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Review

COVID-19 and the role of stem cells

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ABSTRACT

There is currently an ongoing coronavirus respiratory disease (COVID-19) pandemic that is caused by SARS-CoV-2 virus, which emerged out of Wuhan, China. In severe cases, the disease can progress to respiratory distress, hypoxia, and multi-organ failure, all of which are associated with high mortality. Mesenchymal stem cells (MSCs) possess potent and broad-ranging immunomodulatory activities. MSCs have demonstrated their impressive ability to inhibit lung damage, reduce inflammation, attenuate the immune response, and aid with alveolar fluid clearance. Studies that investigated the use of MSCs and exosome cells derived from MSCs in treating COVD-19 patients have encouraging results. The conclusion of the results of four clinical studies, as presented in this review article, is reduced patient mortality in more than half of the subjects who were administered MSCs or exosomes derived from MSCs, intravenously, positioning these cells as a possible therapeutic solution for COVID-19. While the studies do have limitations, they do provide a stepping stone based on different approaches in the search for treatment to save patients.

Contents

1. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease that causes patients to have pneumonia-like symptoms. An outbreak of this disease started in 2019 in Wuhan, China, and has since then spread to Europe, United States, and the rest of the world, evolving into a deadly pandemic that has killed more than one million people. This disease is caused by the virus of the name *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2) [52, 53, 58]. Hospitalizations are required for certain subjects (approximately 15%–20%), mostly those who tend to have underlying health conditions of lung, heart, liver, kidney, hypertension, diabetes, obesity, and those who are aged >65 years [3, 9]. About 5% of patients experience severe respiratory difficulties, septic shock, and multiple organ failure [37]. (see Table 1)

The fight against COVID-19 relies heavily on the need to regenerate damaged lung tissue and to treat inflammation. This is

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Table 1
Summary of all the results of the four novel studies aforementioned.

Study on MSCs in China	Study contained 7 COVID-19 patients. Four of them had severe ARDS symptoms. All patients were treated with MSCs and all demonstrated clinical improvements. Five of the patients (1 mild symptoms and 4 severe symptoms) showed significant decrease in CXCR3+CD4, CD8, and natural killer cells.
Study on UC-MSCs in Miami	Study contained 24 COVID-19 patients. They were divided into treatment group and placebo group. After treatment, all patients in the treatment group had reduced levels of GM-CSF, IFN-γ, IL-5, IL-6, IL-7, TNF-α, TNF-β, PDGF-BB, and RANTES, with an increase in IL-10.
Study on MSCs in Iran	Study contained 11 COVID-19 patients with ARDS. They had all been admitted to the ICU. They are infused with prenatal MSCs. Five showed significant improvements while five died. For the ones who survived, there were reductions in TNF-α, IL-8, and C-reactive protein. Furthermore, there was a decrease of IL-6 INF-γ in half the patients.
Study on Exosomes Derived From BM-MSCs	Study contained 24 COVID-19 patients who were given exosomes derived from MSCs. 17 of the patients recovered but 3 remained critically ill and 4 others passed away (reasons unrelated to treatment). In those who made it to recovery, there were reductions in neutrophil count, along with increase in lymphocyte count.

where the need arises for mesenchymal stem cells (MSCs) [5]. These cells can be extracted from different parts of the body. Starting in 2020, there have been multiple ongoing trials for testing the efficacy of MSCs on patients with severe COVID-19, most of which produced promising results [2, 28], making them the most likely cells of choice for cell-based therapy trials [30].

2. Danger of COVID-19

Patients with debilitating COVID-19 infection experience a severe cytokine storm, hyperinflammation, and immunothrombosis; many of them end up developing severe pneumonia. Lung injury can result, paving the path for respiratory failure through the development of acute respiratory distress syndrome (ARDS) [24, 33]. About 67% of subjects with underlying health conditions *and* COVID-19-induced ARDS end up being critically ill with severe respiratory distress (Zhu et al., 2020). ARDS is characterized by an overreaction of the immune system. The result is a massive inflammatory cell infiltration and release of pro-inflammatory cytokines. In these severe cases, the overactive immune system damages lung tissue so patients with ARDS need high-flow oxygen therapy, intensive care, and mechanical ventilation [3, 9].

