

Mesenchymal Stem Cell as a Successful Therapy for COVID-19 Patient: Systematic Review

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Submitted: 2021-10-02. Revised: 2022-01-05. Accepted: 2022-03-30.

Abstract. COVID-19 has been declared a pandemic and continues to spread, leading to health and economic problems and economic burdens worldwide. COVID-19 symptoms are similar to the flu and, in severely infected patients, emerge as an acute respiratory syndrome (ARDS), pulmonary fibrosis, edema, and even organ failure. These are due to an imbalanced immune response with a more severe effect than the virus attack. However, no specific medications and treatments are available in dealing with the COVID-19. Hence, mesenchymal stem cell (MSC) treatment is proposed as one therapeutic approach. The MSCs can produce growth factors and immune protective cytokines that could fight viral infection and are proven to help endothelial cell repair. These capabilities are expected to help resist viruses and tissue repair in a patient body. MSC is believed to prevent acute respiratory infections, the most dangerous stage of COVID-19 pathogenesis. In this study, we collect some literature, reviewing and summarizing them so that we believe that MSC could be an approach to cure COVID-19 patients and improve their responses to the virus. This article reviews the use of mesenchymal stem cells as a potential therapy for COVID-19, and this information can also be used as basic information for developing a stem-cell-based therapy, especially for treating COVID-19.

Key words: COVID-19, Mesenchymal Stem Cells, MSCs therapy

How to Cite: Nandina, R. Q., Eriani, K., Asrizal, C. W., & Azhar, A. (2022). Mesenchymal Stem Cell as a Successful Therapy for COVID-19 Patient: Systematic Review. *Biosaintifika: Journal of Biology & Biology Education*, 14 (1), 36-47.

DOI: <https://doi.org/10.15294/biosaintifika.v14i1.32367>

INTRODUCTION

Over the past year, coronavirus disease (COVID-19) has impacted the global population. By December 2019, many cases of respiratory infection that occurred in Wuhan, China, were thought of as seasonal flu. Later, a new virus was declared after denying the symptom of seasonal flu, avian influenza, SARS, and other pathogens. Genetically related to SARS by 5% (Shang et al., 2020). WHO named the virus SARS-CoV-2. Since then, over 170 million cases and over 3 million deaths have resulted from this virus as of May 30, 2021 (<https://www.worldometers.info/coronavirus/>). This high number makes global scientists actively look for ways to fight this pandemic. One potential approach is mesenchymal stem cell (MSC) therapy.

MSCs have been used in various regenerative cell therapies. They are ideal and widely used because they are easy to separate, extensively expand, and have pluripotent differentiation. Another characteristic of MSCs is their ability to evade immune recognition and suppress the immune response (Zhao et al., 2016). They can differentiate into the mesoderm, endoderm, and even ectoderm cells.

Mesenchymal stem cells have been used to secrete growth factors and immune protective cytokines in cell and organ transplantation. They are safe, do not create teratomas, and could regenerate and repair tissue (Wang et al., 2012). An encouraging instrument for immunoregulatory cell therapy in immune-mediated diseases (Zhao et al., 2016). MSCs with the specific cytokine feature could oppose viral infection, meaning that MSC is likely to survive in a positive COVID-19 patient body and could help resist the viruses. Recently, MSCs have been studied as a therapeutic submission for COVID-19 treatment. However, according to the International Society of Stem Cell Research (ISSCR), there is no approved stem cell-based perspective for preventing and curing COVID-19 infection (Metcalf, 2020). This review will highlight the potential use of MSC as therapy for COVID-19 patients. Firstly, we discuss COVID-19 as general and the disease's trademark, which is cytokine storm. Secondly, we discuss preclinical studies and clinical trials using MSCs as a therapy for treating COVID-19 patients.

METHODS

This review is based on literature research carried out in May 2021 through google scholar and the National Institute of Health (NIH) database. The recent article used from 2017 to the present. The combination keyword used were : “Mesenchymal Stem Cell”, “Sars-CoV-2”, “COVID-19”, “clinical trial for COVID-19”, “MSC as therapy”, “ARDS”. English-written articles were used and selected as a basic condition.

