferation of hyperacute T cells and can prevent the differentiation of monocytes to dendritic cells [30]. Cytokines such as TNF-α, IL1-α, β, IL-6, IL-7, IL-8, IL-9, GM-CSF, and IFN-γ, can be blocked through the HLA-G mediated inhibition of dendritic cells and T cells. Soluble HLA-G 5–7 isoforms, can induce the secretion of IL-10 and TGF-β1, and leads to the inhibition of CD8 + T cell proliferation [31,32]. It was demonstrated that HLA-G can increase the production of antiinflammatory cytokine IL-10 and TGF-β1. It was shown that endocytosis of soluble HLA-G with KIR2DL4 is required for the inhibition of NK cells and cytokine production [33]. On the other hand, it has been reported that HLA-G homodimers are required for the secretion of TNF-α, IL-4, and IL-6 [34]. In a study conducted by Zhang and et al., a high membrane expression of HLA-G was demonstrated in a patient with COVID-19 [35]. It was hypothesized that HLA-G may have a role in the modulation of the hyperinflammation induced by the SARS-CoV-2. High expression of surface HLA-G may be associated with a worse clinical course of COVID-19 and this may be explained with the exhaustion of cytotoxic CD8 + T lymphocytes and NK cells expression by the HLA-G, HLA-E, their soluble forms and their specific receptors [36].

Microbial pathogen associated molecular patterns (PAMPS) directly interact with toll-like ligand receptors (TLRs) expressed on both parenchyma and leukocytes, leading to the initiation of the inflammatory response and leukocyte migration. The expression of TLRs on the cell surface of MSCs suggests their inherent role in modulating early immune response. The microenvironment of MSCs has an important role in the modulating effects of MSCs on the immune system. Mesenchymal stem cells can show both pro- and anti-inflammatory effects according to these environmental stimuli. Through balancing this pro- and anti-inflammatory effects MSCs may regulate immune system, tissue repair and regeneration [37].

Possible mechanisms of MSCs' actions in COVID-19 are shown in Fig. 1.

Mesenchymal stem cells have been observed to reduce inflammation in a swine lung injury model caused by the influenza virus [38]. Furthermore, MSCs have been shown to regulate LPS-induced acute lung inflammation by paracrine regulation of macrophage-derived cytokine storm [39,40].

Mesenchymal stem cells have been showed to improve lung function in inflammatory chronic lung diseases such as asthma, chronic obstructive pulmonary disease (COPD) and pulmonary hypertension, silicosis and idiopathic pulmonary fibrosis [41]. Increased forced expiratory volume has been observed in COPD patients after receiving bone marrow-derived MSCs [42]. Similar to patients with COPD, patients with silicosis had some benefits such as an increase in lung perfusion after receiving MSCs [43]. In addition to improvements observed after MSC administration in chronic inflammatory lung diseases, it has also some benefits in acute inflammatory lung diseases [44]. A randomized phase II START study demonstrated that treatment of allogeneic MSCs for moderate to severe ARDS clinic did not cause toxic effects in patients. In this study, only one of the sixty patients receiving MSC treatment died, which was deemed irrelevant [45]. Although MSCs appear safe, larger studies are needed to prove their efficacy and safety in the acute or chronic inflammatory lung diseases.
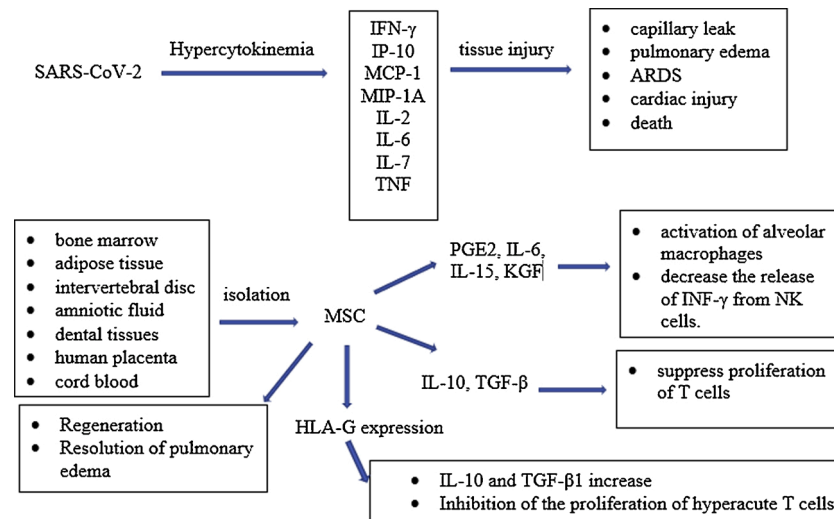
Fig. 1. Possible mechanism of mesenchymal stem cells in COVID-19.

