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A review of the potential use of mesenchymal stem cell therapy for the management of COVID-19 infection

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The COVID-19 disease, which is caused by the coronavirus, SARS-COV2 had affected the world in 2020 causing a high mortality and morbidity in affected patients. Numerous clinical studies performed worldwide have demonstrated the great potential of MSCs used to prevent complications caused by COVID. In this review, we focus on the potency of mesenchymal stem cell (MSCs) for treating critically ill patients at the risk of developing permanent lung damage and discussed the aspects of this proposed treatment using reported clinical trials and hypotheses.

Keywords: COVID-19, Mesenchymal stem cell therapy, SARS CoV-2

INTRODUCTION

The coronavirus disease 2019 (COVID-19) posed a major threat to human health due to cross species transference in December 2019 that made it the causal agent of a widespread pandemic. (Chen et al. 2022)

As of January 16, 2022, a total of 5,551,970 COVID-19 cases out of 328,675,785 have ended in death.

With the evolution of newer mutants including omicron, the incidence of new infections, reinfections, and vaccine advancement infections have increased all over the world. Due to this, the current epidemic is not controlled yet. (Xu et al. 2022)

SARS-COV 2 causes diverse clinical statuses that range from asymptomatic carriers to mild upper respiratory tract symptoms to severe acute respiratory distress syndrome. (Shi et al. 2022)

Critically ill patients, especially older age group and those with comorbidities have a higher rate of mortality due to their hyper responsive immune system. These include active inflammatory and cytokine storms, which causes lung tissue damage, dysfunctional air exchange, acute respiratory distress syndrome, (ARDS), multiple organ failure, and even death. (Xu et al. 2022)

Respiratory support and dexamethasone are still the mainstay treatment options for most hospitalized patients. At present, Remdesivir is the only antiviral drug authorized by the FDA. (Yao et al. n.d.)

Clinical data shows that post-discharge, critically ill patients still need suitable intervention to improve their long-term recovery. (Shi et al. 2022)

Considering the rapid SARS-CoV-2 mutagenesis which can render the current vaccines ineffective too, alternative therapies are ultimately needed to establish a better management plan.

Therefore, cell-based approaches can be used along with conventional therapies that can aid in the recovery of pulmonary function and decrease the death rates of severely affected patients.

In particular, mesenchymal stem cells (MSCs) are probable candidates to modify the virus-dependent cytokine storm due to their immunosuppressive and anti-inflammatory characteristics. (Karakaş et al. 2022).

The effective therapeutic role of MSCs in the in-vitro models and clinical trials of acute lung injury, ARDS, and lung fibrosis suggest the potential of MSC treatment for COVID-19. (Xu et al. 2022)

PATHOGENICITY OF SARS-CoV-2

Lung is the most frequently damaged organ when the body is infected by COVID-19. This can be elucidated by an increase in the ACE-2 expression within the alveolar type II and the capillary endothelial cells (Yousefi Dehbidi et al. 2022). (Figure 1)

ACE-2 functions as a receptor for SARS-COV2 and is broadly expressed in many other organs too. These include the heart, kidneys, gastrointestinal tract, liver, and the brain, all of which can become a part of a systemic infection. These patients would then present with Kawasaki syndrome, myocarditis, acute coronary syndrome, cerebrovascular accidents or focal areas of neuroinflammation, acute kidney failure, gut alterations, acute liver injury and hepatic dysfunction causing coagulopathies (Yousefi Dehbidi et al. 2022).

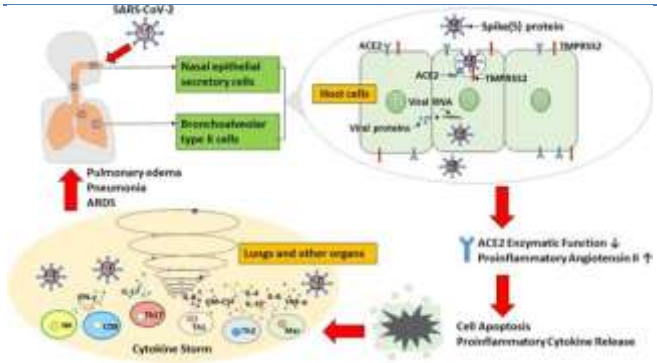

Fig.1. Schematic diagram of how SARS-CoV-2 causes COVID-19. SARS-CoV-2 enters the respiratory tract. Surface S proteins bind to the secretory cells of the nasal epithelium and to the membrane protein ACE2, which is highly expressed in bronchoalveolar type II cells. Through phagocytosis, SARS-CoV-2 enters the host cell, thereby partially or completely abrogating the enzyme ACE2 and increasing angiotensin II concentrations. A high concentration of angiotensin II in the lung promotes apoptosis releasing proinflammatory cytokines and triggers an inflammatory response causing symptoms of pneumonia in COVID-19 patients and to ARDS in severe cases (Xiao et al. 2020).