A total of 48 articles were selected and then screened. As we screened these articles, 18 articles were then excluded. Those articles were excluded as they did not meet our criteria to answer our question for this review. Six articles were then added in the drafting phase to deepen our discussion and bring more evidence of MSC used

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RESULT AND DISCUSSION

COVID-19 Disease

The SARS-CoV-2 virus causes a disease called COVID-19. CoV (Coronavirus) is a large family of viruses. The structural analysis showed that SARS-CoV-2 is enveloped, single-stranded RNA virus with nucleocapsids classified as the genus β -Coronavirus and has 76.6% similarity to SARS-CoV (Zhou et al., 2020),(Lu et al., 2020). SARS-CoV-2 spreads through the airway: droplets, respiratory secretion, or direct contact (Guo et al., 2020). The incubation period of SARS-Cov-2 is 2-8 weeks for the symptom to outcome (WHO, 2020). The first step of this virus to enter the host is identifying the angiotensin-converting enzyme 2 (ACE2) receptor by its spike protein. Therefore,

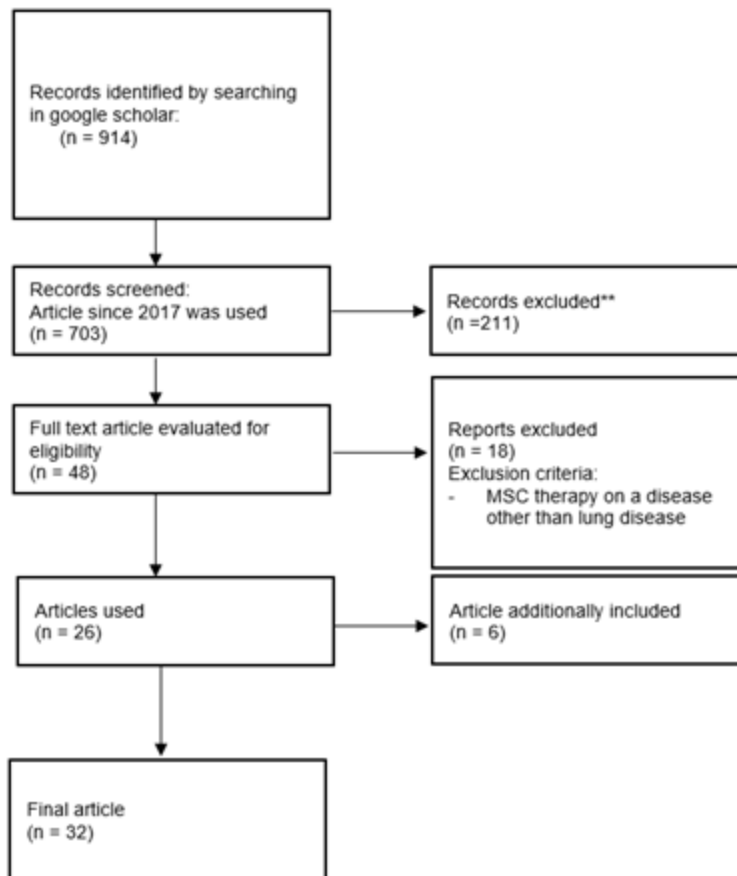


Figure-1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram outlining the systematic review process.

for COVID treatment. In addition, clinical trials using MSC were collected from NIH databased using the keyword "MSC for COVID-19". Data collected from reviewed articles were processed using Mendeley, Ms.word, and pictures made with