4. COVID-19 patient's treatment

Several agents such as lopinavir-ritonavir, remdesivir, favipiravir, and hydroxychloroquine have been tested in clinical trials for the treatment of COVID-19 [46,47].

Hydroxychloroquine (HCQ) is an antimalarial drug and it seems to block viral entry into host cells and suppress cytokine production including IL-6 and TNF-α. In addition, it inhibits the lysosomal activity and autophagy in host cells [48]. In a case-control study of 36 adults with COVID-19, use of HCQ (200 mg three times per day for 10 days) was associated with a higher rate of undetectable SARS-CoV-2 RNA on nasopharyngeal specimens at day 6 compared with no specific treatment (70 versus 12.5 %, (P < 0.001) [47]. Ventricular arrhythmias, QT prolongation are cardiac toxicities that can be seen during the use of antimalarial drugs and these adverse effects may worsen the clinical course of COVID-19. [49]. Favipiravir is an antiviral agent that inhibits the RNA polymerase of RNA viruses. In a randomized clinical trial, 120 patients with mild-moderate COVID-19 received favipiravir treatment and 7 day's clinical recovery rate was 71.43 % [47]. Lopinavir is a protease inhibitor used to treat HIV infection. In a randomized trial of 199 patients with severe COVID-19, the addition of lopinavir–ritonavir to standard care didn't decrease the time to clinical improvement compared with standard care alone. Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (25 % vs 19 %) [46]. Remdesivir inhibits viral RNA polymerases. In hospitalized patients with severe COVID-19 who received remdesivir, clinical improvement was observed in 68 % of the patients [50].

Bamlanivimab, etesevimab, casirivimab and imdevimab are monoclonal antibodies against SARS-CoV-2. Two combination products, bamlanivimab plus etesevimab and casirivimab plus imdevimab, are available through Food and Drug Administration (FDA) Emergency Use Authorizations (EUAs) for the treatment of mild to moderate COVID-19 in nonhospitalized patients who are at high risk for progressing to severe disease and/or hospitalization. However, FDA has recently revoked the EUA for bamlanivimab because of the increasing number of reports of SARS-CoV-2 variants that are resistant to bamlanivimab alone [51].

It is difficult to maintain adequate blood supply during the pandemic. Recently, human red blood cells have been produced in vitro using hematopoietic stem cells, embryonic stem cells and induced pluripotent stem cells [52]. There have been no licensed cell-based therapeutic interventions for COVID-19, according to the International Society for Stem Cell Research (ISSCR). On the other hand, MSCs have been used in a limited number of cases with COVID-19 [12]. Safety and efficacy of MSCs have been demonstrated in regenerative medicine,

graft versus host disease (GVHD), pulmonary, cardiovascular, neurological, liver, kidney, and rheumatological diseases [53,54] but there is limited data about the outcome of MSC transplantation in COVID-19 and these are based on case series. Previous case reports revealed that intravenous administration of MSCs could prevent hypercytokinemia and enhance endogenous repair by the regenerative ability of the stem cells. Mesenchymal stem cell therapy has been reported to induce a reduction in serum levels of proinflammatory cytokines and chemokines owing to immunosuppressive capabilities [55,56]. According to the mass cytometry streaming results, COVID-19 causes total dysfunction of lymphocytes. Mesenchymal stem cells reverse the lymphocyte subsets mostly through dendritic cells. They are ACE-2 negative, therefore they have a natural immunity against SARS-CoV-2 [55].