TREATMENT MODALITIES AVAILABLE AT PRESENT

Till date, adjuvant therapeutic strategies, including corticosteroid-mediated inflammation reduction, plasma-based congestion treatment, antibiotic treatment of secondary bacterial infections, non-specific antiviruses, immune mediated therapy, metabolic and nutritional support, probiotic therapy, and lung transplantation have been the protocol treatment for COVID-19.

ECMO, also called extracorporeal membrane oxygenation, is an invasive mechanical ventilation technique used to provide continuous external breathing and circulation for critically ill patients with severe comorbidities like respiratory and cardiac failure. These devices are often expensive, and their global resources are limited. (Chen et al. 2022)

The cytokine storm created in the lungs causing severe conditions like ARDS, ALI, pulmonary edema, and secondary bacterial infections by the virus accounts for most of the failure of these treatments (Chen et al. 2022).

An immunotherapeutic drug called tocilizumab (Actemra) blocks only the cytokine IL-6. However, a treatment that can affect a variety of cytokines is desperately needed (Yasamineh et al. 2022).

These trials expedite the search for effective medications that can stop mild forms of the disease from worsening and enhance the treatment plans for severely and critically ill COVID-19 patients. It is vital that efficient treatments are created, especially for very ill patients, in order to lower the mortality and enhance therapeutic results (Chen et al. 2022).

MSCs AND THEIR EFFECT

The use of stem cell therapy has been shown to be effective in treating many types of diseases. Several studies have shown that mesenchymal stem cells (MSCs) have powerful immunoregulatory and reparative properties in injured tissues (Chen et al. 2022). (Figure2).

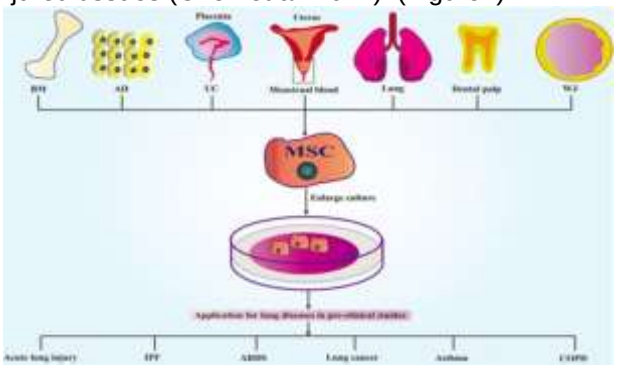

Fig.2. MSCs can be isolated from different adult tissues, including preferably bone marrow, peripheral blood and adipose tissues (AD) such as abdominal fat, infrapatellar fat pad, and buccal fat pad, and neonatal birth-associated tissues, including placenta, umbilical cord, amniotic fluid, and cord blood, Wharton jelly, lungs, dental pulp and then stored for future applications (Chen et al. 2022)

As a result of enhanced host cell phagocytosis, bacterial clearance and antibacterial peptide production, MSCs help in decreasing the host's damage caused by inflammation while simultaneously increasing the host cell's resistance to sepsis and ARDS.

They also express the interferon-stimulated genes (ISGs) that are known to have antiviral properties. They secrete cytoprotective agents that contribute to the regeneration of damaged pulmonary tissue in ALI and ARDS diseases. Angiopoietin and keratinocyte growth factors secreted help in restoring alveolar epithelium and the endothelial cells in ALI and ARDS models. Due to a combination of these properties, MSCs are promising candidates for treating pulmonary inflammation induced by COVID-19. (Sadeghi et al. 2020). (Figure 3)

They might have a broader range of acts as compared to medications which commonly have a restricted number of targets (Yasamineh et al. 2022).

Multiple clinical trials have demonstrated the effectiveness of MSCs while being safe at the same time (Yousefi Dehbidi et al. 2022).