ACE2 positive cells could potentially be infected by this virus (Rothan & Byrareddy, 2020). During the viral entry to the cell, the spike proteins on the envelope of SARS-CoV-2 are divided into S1 and S2 subunits (Kirchdoerfer et al., 2016). S2 subunit

was responsible for viral particle membrane fusion containing the functional elements required, while S1 protein/receptor interaction is a key determinant of SARS-CoV-2 infection to the host cell (Yan R et al., 2020). The proteolytic cleavage of S1 will initiate the interaction with the ACE2 receptor peptidase domain (Samavati & Uhal, 2020). Serine protease (TMPRSS2) is required to achieve the cleavage of S1 protein by acid-dependent proteolytic cleavage (Hoffmann et al., 2020). Lung alveolar epithelial cells contain many ACE2 protein receptors, and they express TMPRSS2 largely; the presence of these ACE2 and TMPRSS2 will facilitate the binding of SARS-CoV-2 spike-S-Glycoprotein to infect the host (Raza et al., 2021). This result suggests that alveolar pneumocytes in the lung are the possible host for SARS-CoV infection.

The cytokine storm in the lung is the trademark pathognomonic of SARS-CoV-2 pathogenesis. The critically severe COVID19 in ICU patients showed the IL-2, IL-7, IL-10, GCSF, IP10, MCP1, MIP1A, and TNF- α on a high level, causing breathing disfunction, pneumonia, and acute respiratory syndrome (ARDS) (Huang et al., 2020). Around one week after COVID-19 symptoms, T and B cells are detected within the blood to respond against SARS-CoV-2. These cells are vital to indicate infection; CD8+ T cells will directly attack and kill infected cells, while CD4+ T cells will play a pivotal role in priming both CD8+ T cells and B cells (Tay et al., 2020). Accumulation of mononuclear cells was found in COVID-19 patients' lungs, with low levels of

hyperactive T cells in the peripheral blood. This finding indicates that T cells are moved from the blood to the infected site to overcome the viral infection (Xu et al., 2020).

Normally, the first response from an immune system in healthy adult COVID positive is the activation of innate immunity, becoming the initial defense towards infection (Robb et al., 2016), followed by a production of Th1 and Th2 cells. Pro-inflammatory cytokine and cellular immunity will be released and controlled by Th1 cells. Meanwhile, Th2 released an anti-inflammatory cytokine. In a healthy adult with COVID-19 infection, a balance of Th1 and Th2 activity were observed, telling us that severe cases of COVID-19 patients are caused by the unbalanced Th1 and Th2 cells (Meftahi et al., 2020). The patients infected with COVID-19 reported in a clinical study to have a large amount of IL1B, IFN γ , IP10, and MCP1, leading to activation of T-helper-1 (Th1) cell response. In addition, patients who need to be admitted to the ICU have a higher GCSF, IP10, MCP1, MIP1 α , and TNF α than patients who do not, indicating the severity of the disease is affected by the cytokine storm. A study also found IL-2, IL-6, IL-7, IL-10, TNF- α in a critically severe COVID19 patient (Huang et al., 2020). With those findings, inhibiting the inflammatory response is the key to curing the COVID-19 lung inflammatory (figure 1).

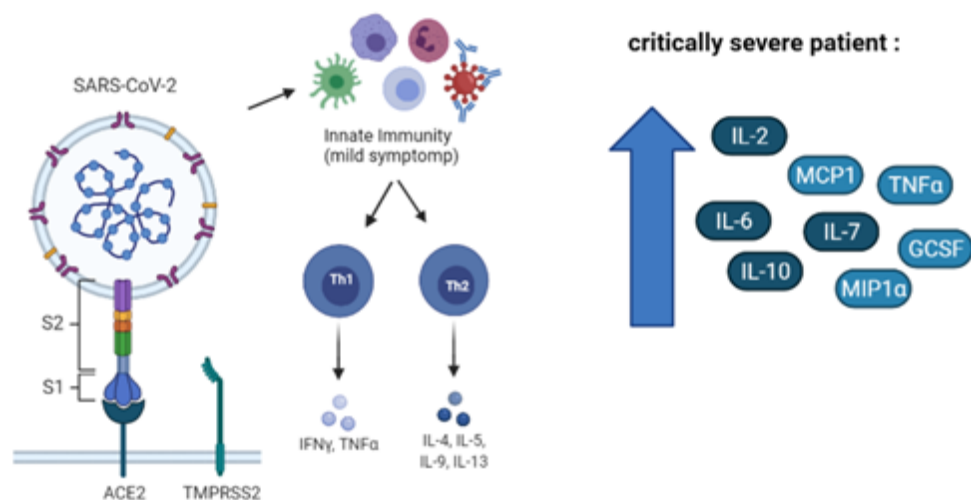


Figure-2. The SARS-CoV-2 infection (Kirchdoerfer et al., 2016, Yan R et al., 2020, Raza et al., 2021) and schematic immune response (Robb et al., 2016, Meftahi et al., 2020, Huang et al., 2020). The figure is made with BioRender <https://app.biorender.com/>