When a cytokine storm starts, it is accompanied by more aggressive tissue-based immunity, leading to increased tissue damage. During this massive overreaction by the immune system, there is secretion of myeloid/macrophage-derived cytokines, including exacerbated production of interleukin (IL)-6, IL-8, IL-1α, IL-1β, tumor necrosis factor-alpha (TNF-α), granulocyte colony-stimulating factor (GSCF), CCL-2, CCL-3, and CCL-5. These pro-inflammatory cytokines attract macrophages, monocytes, and T cells to the infection cell. What follows is an excessive inflammatory response which leads to further accumulation of immune cells in the lungs, promoting additional inflammation in lung tissue [45].

A percentage of COVID-19-induced ARDS patients end up with multiple organ failure and death, tied to the damage sustained by the cytokine storm. Mortality in patients with COVID-19 and ARDS was reported to be 52.4% [52, 53]. For patients who survive these complications, significant morbidity follows because of neuromuscular weakness, myopathy, and residual lung fibrosis. Such consequences can persist up to five years after recovering from ARDS, resulting in increased healthcare utilization and cost [19].

3. Mesenchymal stem cells and immune system modulation

MSCs are multipotent cells capable of self-renewal and can give rise to unique, differentiated mesenchymal cells (da Silva Meirelles et al., 2008). They can be isolated from bone marrow, adipose tissue, umbilical cord, and placenta. They can attenuate overactive immune and hyperinflammatory processes, promote repair and regeneration of tissue, and secrete antimicrobial molecules; they can do so with low immunogenicity (low levels of class I and class II human leukocyte antigen) [6, 25].

MSCs execute paracrine modulation of the immune response by the release of soluble factors known as the secretome. The secretome is comprised of cytokines IL-10 (anti-inflammatory), IL-1RA, TGF-β (anti-inflammatory), hepatocyte growth factor (HGF) (anti-inflammatory), indoleamine 2,3 dioxygenase (IDO), and nitric oxide [27]. These cytokines can modulate the activation and proliferation of effector T cells, natural killer cells, neutrophils, and mononuclear cells toward an anti-inflammatory phenotype. Their mechanism of action results in modulation of T cell function by the inhibition of the Th17 response, induction of regulatory T cells (the count of which is reduced in COVId-19 patients), a shift from Th1 to Th2 cell phenotype, and an increase in the generation of regulatory T cells. MSCs have also demonstrated their ability to inhibit the proliferation and maturation of $CD19^+$ cells, $CD4^+$ Th 1 cells, $CD8^+$ T cells, macrophages, monocytes, and neutrophils [13, 42].

The immunomodulatory functions of MSCs aren't new to the field; they have been studied for the treatment of inflammation and regeneration of damaged tissue in autoimmune diseases of type 1 diabetes [4, 7], inflammatory disorders [14], steroid-refractory graft-vs-host disease (GVHD) [26], and systemic lupus erythematous [50]. [18, 36] have done work with MSCs on lung tissue and reported reduced inflammation and fibrosis. For subjects with ARDS induced by COVID-19, it has been reported that MSCs – which tend to mainly accumulate in the lungs after injection – produced variable, but promising, results. The general outcome was an improvement in the lung microenvironment, inhibition of overactive immune system, promotion of tissue repair, and prevention of long-term pulmonary function [10, 55].

4. Types of mesenchymal cells

1 Umbilical cord derived MSCs (UC-MSCs)

They are derived from umbilical cords discarded after delivery; as such, they do not cause any ethical controversies [41]. Administration of UC-MSCs is minimally invasive, lacks significant immunogenicity, permitting allogenic transplantation without immunosuppressive drugs [43, 46]. As established by [32], UC-MSCs were more effective than human bone marrow-derived (BM) MSCs at restoring impaired alveolar fluid clearance and permeability *in vitro* airway epithelial cell models.