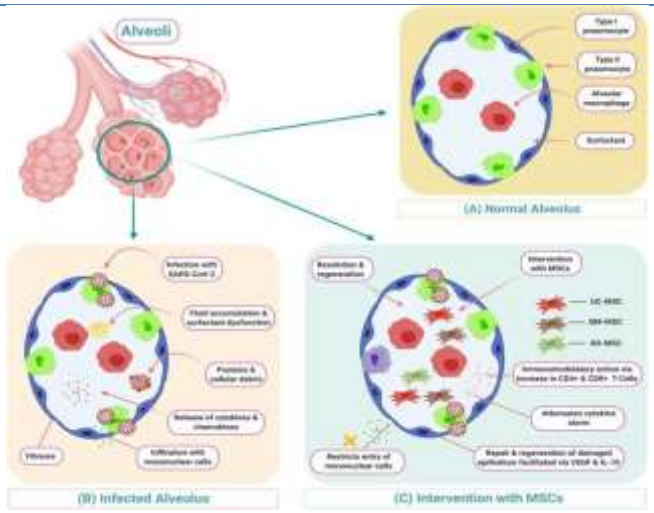

Figure.3: Description of COVID-19 and possible MSC therapy intervention including a demonstration of MSC's immunomodulatory actions (Jeyaraman et al. 2021)

CLINICAL STUDIES USING MESENCHYMAL STEM CELL THERAPY

STUDY NO: 1

Among the 101 eligible patients, 65 were randomly assigned to the UC-MSC group and 35 to the placebo group, respectively.

The baseline characteristics including age, sex, body weight, time from onset of symptoms, distribution of comorbidities, concomitant medication, median time from symptoms onset to study baseline and lesion proportions assessment from chest CT were highly consistent between the two groups of patients.

From April 8, 2020, to March 31, 2021, patients received follow-up visits for a median of 32 days.

Three radiologists independently assessed for lung damage at months 1, 3, 6, 9, and 12.

At months 6 and 12, 11.8% and 17.9% of patients in the MSC group showed normal CT images. However, no patient showed a normal CT scan in the placebo group.

To compare the long-term restoration of lung function and integrated reserve capability between the two groups of patients, we examined the 6-Minute walk distance (MWD) at months 3, 6, 9, and 12.

The median 6-MWD test gradually increased over time in both the groups. At each follow-up point, the test reported a numerically increased distance in the patients treated with UC- MSCs compared with the placebo group. The median percentage was 83.4%, 86.8%, 90.3% in the MSC group, and 80.7%, 84.7%, 85.7% in the placebo group at 3,6,12 month respectively.

Intervention with MSCs also showed some effect on various components in the body. (Figure 4)

At each follow-up time, fatigue or muscle weakness, sleep difficulties, pain, and usual activity were lower in the MSC group than in the placebo group (Shi et al. 2022).

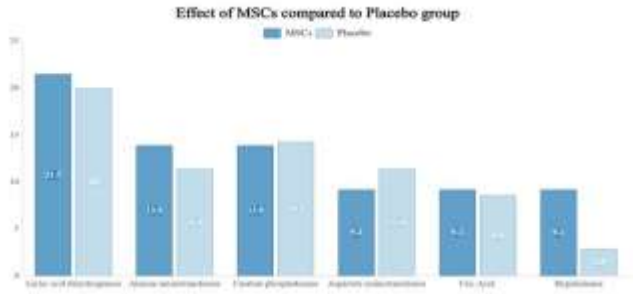

Figure.4: In one of the adverse event seen in MSC's group was 21.5% increase in serum lactic acid dehydrogenase in the MSC group, compared to 20% in the placebo group; a 13.9% elevation of serum alanine aminotransferase, compared to 11.4% in the placebo group; a 13.9% increase in creatine phosphokinase, compared to 14.3% in the placebo group; a 9.2% increase in aspartate aminotransferase, compared with 11.4% in the placebo group; 9.2% increase in uric acid compared with 8.6% in the placebo group; and 9.2% increase in hypokalemia compared with 2.9% in the placebo group.' (Shi et al. 2022)

STUDY NO: 2

In another double-blind, placebo-controlled phase 2 trial, it was seen that MSC administration significantly reduced solid component lesion volume in patients with severe COVID-19 within 28 days. In the subsequent one-year follow-up period, the patients who received MSC treatment showed reduced solid component lesion volume and improved pulmonary function, indicating that MSC therapy might have long-term benefits.

