An overview of Mesenchymal stem cell therapy in COVID-19 patients (Review)

Abstract

An infection causes coronavirus disease (COVID-19) with a virus from the coronavirus family known as SARS coronavirus. By entering the coronal protein into the host's angiotensin-4 receptor, the virus affects lung cells and other organs, including the heart and immune system. While there is currently no particular treatment for COVID-19 disease, Mesenchymal stromal cells (MSCs) have been proposed as a potential therapy to treat drug-resistant lung infections.
In this article, the keywords Mesenchymal stromal cells, stem cells, and COVID-19 were searched in the titles and abstracts of articles published in reputable international scientific databases. After several stages of removing duplicate and unrelated items, 39 articles were finally used. MSCs, due to their unique properties, including immune system regulation and tissue regeneration capabilities, significantly affect the treatment of COVID-19. Also, in this regard, several studies have obtained permission to reach the clinical phase and are currently being investigated. There is a pressing need for extensive research to evaluate the efficacy and safety profile of MSCs therapy in COVID-19 patients.

Keywords: Covid-19, Stem cell, Mesenchymal

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Introduction

Since the end of 2019, concern worldwide has been raised due to the rapid spread of the COVID-19 disease, which is brought on by the coronavirus-2's acute respiratory syndrome. The growth and spread of the global epidemic caused the World Health Organization (WHO) to declare the novel coronavirus (COVID-19) outbreak a global pandemic. COVID-19 disease is more contagious than previous coronavirus infections, including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and it has confusing manifestations which may range from asymptomatic patients to patients with acute respiratory distress syndrome and severe pulmonary fibrosis (1).

Currently, several treatment options have been put forth, including the development of a vaccine which has faced many challenges. Other options include plasma therapy, antibiotics for treating secondary bacterial sepsis, non-specific antiviral agents, etc., none particularly effective in treating COVID-19 in its most severe cases. The virus's cytokine storm in the lungs is the primary cause of these therapeutic techniques' failure. The cytokine storms present as inflammatory lesions or discoloration of the background in computed tomography imaging (2). Most patients in the early stages of the disease do not have severe clinical manifestations; however, in the later stages of the disease progression, a sudden deterioration in the patient's condition is observed, with rapid failure of multiple organs and acute respiratory syndrome, leading to the patient's death in a short time; cytokine storm is a possible result of this. Thus, it is a disease that sometimes harms multiple organs (3,4).

A new hope has emerged for the treatment and control of the 19-Covid-19 pandemic in light of the unique abilities of mesenchymal stem cells (MSC) to modulate the immune system and tissue regeneration (2). However, several difficulties are covered in this article that must be overcome to develop MSC-based COVID-19 treatment methods that are safer and more efficient.

COVID-19 treatment methods

Many prevention and treatment options are being evaluated and tested for the treatment of COVID-19 patients. Still, Remdesivir is clinically the most advanced antiviral combination with a wide range of activities, affecting both SARS-CoV and MERS-CoV. Remdesivir has also shown potent activity against SARS-CoV-2 in cell culture-based methods and model animals infected with this virus (5). This drug's preventive and therapeutic use as a combination of other antiviral drugs, such as lopinavir, ritonavir, and interferon, has been discussed elsewhere (6).

Immunosuppression with corticosteroid drugs is not usually recommended for treating this disease and may exacerbate lung damage. On the contrary, blocking the IL-6 pathway may be helpful for patients with excessive inflammation. In studies conducted in 2020, cytokines and immunosuppressors such as IL-6 inhibitors (siltuximab) and (IFN-γ or TNF-α) were used as a treatment for COVID-19 (7,8).

As antiviral drugs, monoclonal antibodies have been shown to prevent the virus's binding to ACE2 (9). Phosphoinositides play essential roles in the endocytosis process. Evidence indicates that applying YM201636 as phosphatidyl-inositol 3-phosphate 5-kinase inhibitors prevents the entry of SARS-CoV-2 pseudovirion into 293/h ACE2 cells. According to these results, PIKfyve is a valuable drug for viruses that enter the cell through endocytosis (10).

A method to discover a suitable drug for COVID-19 is to create a computer simulation using artificial intelligence. In a study in 2020, cloning human induced pluripotent stem cells (iPSC) and artificial lung cell models (aiLUNG) were used and infected using data related to SARS-CoV-2 genotype and phenotype; these models were then validated to discover a suitable drug for this disease (11).

The current challenge with treatment or prevention using a vaccine is that the delta strain of SARS-CoV-2 poses a severe threat to countries with low or no access to a vaccine. This issue has raised a wave of research investigating the unique mutations creating this strain and the minor changes in the proteins due to this research. There is a site for powerful binding antibodies at the amino end of the spike protein of this virus, where a mutation occurring in the delta strain prevents the antibody from binding to the spike (12). Data obtained in England and Scotland indicate a relatively high level of protection against this strain in people who receive two doses of each of the Pfizer-BioNTch and AstraZeneca vaccines (12,13). Finally, the rapid emergence of mutations and viral variants necessitates the rapid expansion of vaccination programs. Moreover, non-pharmacological interventions should be implemented as an integrated public health response (14).