Mesenchymal Stem Cell for COVID-19

The Mesenchymal Stem Cell (MSC) is promising to be a cell-based reliable therapy to combat diseases (Golchin & Farahany, 2019). MSCs are attractive cells for therapy because they are multipotent and partially avoid immune cell recognition (Sinclair et al., 2013). MSCs have been studied in various lung diseases, including respiratory virus-induced ARDS, in preclinical and clinical trials (Chen et al., 2020). One way for mesenchymal stem cells to enter the body is through intravenous infusion. Then a small

(Ge et al., 2018) (figure 2).

Some challenges for a successful transplantation treatment are various treatment responses, low numbers, and the response of source-specific immunomodulators. The MSC's repair effect observed in vivo indicates that the clinical effect relies on the transplant microenvironment. However, MSCs in the resting phase does not exhibit the aforementioned potential. MSCs will exhibit immunomodulation or homing potential only when exposed to a stimulating environment. Therefore, priming MSC before clinical trial may be a solution (Raza

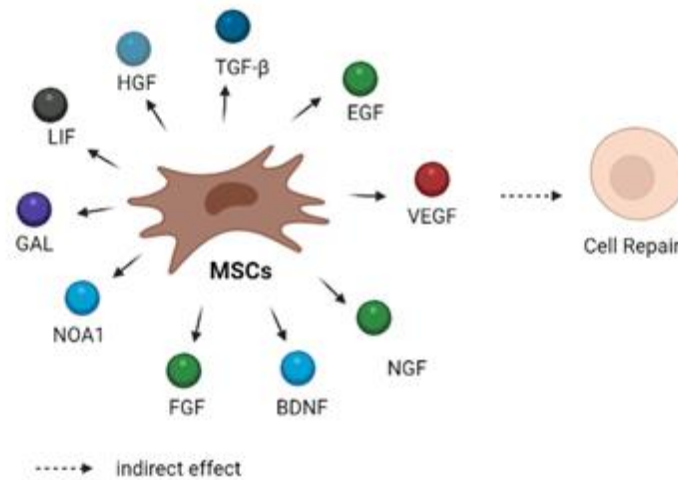


Figure-3. MSCs secretion (Leng et al., 2020) this secretion will help against cytokine storm and indirectly help cell repair (Ge et al., 2018). The figure is made with BioRender <https://app.biorender.com/>

amount will accumulate in the lungs, which may improve the microenvironment of the lung, protect alveolar cells, prevent pulmonary fibrosis, and enhance lung function (Sinclair et al., 2013). Moreover, MSCs are detected to be ACE2 or TMPRSS2 negative, making MSCs free from SARS-CoV-2 infection (Leng et al., 2020). MSCs also highly indicate anti-inflammatory and trophic factors like TGF- β , HGF, LIF, GAL, NOA1, FGF, VEGF, EGF, BDNF, and NGF (Leng et al., 2020). These data prove that the positive effect of treatment using MSCs could be due to these cells' immunomodulation and regenerative ability. MHC I molecules are constitutively expressed by MSCs, and they will express MHC II when the inflammatory mark reaches them, such as Interferon- γ (Galipeau & Sensébé, 2018). In addition, MSCs are proven to help cell repair by secreting VEGF, generating the differentiation of endothelial progenitor cells into endothelial cells

et al., 2021).

