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MINIREVIEWS

Stem cell therapy: A promising treatment for COVID-19

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Abstract

Novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic. SARS-CoV-2 is an RNA virus and has a glycosylated spike (S) protein used for genome encoding. COVID-19 can lead to a cytokine storm and patients usually have early respiratory signs and further secondary infections, which can be fatal. COVID-19 has entered an emergency phase, but there are still no specific effective drugs for this disease. Mesenchymal stem cells (MSCs) are multipotent stromal cells, which cause antiapoptosis and can repair damaged epithelial cells. Many clinical trials have proved that MSC therapy could be a potential feasible therapy for COVID-19 patients, especially those with acute respiratory distress syndrome, without serious adverse events or toxicities. However, more studies are needed in the future, in order to confirm the effect of this therapy.

Key Words: COVID-19; SARS-CoV-2; Mesenchymal stem cells; Pandemic; Stem cell therapy

Core tip: Coronavirus disease 2019 (COVID-19) has become a global pandemic and entered an emergency phase. However, there are still no specific effective drugs for the COVID-19. Many previous studies have shown that mesenchymal stem cell transplantation is a promising choice for COVID-19-infected patients, and further studies need to be done in the future.

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INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) is a severe respiratory disease that was first identified in December 2019 in Wuhan, China. COVID-19 is caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2 and has become a global pandemic. To date, > 100 million SARS-CoV-2 infections and > 2 million deaths have been reported by the World Health Organization (WHO)[1,2]. It has been established that SARS-CoV-2 has sequence homology with SARS-CoV-1, one of the coronaviruses found in bats[3-7].

SARS-CoV-2 is one of the Coronaviridae family of viruses, which includes four types, α, β, γ and δ. SARS-CoV-2, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV),belong to the β group[4,8]. SARS-CoV-2 is an RNA virus and has a glycosylated spike (S) protein used for genome encoding. The angiotensin-converting enzyme (ACE)2, a membrane receptor, binds the S protein. ACE2 is highly expressed on lung alveolar type II cells, and is commonly found in heart, liver, kidney and digestive system cells, but not in bone marrow, spleen, lymph nodes and macrophages[9,10]. The transmembrane protease, serine 2 is also commonly expressed on type II lung cells, which can initiate S protein and help the virus to invade host cells [6,10].

Furthermore, this viral infection leads to cytokine release syndrome, also called cytokine storm, and increases the level of inflammatory cytokines [interleukin (IL)-2, IL-6, IL-8, IL-17, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor (CSF), granulocyte–macrophage CSF], and chemokines (monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, interferon-induced protein 10)[11-13]. As a result, patients show early signs of fever, cough, headache, followed by high fever, pulmonary edema, difficult breathing, acute respiratory distress syndrome (ARDS) and further secondary infections, which can result in potentially fatal consequences[14-17]. COVID-19 usually affects the upper and lower respiratory tract with an incubation period of 2 wk. The diagnosis of SARS-CoV-2 infection is based on an RT-PCR test and specific IgM and IgG in patients[18-20]. However, there are still no specific drugs for treating this infection at present.

MESENCHYMAL STEM CELLS

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into many different types of cells including chondrocytes, osteoblasts and adipocytes, which has been confirmed in a variety of cells. MSCs are usually found in bone marrow, umbilical cord, placenta, adipose fat pads and dental pulp[21,22]. MSCs, which secrete numerous cytokines and chemokines, cause antiapoptosis, and can repair damaged epithelial cells[23,24]. MSCs secrete cytokines and modulate the immune response by regulating cell function and downregulating inflammatory cytokines in graft versus host disease and systemic lupus erythematous [25,26]. Therefore, MSCs may be a potential treatment for COVID-19, as they could move towards injured lung cells and repair them.