Mesenchymal stem cells (MSCs)

Stem cell science is a research field that uses a combination of scientific findings in biology, genetics, and clinical fields to treat various benign and malignant diseases (15) effectively. According to the International Society for Cell Therapy, MSCs are defined as (a) cells adhering to the bottom of the cell culture vessel that (b) can be differentiated into osteocytes (bone cells), chondrocytes (cartilaginous cells), and adipocytes (fat cells), and (c) their phenotypes are positive for CD166, CD146, CD44, CD73, CD90, CD105, and CD29 mesenchymal markers and negative for CD14, CD11b, CD33, CD32, CD31, CD34, CD45, and HLA-DR hematopoietic indicators (8,15). In addition, MSCs possess self-renewal properties and can be differentiated into several cell lines (16).

MSCs contain extracellular matrix receptors, which include adhesion-related antigens (αvβ3, αvβ5) and intercellular adhesion molecules, *viz*. ALCAM (Activated Leukocyte Cell Adhesion Molecule), VCAM-1 (Vascular Cell Adhesion Molecule 1), ICAM-2 (Intercellular Adhesion Molecule 2), and ICAM-1 (Intercellular Adhesion Molecule 1). These receptors facilitate the connection of MSCs with extracellular matrix molecules. MSCs secrete cytokines, chemokines, and growth factors such as IL-6, IL-7, IL-8, IL-11, IL-12, IL-14, IL-15, LIF (Leukemia Inhibitor Factor), G-CSF, GM-CSF, SCF (Stem Cell Factor), M-CSF (Macrophage Colony Stimulating Factor), and flk-3L. They also express the receptors of cytokines such as IL-7R, IL-6R, IL-4R, IL-3R, and IL-1R. This advantage encourages scientists to use them to treat some diseases (17). Bronchi alveolar stem cells (BASCs) are considered PSCs and can withstand damage caused by bronchioles and alveoli, proliferate in the epithelial regeneration process, and differentiate into Clara, AT2, and AT1 cells (18).

The method of using MSC in the treatment of COVID-19

In a meta-analysis of various clinical trials, Yao et al. reported intravenous injection as the most widely used method in trials related to the use of stem cells (19). This injection was performed autogenously/allogeneically through two intravenous or inhalation methods in treating ARDS using injections of MSCs (8). Given the potential of MSCs to express the pro-coagulant tissue factor, their intramuscular injection together with a buffer containing Human Serum Albumin (HSA), a low dose of anti-coagulant drugs as a supplement, and finally preparing the patient with an anticoagulation protocol is preferable to intravenous injection (15). The interest factors include dose, injection frequency, time, and large-scale production capacity.

Effects of MSC injection on the apparent symptoms of COVID-19

Studies have shown that MSC injection in COVID-19 patients improves their clinical symptoms (Table 1). In a study in China, allogeneic intravenous injection of three successive doses of human umbilical cord MSCs (hUC-MSCs) at 5×10^6 cells/kg of the patient's weight with an interval of 3 days in a 65-year-old female COVID-19 patient with dysfunction of several organs, including the liver, and requiring a ventilator for inhalation improved her initial vital symptoms and inhalation without the need for a ventilator after 1 and 4 days of the second injection, respectively. Moreover, the recurrence of all biological parameters, including the number of T blood cells to normal values, was reported due to reduced inflammation and injuries inside the lungs and other tissues. The patient left the intensive care unit 2 days after the third injection with no side effects (20). It should be noted that stem cell therapy can be viewed as a highly effective adjunctive therapy rather than a stand-alone therapy, for example, in a study, A 66-year-old female patient suffered from cough, sore throat, and fever after contact with a confirmed case of COVID-19. She was admitted to the isolation ward for standard isolation treatment. To investigate the effect of using mesenchymal stem cells in this patient, the cell products of MSCs were suspended in 100 mL of saline in strict accordance with standard operating procedures, and the total number of infused cells was 1×10^6 cells per kilogram. The patient's weight was 65 kg, and the total number of cells was about 6.5×10^7. after stem cell therapy, the symptoms and laboratory results have improved, but the absolute lymphocyte count did not return to normal and has poor absorption of exudative pulmonary lesions. The patient needs high-flow nasal cannula oxygen therapy (HFNC) combined with intermittent noninvasive ventilator-assisted ventilation. Therefore, convalescent plasma (CP) was injected twice on February 20 and 21. The absolute lymphocyte count returned to normal on the fourth day after CP treatment. They note that the intravenous infusion of CP and MSCs for treating severe COVID-19 patients may have synergistic characteristics in inhibiting cytokine storm, promoting the repair of lung injury, and recovering pulmonary function (21). In another study by zhang et al., a 54-year-old man presented to Yanggu People's Hospital, Shandong, with a 4-day history of cough, chest tightness, and fever.