Bone marrow MSC-derived exosomes have shown effective results in reducing acute phase reactant and neutrophil counts, increasing T cell counts, and also in improving oxygenation in severe cases. These data support the potential of MSCs being therapeutic for severe cases with progressive lung damage.

Some MSC-related adverse events have still been recorded. The major clinical symptoms included facial flushing, fever, shivering, headache, liver dysfunction, heart failure, and allergic rash. However, these adverse events were recorded in both MSC-treated patients and controls, indicating that the side effects might be infusion-related. Furthermore, the speed of transfusion and the baseline status of patients with co-existing illnesses may also be associated with the occurrence of these adverse events (Xu et al. 2022)

STUDY NO: 3

Patients were enrolled between January 23, 2020 and January 31, 2022. At the Chinese Center for Disease Control and Prevention, the protocol for real-time reverse transcription polymerase chain reaction (RT-PCR) was

used to confirm HCoV-19 infection in all enrolled patients (age 18-95).

In the event that no improvement has been observed after standard treatments, the patient would be suggested to participate in this study. Any patient diagnosed with cancer, or who had been diagnosed with a critically severe condition by their doctor, was not eligible. Those patients who were participating in other clinical trials or who had participated in other clinical trials within three months were excluded.

MSCs were suspended in 100 ml of normal saline, and the total number of transplanted cells was calculated by 1 × 106 cells per kilogram of weight. While expectant treatments were being conducted, the window period for cell transplantation was defined as when symptoms/signs were still getting worse, approximately forty drops were injected per minute over the course of forty minutes.

After receiving the investigational product, the investigators observed the patients for 14 days. A trained group of doctors recorded and certified the clinical, laboratory, and radiological outcomes. Additionally, therapeutic measures (such as antiviral medicine and respiratory support) and outcomes were examined. (Table 1)

Table 1: Diagnostic Tests for SARS-COV performed before and after MSCs Transplantation (Leng et al. 2020)

DIAGNOSTIC TESTS	HCOV-19 NUCLEIC ACID (PCR)	MASS CYTOMETRY	SERUM CYTOKINE
PRE - TRANSPLANT	POSITIVE	DECREASED (T CELLS AND DENDRITIC CELLS) ↓	INCREASED ↑
POST - TRANSPLANT	NEGATIVE (13th Day)	INCREASED (T CELLS AND DENDRITIC CELLS) ↑	DECREASED ↓

In this study, seven confirmed COVID-19 patients were enrolled, including one critically severe type, four severe types, and two common types for MSC transplantation, and three severe types for placebo treatment.

In the days preceding the MSC transplantation, the patients had high fever (38.5°C + 0.5°C), weakness, shortness of breath, and low oxygen saturation (89%), the C- Reactive protein was 105.5g/L.

Two to four days after transplantation, all the symptoms disappeared in all the patients, the C-Reactive protein decreased to 10.1g/L and oxygen saturations rose to 95% at rest, with or without oxygen uptake (5 liters per minute) showing that the inflammation status was improving rapidly, and pulmonary alveoli had restored their ability to exchange air (Leng et al. 2020)

STUDY NO: 4

According to a clinical study involving seven COVID-19 pneumonia patients in Beijing Youan Hospital, China, MSC transplantation improved the outcomes of all patients by 14 days after MSC injection without causing adverse effects. In the two days following MSC injection, the patient's pulmonary function and symptoms improved significantly. Within 1 week, cytokine-secreting immune cells such as CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells disappeared. The level of the proinflammatory cytokine TNF-α was greatly decreased, which indicated the potential of MSCs in treating patients with severe ARDS(Xiao et al. 2020)

MSCs would reduce proinflammatory cytokines (TNF-α, IFN-γ, IL-6, and MCP-1) and increase the release of soluble anti-inflammatory factors (IL-10, IL-1β, PGE2, MIF, VEGF, and IDO). Additionally, they could exert an anti-fibrotic effect at the lung injury focus through TGF-β factor inhibition. Altogether, human amniotic membrane stem cell therapy would prevent multiple organ failure progression in patients who suffer from COVID-19 (Riedel et al. 2021)

STUDY NO: 5

Leng and colleagues conducted a pilot trial on MSC transplantation for seven SARS-CoV-2 positive individuals. For two weeks of MSC therapy, they administered

1x 106 clinical-grade MSCs per kilogram of body weight intravenously and monitored the patients using various hematological and pulmonary compliance measures. They noticed that pulmonary compliance had significantly improved clinically.