MSCs have proved effective in both experimental research and clinical studies, including many immune-mediated inflammatory diseases, with good safety and low risk[23,24]. Previous studies have shown that MSCs could reduce H5N1 influenza virus in older patients with acute lung injury, and improve the survival rate of H7N9-infected patients with ARDS without serious complications[27,28]. MSCs can also intervene in the activation of inflammatory cytokine secretion in dendritic cells (DCs) [29,30]. Ling *et al*[31] found that stage-specific embryonic antigen-1, stem cell antigen-1, cytokeratin-7 and ACE2 were expressed in lung epithelial cells and ACE2 was expressed in lung stem cells. Furthermore, SARS-CoV-infected lung cells that lacked differentiated stem cells failed to repair. For this reason, MSC transplantation may be a feasible therapy for COVID-19.

MSC THERAPY FOR COVID-19

The COVID-19 pandemic has entered an emergency phase, but there are still no specific effective drugs for this infection[32]. Due to the lack of effective therapy for COVID-19, current treatment is based on individual symptoms and supportive treatment. Most patients receive oxygen therapy and extracorporeal membrane oxygenation is recommended for refractory hypoxemia[33].

At present, drugs for COVID-19 include antiviral drugs, antimalarial drugs, anti-human immunodeficiency virus drugs, anti-inflammatory drugs, and monoclonal antibodies, such as remdesivir, chloroquine, lopinavir/ritonavir, nitazoxanide, and traditional Chinese medicine, which have been used in China and western countries [34-41]. Many studies on IL-1, IL-2, IL-6 and TNF-α drugs have demonstrated that they can suppress the inflammatory response in COVID-19 patients, and have provided some clues on anti-inflammatory therapy to treat SARS-CoV-2 infection with better outcomes[42]. Etoposide-based therapy has been proposed as a new treatment for COVID-19, which requires further clinical trials[43]. There are currently several ongoing clinical trials of drugs and vaccines for the treatment of COVID-19.

Zheng *et al*[44] showed that MSC therapy for ARDS resulted in no infusion toxicity or serious adverse events. Another study involving patients with ARDS who were treated with an infusion of allogenic bone-marrow-derived human MSCs demonstrated good safety and no treatment-related adverse events. Furthermore, this treatment reduced lung injury in a sheep model[23,45]. Therefore, MSC-based therapy demonstrated promising results for ARDS without any prespecified adverse events, and was both tolerable and safe. However, there are no long-term data on MSC-therapy-associated adverse events[46,47].

CD147 is a marker of undifferentiated embryonic stem cells, and is the second entry receptor for SARS-CoV-2. Its protein is expressed in tissue-specific stem cells of human bone marrow origin. Inhibition of CD147 can prevent inflammatory processes in diabetic complications[48,49]. SARS-CoV-2 infection can trigger pulmonary fibrosis in normal tissue, and probably originates from resident stem cells, which are also called MSC-like cells. In the early stage of COVID-19 pneumonia, type II pneumocytes are involved in the initial step of pulmonary fibrosis. Anti-CD147 antibodies that can suppress the normal lung cell differentiation of fibroblasts *in vitro* have been investigated, and MSC transplantation may lead to immunosuppression and tissue regeneration[50,51].

In the first study of MSCs, Leng *et al*[14] treated seven patients with COVID-19 pneumonia with an injection of MSCs, and showed a significant reduction in clinical symptoms and a decrease in serum proinflammatory cytokines without adverse effects. Most of the patients were negative on the SARS-CoV-2 nucleic acid test within 2 wk after MSCs transplantation. Chen *et al*[52] observed that all patients showed clinical improvement, including 64% of patients with chest CT improvement, but little improvement in immunomodulation and cardiotoxicity during MSC therapy.