In a previous case study from China, a female patient with COVID-19 had improvement in the results of laboratory tests and regression in the lesions observed in thorax computed tomography (CT) 21 days after the transfusion of umbilical cord-derived MSCs. Similarly, it was reported that a critically ill 65-year-old female patient with COVID-19 had progression even receiving lopinavir/ritonavir, IFN-α, oseltamivir, moxifloxacin, methylprednisolone, and immunoglobulin recovered after three umbilical cord-derived MSC infusions (5×10^7 cells/infusion), at three-day intervals. Before the administration of umbilical cord-derived MSCs, laboratory tests showed an abnormal ratio of white blood cells, neutrophils, and lymphocytes in peripheral blood. Twenty-four hours following the administration of umbilical cord-derived MSCs; C reactive protein (CRP), liver function, and other clinical symptoms began to improve, and the patient did not need mechanical ventilation. After administration of the second transfusion, white blood cell, neutrophil and lymphocyte counts were observed to return to normal levels along with the T subgroups. Two days after the third transfusion, the SARS-CoV-2 test was negative. In the sequential CT evaluation before and after cell administration, resolution of the pneumonia was observed. Also, no adverse effects were observed due to the umbilical cord-derived MSC infusion, indicating that the treatment was well tolerated [57].

In the study conducted by Leng et al., MSCs was applied to 7 confirmed COVID-19 cases, including 1 critical severe type, 4 severe type and 2 common type. In the same study, 3 severe type cases constituted the placebo control group. A single dose of 1×10^6 cells/ kilogram body weight MSCs in 100 mL of saline were given to each patient intravenously. 2~4 days after MSC infusion, all the symptoms (fever, fatigue, dyspnea, and hypoxemia) resolved in all patients. No acute infusion-related allergic reaction or secondary infection was observed after MSC treatment. In the critically severe patient, both fever and dyspnea disappeared on the 4th day after MSCs treatment. The

lesions observed in thorax CT reduced on the 9th day after MSC treatment. In severe patients, regulatory T cells as well as dendritic cells increased after MSC transfusion. On the otherhand, only one patient in the control group showed improvement, one case showed symptoms of ARDS and the other patient died [55].

One small clinical study evaluated human umbilical cord-derived MSC transfusion in severe COVID-19 patients who did not respond to standard treatments after 7–10 days. Standard treatments are supplemental oxygen, umifenovir / oseltamivir, and if indicated, antibiotics and glucocorticosteroid treatments. In this randomized controlled study; due to lack of sufficient umbilical cord-derived MSC, it was impossible to randomize the participants. Umbilical cord-derived MSC transfusion was given to 12 of 41 patients eligible for the study and 29 patients received standard therapy only. Demographics, laboratory results, and disease condition among the study arms were balanced. All 12 patients who received umbilical cord-derived MSC transfusion did not require mechanical ventilation and were discharged from hospital, while 4 patients who received only standard therapy progressed to severe illness requiring mechanical ventilation and 3 of them died. The results were not statistically significant and the evaluation of the study is limited by the small sample size and lack of randomization [58]. Another non-randomized controlled phase 1 trial was planned to observe the safety of umbilical cord-derived MSC in the treatment of moderate to severe COVID-19 patients with lung involvement. Eighteen hospitalized patients with COVID-19 were included in the study (n = 9 for each group). Patients in the treatment group received three cycles transfusion of umbilical cord-derived MSCs (3×10^7 cells per infusion) on days 0, 3 and 6. The two groups received a standard COVID 19 treatment protocol. Adverse clinical events, duration of symptoms, laboratory data, hospitalization time, sequential thorax CT images, PaO2 / FiO2 ratio, cytokine level changes and anti-SARS-CoV-2 IgG and IgM antibody levels were analyzed. No serious umbilical cord-derived MSC infusion-related adverse events were observed. Two patients who received umbilical cord-derived MSC experienced mild facial flushing and fever and one patient experienced mild hypoxia of no clinical significance 12 h after umbilical cord-derived MSC infusion. One patient in the treatment group and 4 patients in the control group required mechanical ventilation. All patients recovered and discharged. The trial indicates that intravenous umbilical cord-derived MSC transfusion is safe and well tolerated in patients with moderate to severe COVID-19 [59].