This pilot investigation also revealed that since MSCs lack ACE-2 and TMPRSS-2 receptors, they are not susceptible to SARS-CoV-2 infection. CT imaging post-treatment showed no evidence of pneumonic consolidation (Jeyaraman et al. 2021).

NEW ADVANCES OF MSCs

It is possible to increase the clinical potency and application of MSCs through a variety of techniques, including genetic engineering, particle engineering, and small molecule priming. Interleukin-6 is one of the possible targets since it is well documented to play a significant role in producing the cytokine storm in critical COVID-19 cases. Altering the release of cytokines utilizing bioengineering technologies may enhance therapeutic effectiveness and finally enhance the present clinical advantages of MSC administration (Karakaş et al. 2022).

In viral pneumonia, synthetically produced stem cells - "LIFNano" LIF (leukemia inhibitory factor) is indispensable for fighting the chemokine storm in the lungs. LIF is released by MSCs, but as a solution it lacks efficacy due to its cell-based nature and prohibitive costs. Nanotechnology has made it possible for synthetic stem cells to be delivered as LIFNano, which has a potency 1000 times higher than soluble LIF. The therapeutic

effects of LIFNano on EAE, a model of Multiple Sclerosis (MS), were evident within 4 days, similar to the effects found on pneumonia using MSC therapy for COVID-19. It has been shown that neural stem cell derived LIF is the sole factor responsible for EAE benefit in previous studies. LIFNano, a transpiring alternative of cell-based therapy, meets the requirement for high-volume and off-the-shelf therapeutic agents capable of renewing affected tissues and repressing chemokine storms in pneumonia. Low volume vials make global distribution simple. A combination of inhalation and intravenous delivery is an option (Metcalfe, 2020).

CHALLENGES FOR MSC-BASED THERAPY FOR COVID-19

Although most studies have shown that MSC treatment is mostly safe and well tolerated some adverse events have still been recorded.

One of the most frequent limitations on MSCs therapy is eligibility. Patients who have undergone organ transplantation, long-term immune suppression, those with a history of malignant tumor or other critical systemic disorders, severe allergies, co-infected with HIV, tuberculosis, influenza, and other respiratory viruses, as well as pregnant and breastfeeding women will be excluded from the clinical trial.

Early adverse events included anaphylactic reactions, which worsen dyspnea, wheezing, anxiety, hypotension, and bronchospasms in severe cases; allergic reactions, which typically include maculopapular rashes and/or urticaria without fever or hypotension (Yasamineh et al. 2022).

A significant problem is what happens to MSCs immediately after intravenous infusion. After systemic MSC delivery, the bulk of therapeutic cells are injected into the lung, where they have a brief lifespan, but they can easily generate emboli there. Thus, patients with COVID-19 who have hypercoagulopathy may encounter unfavorable side effects due to the stimulation of an innate immune response. However, they also have the ability to rapidly expel themselves from the circulation there (Chen et al. 2022).

It is also challenging to understand future evaluations, side effects, and the beneficial effects of MSCs therapy in COVID-19 patients while concurrently taking conventional medications such as Remdesivir and dexamethasone.

Finally, the absence of a consistent management protocol results in variations in the key elements of cell therapy, such as the source of MSCs, stem cell preconditioning, delivery method, dose, frequency, and appropriate disease stage for MSC therapy (Yasamineh et al. 2022).

CONCLUSION

This narrative review was aimed at finding the effectiveness of Mesenchymal Stem cells in severe COVID-19 patients. MSCs function well as a candidate for decreasing inflammation, repairing lung injury and preventing long term pulmonary complications.

Multiple studies have confirmed its safety and therapeutic efficacy.

Intervention with MSCs restricts entry of mononuclear cells, attenuation of cytokine storm, repair and regeneration of damaged epithelium facilitated via VEGF AND IL-10, and an immuno-modulatory action via increase in CD4+ and CD8+ T cells thereby helping in complete resolution and regeneration of damaged tissues.

Future trials designed to enhance MSCT as a feasible treatment option involves new variety of techniques including genetic engineering, particle engineering, and small molecule priming.

In conclusion, MSCs can play a powerful role in combating not only COVID-19 but in various other chronic incurable conditions.

Further studies and trials need to be conducted in larger groups for better understanding of stem cell therapies.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

All authors read and approved the final version.

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