Human umbilical cord-derived MSC (UC-MSC) transplantation has been carried out in COVID-19 patients. A female patient with severe COVID-19 was treated with an human UC-MSC injection, which resulted in good efficacy without side effects[53]. Twelve patients with severe COVID-19 treated with UC-MSC transplantation reported improvements in clinical outcome, reduced C-reactive protein and IL-6 levels, and no mortality[54,55]. A Phase I clinical trial of UC-MSCs for COVID-19 found no serious adverse events, and lung lesions in four moderate–severe patients completely disappeared within 2 wk after injection[56]. Adipose-tissue-derived MSCs were used to treat 13 severe COVID-19 pneumonia patients, and 70% of patients had clinical improvement and reduced levels of inflammatory factors[57]. Tang *et al*[58] used menstrual-blood-derived MSCs to treat severe COVID-19 patients, and found that bilateral pulmonary exudation had been absorbed and SaO_2 and PO_2 were also improved. Similar to MSCs, immunity- and matrix-regulatory cells (IMRCs) also have self-renewal and mesenchymal differentiation ability. Following injection of IMRCs, COVID-19 patients recovered and tested negative for the virus, while many inflammatory cytokines such as IFN-α2, IL-3, M-CSF and TNF-α were suppressed[59]. Previous studies have shown that MSC therapy may activate the immune system, stem cells can repair tissues, and then prevent the cytokine storm and release anti-inflammatory mediators. Consequently, this may prevent pulmonary fibrosis caused by SARS-CoV-2 infection. The MSCs were resistant to viral infection due to expression of interferon-stimulated genes [60-62]. The characteristics of included studies are shown in Table 1.

Recent studies have indicated that MSCs are able to secrete immunomodulatory factors that could suppress the cytokine storm, promote tissue regeneration and inhibit tissue fibrosis. Given the previous preclinical and clinical studies, MSC therapy has shown good safety and efficacy in the treatment of respiratory failure or ARDS[63,64]. Therefore, MSC injection showed promising results for therapy of COVID-19 patients [65]. In addition, many clinical trials on MSCs for COVID-19 (NCT04315987, NCT04313322 and NCT04333368) are ongoing worldwide. More clinical data will support this effective therapy. However, the number of patients in these studies is small, and the long-term safety and efficacy of this treatment require further invest-

Table 1 Characteristics of included stem cell studies of Coronavirus disease 2019

Ref.	Disease	Treatment	*n*	Results
Leng *et al*[14], 2020	COVID-19 pneumonia	MSCs	7	Improve outcome without adverse effects
Chen *et al*[52], 2020	Severe COVID-19 pneumonia	MSCs	25	All patients gained clinical improvement and 64% gained chest CT improvement
Liang *et al*[53], 2020	Severe COVID-19 pneumonia	UC-MSCs	1	Most of the laboratory indexes and CT images showed remission without side effects
Shu *et al*[55], 2020	Severe COVID-19 pneumonia	UC-MSCs	12	The UC-MSC treatment group had shorter clinical improvement time, reduced CRP and IL-6 levels, and no mortality
Meng *et al*[56], 2020	Moderate and serve COVID-19 pneumonia	UC-MSCs	9	No serious adverse events were observed and all the patients recovered and were discharged
Sánchez-Guijo *et al*[57], 2020	Severe COVID-19 pneumonia	AD-MSCs	13	70% of patients had clinical improvement and no adverse events were related to the therapy
Tang *et al*[58], 2020	Severe COVID-19 pneumonia	MB-MSCs	2	Bilateral pulmonary exudation had been absorbed and SaO_2 and PO_2 were also improved

COVID-19: Coronavirus disease 2019; MSCs: Mesenchymal stem cells; UC-MSCs: Umbilical cord-derived MSCs; AD-MSCs: Adipose tissue-derived MSCs; MB-MSCs: Menstrual blood-derived MSCs; CT: Computed tomography.

igation. The consistency of MSC quality cannot be guaranteed, and the dose was also inconsistent in these studies. The heterogeneity, secretory and immunomodulatory capabilities of MSCs are unclear; therefore, the results from different studies are difficult to compare. Further study would develop clinical preparation and treatment standards for MSCs in COVID-19 patients, and larger numbers of patients remain to be included in MSCs studies.

CONCLUSION

MSC transplantation has proved to be a promising choice for COVID-19 patients, and more studies need to be completed in the future. This therapy has been shown to have few side effects. MSCs may be a safe and effective therapeutic strategy, or as part of a combination therapy for COVID-19 patients.

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