The real-time polymerase chain reaction (RT-PCR) assay confirmed that the patient's specimen tested positive for COVID-19. The human umbilical cord Wharton's jelly-derived MSCs (hWJCs) injected into the patient were from fresh culture. Patients received dexamethasone 2 mg before intravenous infusion of hWJCs. hWJCs were suspended in 100 mL of normal saline, and the total number of transplanted cells was calculated by 1×10^6 cells per kilogram of weight. Before the hWJC transplantation, the patients had symptoms of high fever (38.5 °C ± 0.5 °C), weakness, shortness of breath, and low oxygen saturation. However, 2~7 days after transplantation, all the symptoms disappeared, and the oxygen saturation rose to 98% at rest. In addition, no acute infusion-related or allergic reactions were observed within two h after transplantation. Similarly, no delayed hypersensitivity or secondary infections were detected after treatment (22).

Table 1. MSCs therapy in COVID-19 patients

Intervention	Number of patients	Diseases severity	Administration Method	Key findings	References
BMSCs were given one time (1×10^6 cells per kilogram of weight).	7	1 Critically severe, four severe, and two common types	IV	Systemic inflammation reduced	Leng et al. (5)
hUC-MSCs were given three times (5×10^7 cells each time) with a 3-day interval.	18	moderate and severe ill	IV	The PaO_2/FiO_2 ratio improved; Lung lesions of patients were well controlled	Wang et al. (23)

hUC-MSCs were given once (2 × 10^6 cells per kilogram of weight).	12	critically ill	IV	Clinical symptoms, including weakness and fatigue, shortness of breath, and low oxygen saturation, were improved	Shu et al. (24)
hUCMSCs were given three times (1 × 10^6 cells each time) with a 3-day interval.	1	severe	IV	Absolute lymphocyte count was improved	Peng et al. (21)
hUCMSCs were given three times (5 × 10^5 cells each time) with a 3-day interval.	1	critically-ill	IV	Systemic inflammation reduced	Liang et al. (20)
hWJCs were given one time (2 × 10^6 cells per kilogram of weight).	1	Critically ill	IV	Systemic inflammation reduced	Zhang et al. (22)
Patients received a first dose (1 × 10^6 per kilogram of weight) of AT-MSCs (day 1) and were scheduled for a second dose if deemed clinically appropriate by the treating physician, between 48 and 96 h later.	13	severe	IV	Systemic inflammation reduced	Sanchez-Guijo et al. (25)
The total 100 mL of the MenSCs (allogeneic) was administrated three times.	2	-	IV	Systemic inflammation was reduced. Both the SAO_2 and PO_2 improved, and chest CTs showed the adsorption of bilateral pulmonary exudates	Tang et al. (26)
CDCs were given 2 times (150 × 10^6 and (75× 10^6 cells).	6	critically ill	IV	Systemic inflammation reduced	Singh et al. (27)
In total, 15 ml of Exosomes derived from BMMSCs were administered.	24	severe	IV	Systemic inflammation reduced	Sengupta et al. (28)
BMSCs were given 3 times	12	Critically ill	IV	OVID-19 IgG Spike protein	Kaushal et al. (29)

				reduced significantly	
UC-MSCs (3×10^7 cells per infusion) were administrated three times on days 0, 3, and 6.	4	severe	IV	percentage of inspired oxygen (PaO_2/FiO_2) ratio improved after UC-MSCs treatment	Meng et al. (23)
WJ-MSCs (3×10^6 cells per kilogram of weight infusion) were administrated three times on days 0, 3, and 6.	10	critically ill	IV	Systemic inflammation reduced	Adas et al. (30)
Patients received a dose (1×10^6 per kilogram of weight) of UC-MSCs.	20	critically ill	IV	UC-MSC administration increased the survival rate.	Dilogo et al. (31)
UC-MSCs (2×10^6 per kilogram of weight) was administrated.	8	severe	IV	the intravenous transplantation of hUC-MSCs accelerated partial pulmonary function recovery	Feng et al. (32)
MSCs were given 3 times (1×10^6 cells each time).	5	severe	IV	MSC infusion improved pulmonary function and overall outcome	Haberle et al. (33)

BMSCs: bone marrow mesenchymal stem cells. hUC-MSCs: human umbilical cord-derived MSCs. HWJCs: human umbilical cord Wharton's jelly derived MSCs. AT-MSCs: adipose tissue-derived MSCs. MenSCs: menstrual blood-derived MSCs. IMRCs: immune-and-matrix-regulatory cells. CDCs: allogeneic cardiosphere-derived cells