Mesenchymal Stem Cell Therapy for COVID-19 patient

Seven COVID-19 positive patients were registered to a preliminary study for MSC transplant: one critically severe patient, four severe patients, two common patients, and also three severe patients for placebo control. The patients' symptoms were high fever ($38.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$), fatigue, low oxygen saturation, and shortness of breath. All patients obtained a single dose of 1×10^6 MSC/kg body weight. Around 2-4 days after the transplantation, all symptoms were gone in all patients, the oxygen saturations increased to $\geq 95\%$ at rest, indicating the lung regained its function. No effects were detected after treatment. Then 13 days after the transplantation, SARS-CoV-2 infection turned out to be negative (Leng et al., 2020). The immune system profile showed no increased regulatory T

cells (CXCR3-) or dendritic cells (DC, CXCR3-) for the two common patients. In contrast, in the severe patients, there was an increase of both the regulatory T cells and DC after the cell therapy, especially for the critically severe patient. In addition, the amount of CD4+ T cells, CD8+ T cells, and NK cells was significantly increased for critically ill patients before the MSC transplantation, causing the cytokine storm. However, the overactivated T cells and NK cells nearly disappeared, and the number of other cell subpopulations almost returned to normal levels six days after the MSC transplantation (Leng et al., 2020).

After injection, there was a significant decrease of TNF- α as a pro-inflammatory cytokine and a significant increase of IL-10, an anti-inflammatory cytokine. Mesenchymal stem cells inhibit the effect of IL-1 by regulating T cells and controlling IL-1 receptors by antagonizing its expression. Mesenchymal stem cell inhibits the expression of IL-1, TNF- α , and IFN- γ in lung tissue, which will significantly decrease pro-inflammatory factors. They also enhance the expression of IL-10 and regulatory T cells, ultimately increasing anti-inflammatory factors and then reducing the inflammatory response. Due to its immunosuppressive ability, the levels of pro-inflammatory cytokines and chemokines significantly decrease, thereby attracting fewer monocytes/macrophages to the fragile lungs and at the same time attracting more regulatory dendritic cells induced into the niche of inflamed tissue (Leng et al., 2020).

Forty-three clinical trials on MSC for COVID19 have been recorded at the National Institute of Health (NIH) database as of May 2021 (<https://clinicaltrials.gov/ct2/results?cond=Mesenchymal+Stem+Cells&term=lung+COVID19&cnt ry=&state=&city=&dist=&Search=Search>) (Table.1). Based on the data, some countries dominate conducting clinical tests using Mesenchymal Stem Cells (MSC), like China and the United States. Indonesia has conducted two trial clinics registered in the last year and is still processing. Of the 43 clinical trials, 11 trials used MSC from Umbilical cord, four from Wharton jelly, four trials used adipose tissue MSC, two trials used dental pulp MSC, one trial from cord blood, one trial from a placenta, one trial from the mucosa, and one trials used exosome derived MSC. Another 17 did not mention the specific sources used, some using MSC from stem bank cells. Clinical trials were undertaken on patients over 18-19 years old and were not gender-

restricted. Cell doses varied from 0.5×10^6 to 1×10^7 cells/kg body weight and were given in 1-3 injections. However, no updated result was posted on this site and may be posted separately.

Table 1. List of Registered Clinical Trials Using Mesenchymal Stem Cell for Treating COVID-19 on NIH database (<https://clinicaltrials.gov>)