5. Risks of mesenchymal stem cell treatment in COVID-19 patients

Mesenchymal stem cell transfusion appears to be safe. Possible risks include the failure of cells to function as expected, the potential of MSCs to proliferate or transform into incorrect cell types, product contamination, tumor growth, infections, thrombus development, and administration site reactions [60].

5.1. Thromboembolism risk

Previous studies revealed that critically ill and severe COVID-19 patients have high risk for disseminated intravascular coagulation (DIC) and thromboembolism [61,62]. Mesenchymal stem cell products express TF/CD142, which is a procoagulant tissue factor [63]. Recent studies showed that TF/CD142-expressing MSC products could provoke the pro-thrombotic state of COVID-19 [64,65]. Several studies reported DIC and thromboembolism occurred after the administration of TF/CD142-expressing MSCs. Bone marrow-derived MSCs have low TF/CD142 expression [66]. Adipose tissue-derived MSCs highly express TF/CD142, and a study revealed a significant increase in the coagulation activation markers for infusion of 4×10^6 cells/kg vs. controls in healthy volunteers with normal coagulation tests [67]. In the study conducted by Tatsumi et al. researchers demonstrated that the administration of

adipose tissue-derived-MSCs may cause thrombus formation [68]. Similar findings were reported by other studies in which umbilical cord-derived MSCs were given through peripheral vein injection [69]. The expression level of TF/CD142 on MSCs is less important in intramuscular administration compared to intravenous administration because in intramuscular administration, MSCs are directed to the extravascular area (avoiding blood contamination). So, higher cell doses can be used in intramuscular administrations compared to intravenous administrations. High doses should be avoided in hypercoagulable patients. On the other hand, MSCs with low or absent TF/CD142 may be used through intravenous administration in hypercoagulable patients with relevant treatment protocols (e.g., with anticoagulation) [66].

5.2. Tumorigenicity

Long-term culture, media, and growth factors may be related to an increased probability of malignant transformation. Analysis of telomerase in MSCs at higher passages show decreased telomerase activity during in vitro culture. During long-term culture, MSCs lose their ability to differentiate and start to exhibit morphological changes [70,71].

A meta-analysis of 36 studies in which bone marrow-derived MSCs were used, showed that there was no relation between the use of MSCs and tumorigenic potential, and no serious adverse effects of the treatment were reported [72].

In the study conducted by Campioni et al., researchers expanded BM-derived hMSC samples from chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). They revealed that in ALL and in CLL, the BM-MSC has a normal karyotype, thus supporting a distinct origin from hematopoietic cells. The presence of cytogenetic aberrations in expanded HM-MSC derives from the persistence of contaminating hemopoietic cells. The presence of in vitro hMSC aneuploidy is associated with lymphoid neoplasias carrying chromosome abnormalities, therefore hMSC should be characterized before clinical application [73].

5.3. Mesenchymal stem cell adverse reactions

There is a risk of virus and prion transmission after the administration of the cells [74]. In the study of Leng et al., no acute infusion-related allergic reaction or secondary infection observed after MSC administration [55].

Some of the other concerns about the MSC clinical use are about the manufacturing processes and cost. There are many variables in MSC production, such as isolation methods, media composition, and culture time. All of these production steps may have an impact on the efficacy of the MSC product, therefore, quality control and related assays need to be clearly defined. In addition, alternative manufacturing models should be considered in order to lower costs for health care systems [75].

In conclusion, MSCs are ACE-2 negative cells; therefore can escape from SARS-CoV-2. They prevent hypercytokinemia and help the resolution of the pulmonary edema and other damages caused during the course of COVID-19. In addition, MSCs enhance the regeneration of the lung and other tissues affected by SARS-CoV-2. The case series showed the beneficial effects of MSCs in COVID-19 treatment. However, there are some concerns about the safety of MSCs, particularly about the increased risk of DIC and thromboembolism due to the expression of TF/CD142. Prospective, randomized, large scale studies are needed to reveal the optimum dose, administration route, time, efficacy, and safety of MSCs in COVID-19 treatment.

Author contributions

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Critical revision of the manuscript for important intellectual content: All authors.

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Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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