Mechanism Of Action

About the mechanism of action, it should be explained that an increase in the number of CD3+ T, CD4+ T, and CD8+ T cells was observed significantly to the normal level after the injection of hUC-MSCs, indicating the return of lymphopenia. This process is a common feature of COVID-19 patients and is associated with disease severity and mortality. In addition, gradual decreases were reported in the numbers of white blood cells and neutrophils, the ratio of neutrophils to lymphocytes, the D-dimer level, and serum concentrations of bilirubin, ALT, CRP, and AST, thereby improving some other vital signs. These can indicate the inhibition of inflammation and modulation of the immune system by MSCs (34). It has been shown that intratracheal administration of MSCs reduced inflammation and increased lung tissue permeability in an animal model of systemic inflammation by secreting PGE2, granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF), which in turn induce IL-10 (35). In addition, MSCs release anti-inflammatory factors such as IL-10 and IL-4 to suppress lymphocyte activation and inflammatory cytokines, such as IL-1, 6, and 17 (36). Furthermore, MSCs appear to modulate the immune system when lung injury is induced by respiratory viruses, which may also explain MSC treatments for COVID-19. UC-MSCs were shown to reduce permeability and elevate alveolar fluid clearance after treatment with avian influenza virus (H5N1)-induced lung injury in mice (37). Another mechanism proposed to explain stem cell treatment's effect on covid-19 patients is reducing cell death. One study found that patients with ARDS treated with MSCs significantly improved and decreased cell death levels (38). Although MSCs may counter-regulate cell death through anti-inflammatory and immunomodulatory actions, direct evidence has not been provided that they reduce cell death in COVID-19 patients.

Safety

Generally, the review of previous articles shows that no specific complication has been observed in most of the studies, such as a study by Leng et al. Neither an acute infusion-related reaction nor an allergic reaction was observed within two hours of transplantation. Additionally, a study conducted by Meng et al. showed no evidence of delayed hypersensitivity or secondary infections after treatment (5). The UC-MSC infusion was without serious adverse effects. In this study, Within four hours of receiving UC-MSCs, 50% of patients experienced transient facial flushing and fever (23). According to a study conducted by Shu et al. The infusion of UC-MSC did not cause adverse reactions in patients (such as rash, allergic reactions, or febrile reactions) (24). According to a study conducted by Feng et al., After discharge, none of the patients in the UC-MSC group reported any adverse reactions, such as skin itchiness, dizziness, loss of appetite, or foggy vision. Two patients had mildly elevated levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and one patient had mildly elevated levels of CA12-5 (32). According to Lanzoni et al., only two serious adverse events were observed in the UC-MSC group, and 16 serious adverse events were observed in the control group, affecting two of 12 and eight of 12 subjects, respectively. The control group experienced significantly more severe side effects than the UC-MSC treatment group. Only one serious side effect was possibly related to treatment in the UC-MSC group (39).

Discussion

So far, mesenchymal stem cells or their derivatives have proven the most promising in preclinical investigations and clinical trials to treat COVID-19. It has been discovered that mesenchymal stem cells migrate directly to the lungs after intravenous injection and can secrete many factors that play an essential role in modulating the immune system, protecting alveolar epithelial cells, resisting pulmonary fibrosis, and improving lung function, which is a significant advantage for the treatment of acute lung disease. The fundamental mechanism of MSC therapeutic action in COVID-19 conditions is the production of soluble substances such as cytokines, chemokines, angiogenic factors, growth factors, exosomes, and extracellular vesicles. Although preliminary clinical trials have indicated positive outcomes for the safety and efficacy of intravenous mesenchymal stem cells in patients with lung diseases associated with COVID-19, more in-depth studies are still required. Hence, it is challenging to compare and draw firm conclusions due to the heterogeneity of cell sources, their capacity for secretion, and their various roles in immune system modulation and tissue repair. Therefore, one of the clinic's most critical components of stem cell treatment is overcoming cell heterogeneity. As a result, international agreements and guidelines on clinical criteria for establishing the quality, effectiveness, and compatibility of stem cells in treating Covid-19 disease must be approved and published.

Conclusions

Although using stem cells to treat COVID-19 disease is a promising strategy, the therapeutic approach's limitations must be considered. Therefore, there is a pressing need for extensive research to evaluate the efficacy and safety profile of these treatments, as well as for the thorough resolution of several issues, such as MSC fate upon infusion, homing ability, and MSC resistance to the disease microenvironment.

Ethical Considerations

All ethical principles are observed.

Authors' contributions

All three authors were involved in the design and formulation of the argument.

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Conflict of interest

There is no conflict of interest.

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