Clinical Trial Number	Cell Source	Country
NCT04366271	Umbilical Cord	Spain
NCT04713878	Umbilical Cord	Turkey
NCT04302519	Dental pulp	China
NCT04371601	Umbilical Cord	China
NCT04288102	Umbilical Cord	China
NCT04390152	Wharton's Jelly	Colombia
NCT04339660	Umbilical Cord	China
NCT04377334	MSC	Germany
NCT04392778	MSC	Turkey
NCT04713878	MSC	Turkey
NCT04429763	Umbilical Cord	-
NCT04629105	MSC	United State
NCT04273646	Umbilical Cord	China
NCT04416139	MSC	Mexico
NCT04457609	Umbilical Cord	Indonesia
NCT04355728	Umbilical Cord	United State
NCT04382547	Mucosa	Belarus
NCT04461925	Placenta	Ukraine
NCT04293692	Umbilical Cord	China
NCT04456361	Wharton Jelly	Mexico
NCT04780685	MSC	United State
NCT04366063	MSC	Iran
NCT04336254	Dental Pulp	China
NCT04611256	adipose tissue	Mexico
NCT04371393	MSC	United State
NCT04252118	MSC	China
NCT04625738	Wharton's Jelly	-
NCT04898088	MSC	Turkey
NCT04315987	MSC	Brazil
NCT04366323	Adipose Tissue	Spain
NCT03042143	MSC	United Kingdom
NCT04352803	Adipose Tissue	-
NCT04269525	Umbilical Cord	China
NCT04390139	Wharton's Jelly	Spain
NCT04565665	Cord Blood	United State
NCT04276987	MSCs-derived exosomes	China
NCT04527224	Adipose Tissue	-
NCT04798716	MSC-exosomes	United State
NCT04466098	MSC	United State
NCT04535856	MSC	Indonesia
NCT04537351	MSC	Australia
NCT04492501	MSC	Pakistan
NCT04447833	MSC	Sweden

Among several sources of MSCs, the umbilical cord mesenchymal stem cells (hUCMSCs) are the most used because they are easy to collect and culture (Shu et al., 2020) (figure 3). A Chinese clinical trial (No registration: ChiCTR2000031494), using umbilical cord mesenchymal stem cell as a treatment to 41 patients (12 patients as treatment group, and 29 as controlled group), showed a great improvement to all patients treated. These patients received an intravenous drip of 2×10^6 cells/kg body weight. The mortality rate was 0% in the treatment group and 10.34% in the controlled group. In the hUCMSC treatment group, several symptoms, such as weakness, chest tightness, and low oxygen saturation, were improved for 11 (91.67%) patients, while in the controlled group, only 15 (51.72%) patients showed improvement at day 14. The level of inflammatory factors was significantly decreased, and the lymphocyte level was back to normal in a shorter time (Shu et al., 2020).

potential side effects of corticosteroids. The patient was diagnosed with severe COVID-19 with severe pneumonia, acute respiratory distress (ARD), organs damage (liver, respiratory system, and blood), moderate anemia, hypertension, type-2 diabetes, acute gastrointestinal bleeding, electrolyte imbalance, immunosuppression, and other symptoms (Liang et al., 2020). It has been reported that the symptoms of elderly patients may be more severe than younger patients, and the ICU admission rate is also higher. A study showed that cytokine storm risk increased in elderly adults, pointing out that aging is correlated with an elevated level of the pro-inflammatory cytokine, called “inflamm-aging” (Meftahi et al., 2020). The patient then received 5×10^7 cells UCMSC three times for three days and a daily injection of thymosin $\alpha 1$ and antibiotics. The gradual decrease in bilirubin, CRP, ALT, and AST concentrations and improvement of other vital signs were shown after the second injection. White blood cells and neutrophils dropped to an acceptable level, and

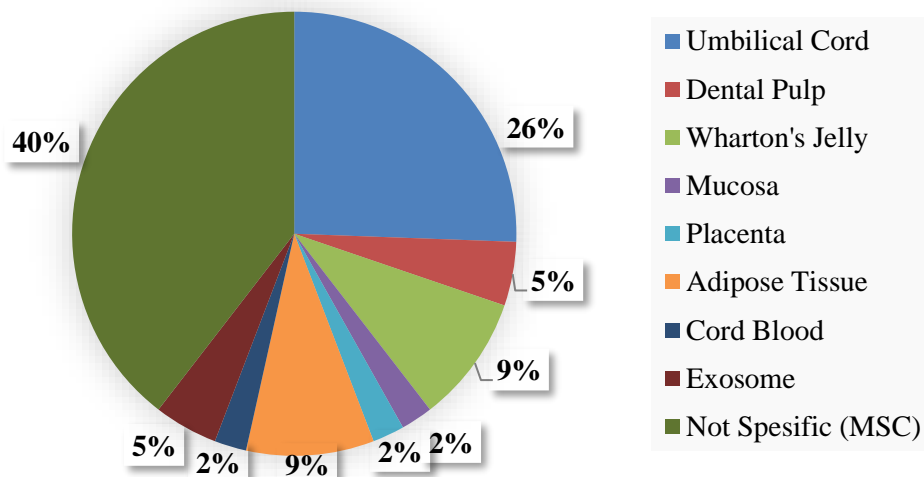


Figure-4. Percentage of used MSCs sources on the registered clinical trial. Almost half of the MSCs used were not mentioning the sources, but the most MSC source used was umbilical cord MSCs.

Another clinical study was done on a 65-year-old female COVID-19 patient who had various diseases, such as fever of 38.2°C, coughing with white foamy phlegm, asphyxiate, oxygen saturation of 81% hypertension after one day. After two days, neutrophils increased to 87.9%, lymphocytes decreased to 9.8%, and neutrophils increased to 95.1% after five days. Then, antiviral therapy and inhalation of IFN- α were combined with multiple drug therapy. After 12 days of the conventional treatment, the patient's inflammatory symptoms remained severe, and there were

lymphocytes also increased to normal levels. A significant increase of CD3+ T cell CD4+ T cell, and CD8+ T cell count to normal levels was observed. This study also indicates that when hUCMSCs are combined with other immunomodulators, they may reduce inflammation and help recover damaged tissues (Liang et al., 2020).

Besides umbilical cord MSC and other sources of MSC mentioned before, other sources of MSC, which are menstrual blood MSC and MSC's secretome, seem promising to be explored. A

clinical trial using menstrual blood MSC (No.ChiCTR2000029606) reported that 2 patients treated with menstrual blood MSC showed positive outcomes. The first patient was a 37 years old woman with fever and dyspnea also hypertension history. Her immune profile showed increased neutrophil, decreased leukocytes, decreased hemoglobin, increased inflammatory indicator, C-reactive protein (CRP), and high IL-6. After five days hospitalized with supportive treatment and showing no improvement, she was injected with 1×10^6 MSC/ kg body weight three times (1-2 days interval). Two days after the third dose, the patient showed improvement as the fever and dyspnea got better, increased the number of lymphocytes, and decreased the number of inflammation indicators. Chest X-ray also showed exudate lesion absorption in bilateral lungs, and the SARS-CoV-2 turned negative (Tang et al., 2020). The second patient was a 71 years old woman with fever for 20 days dyspnea cough for ten days. The immune profile shows increased neutrophil, decreased lymphocytes, C-reactive protein (CRP), and normal IL-6. The patient was then treated with MSC via intravenous infusion three times and symptomatic supportive treatment. MSC doses used was 1×10^6 MSC/ kg body weight. The patient showed improvement four days after the third dose, lymphocytes number increased, and inflammatory indicators, especially CRP, decreased. Chest X-ray also showed high-density exudate absorption in the lower and middle lungs. The SARS-CoV-2 expression also turns negative five days after the third dose (Tang et al., 2020).

Another clinical trial in Indonesia used secretome-MSCs (S-MSCs) from hypoxia-MSCs (H-MSCs), an active soluble molecule released by MSC. It was stated that H-MSC might increase MSC survival to reach the damaged area. However, blood clots could block MSC way to their targeted area. S-MSCs are used as a strategy to control the cytokine storm and to speed up the improvement of the damaged lung. This clinical trial reported 3 cases treated with three, four, and six doses of 1 mL S-MSCs every 12 h via deltoid intramuscular injection and showed a positive outcome. The first case was a 54 years old male with severe hypertension, and COVID -19 diagnosed, admitted to Intensive Care Unit (ICU) with cough and dyspnea, oxyhemoglobin saturation (SO₂) 80.6%, and CO₂ pressure 22.9 mmHg, which is below normal (38-42mmHg). Increased white blood cells also showed increased monocyte and decreased lymphocytes and a high

number of CRP.

The patient was then treated with S-MSCs, and five days after injection, SO₂ increased (99.6%), CO₂ pressure increased (36.2 mmHg). Normal white blood cell count showed and decreased the number of CRP levels. Chest x-ray still shows bronchopneumonia. Ten days after treatment, the COVID-19 infection turned out to be negative, the chest X-ray showed improvement with no bronchopneumonia, and the CPR number was normal. The second case was a 53 years old male with type 2 diabetes mellitus diagnosed with COVID-19 admitted to hospital with chest pain and fatigue. Chest X-ray showed cardiomegaly with lung edema, bilateral GGOs, aorta elongation, and aorta atherosclerosis. Normal white blood cells, with the increased number of neutrophils, increased monocytes, and decreased lymphocytes, also an elevation in CRP. 6 hours after injection, the patient showed improvement with increased saturation and oxygen pressure.

On the second day of injection, the patient showed normal oxygen saturation, and the laboratory result showed increased neutrophil, normal monocytes, and decreased lymphocytes count, also decreased CRP level. 2 weeks after treatment, the patient had no cough, dyspnea, chest pain, and fatigue, then discharged from ICU. Week later, laboratory report showed normal neutrophil and lymphocyte, chest X-ray also showed normal cardiac and no infiltrate or nodule in both lung. A final case reported was a 72 years old male with mild hypertension, liver failure, long-term stroke, and thalassemia minor diagnosed with COVID-19 with abdominal pain, diarrhea, anosmia, cough, and sore throat for the last three days. Laboratory reports showed decreased white blood cells, with normal neutrophil, lymphocytes, and increased monocytes. Days later, the patient's dyspnea worsened, and he was admitted to ICU. Oxygen saturation decreased, CO₂ pressure decreased and increased neutrophil number, increased monocytes number and decreased lymphocytes count, also elevated CRP level. Chest X-ray also worsened with cardiomegaly and aortic atherosclerosis. A day after the first S-MSC injection, oxygen saturation increased. Furthermore, two days after the last injection, laboratory report showed normal neutrophil count, normal monocytes count, and normal lymphocytes number, also decreased CRP level. 4 days after injection, the patient showed no symptoms, no abdominal pain, diarrhea, anosmia, cough, and sore throat and discharged from ICU (Putra et al.,

2021).

The effect of MSC exerted through paracrine and autocrine pathways. Exerts decreased IL-1, IL-6, tumor necrosis factor-alpha, and enhanced IL-10 in COVID-19 patients. Mesenchymal release TGF- β and hepatocyte growth factor (HGF) will decrease the cyclin D2 and increase p27kip1 expression in T cells, thereby preventing proliferation in the G1 phase and inhibiting proliferation activation of T cells. MSCs also induce apoptosis of activated T cells through the Fas/Fas lig and-dependent pathway, inducing the generation of regulatory T cells, which will suppress IFN- γ and IL-17 secretion and promote IL-10 formation (Galipeau & Sensébé, 2018). However, a study observed that apoptotic or dead MSCs might encourage a suppressive despite missing the response of living MSC functional properties that can cause a physiological mechanism of tissue clearance promoting immune tolerance (Galleu et al., 2017).

Those studies indicate that MSCs are safe and effective in treating COVID19 patients and may be ideal therapeutic or combination treatment for COVID19 patients. Interestingly, MSCs can also help repair tissue damaged by this virus, as some medical treatments can only fight, not only with the anti-inflammatory factor that MSC secreted. The viruses cannot help the organ failure effect, which is more threatening than the viruses attack themselves—in addition, treating MSC culture and studying the MSC phase before clinical use may be helpful.

CONCLUSION

MSCs, with their immunomodulatory and anti-inflammatory effect, became a favorable treatment for COVID-19 patients, as shown by the potential and promising results. Their cytokine secretions will help against cytokine storms in the patient's lung. There are currently 43 MSC-based clinical trials registered for curing SARS-CoV-2 positive patients, with a positive outcome. MSC from the umbilical cord was frequently used, probably thought the most effective MSC. However, further studies are needed to develop these treatments before bringing MSC therapy to clinical application.

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