2 Amniotic membrane derived MSCs

They are derived from the human placenta; the fetal membrane serves as an abundant source for stem cells with immunoregulatory and regenerative properties [44]. Stem cells isolated from there include human amniotic epithelial cells (hAECs) and human

mesenchymal stromal cells (hAMSCs). They possess unique features that place them as candidates for cell therapy: they are easy to obtain without an invasive procedure, have immunomodulatory properties, and there aren't ethical concerns associated with their isolation and replication [39]. These cells have been used in preclinical studies and in clinical trials against respiratory diseases. They ended up reducing the inflammatory response and decreasing the amount of damaged pulmonary tissue in injured lung samples, in the case of *in vivo* models. These features position amniotic stem cells a possible therapeutic agent for COVID-19 [35].

hAECs could modulate the proliferation and migration of T and B lymphocytes, natural killer cells, neutrophils, and macrophages. Moreover, these cells can reduce the pro-inflammatory cytokines of TNF-α, IFN-γ, IL-6, and MCP-1, and increase the release of anti-inflammatory factors of IL-1, IL-10, TGF-β, HGF, IDO, and IL-1β [1, 8]. Their actions alter the surrounding microenvironment by stopping inflammation [40].

For the other type of amniotic cells, [29] showed that hAMSCs could alleviate the inflammatory microenvironment in a neonatal hypertoxic lung injury rat model. After hAMSC infusion, the pro-inflammatory cytokine expression was reduced, along with a reduction in pulmonary edema. Another research by [56] reported a potential hAMSC therapy for ARDS. They transfected these cells with Nrf 2, a key transcription factor for antioxidant protein expression. The transfected cells were able to ameliorate lung fibrosis and inflammation, thereby improving the cell-based therapy for acute lung injury (ALI) and ARDS.

3 Adipose-derived MSCs (ASCs)

They are derived from adipose tissue via a minimally invasive lipoaspiration procedure – which have also been reported as a safe therapeutic tool to treat COVID-19 patients [34], with significant anti-inflammatory effects in veterinary and human clinical studies [17]. Obtaining MSCs from adipose tissue is more feasible than from other sources due to the accessibility to subcutaneous adipose tissue and the higher concentration of MSCs in adipose tissue than other tissues in the body [12]. Another advantage is that their potency is maintained with the age of the donor, unlike BM-MSCs. ASCs have also been shown to promote the development of regulatory T cells more than BM-MSCs [49].

5. COVID-19: method of cell entry

SARS-CoV-2 is an enveloped, positive stranded RNA virus. The virus can enter a cell – for the purpose of viral replication – through the receptor binding domain (RBD) of the spike (S) protein, which binds to a cell surface receptor called ACE2 (angiotensin converting enzyme receptor 2) [15]. This receptor is highly distributed in all adult cells, including lung, heart, kidney, liver, and endothelial cells. Out of these cells, lung alveolar type II cells (surfactant producing cells) and capillary endothelial cells show the highest expression of ACE2, which should explain why lung tissue is the site of high replication rate and infectivity by the virus [20]. Once the virus has replicated in the lung tissue, a cytokine storm ensues and the elevated levels of pro-inflammatory cytokines result in lung tissue edema, air exchange dysfunction, and possibly ARDS [54].

A recent clinical study by [28] included seven patients with transfusion of UC-MSCs that lacked ACE2 expression, preventing entry of COVID-19 in transplanted cells. This trial had promising preliminary results in very critically ill patients, some of whom recovered from a major COVID-19-induced pneumonia, with the disappearance of CT-scan lesions. Based on this work, [11] carried out bioinformatics and molecular analyses in several sources of MSCs from adult and fetal tissues, and pluripotent stem cells, on evaluating the expression of ACE2 and assessing their signaling pathways associated with their anti-inflammatory activity. ACE2 expression was found to be significantly higher in MSC-derived from adipose tissue and adult bone marrow, compared with MSC-derived from UC or placenta ($P = 0.03724$). MSCs that expressed lower levels of ACE2 were also associated with lower expression of genes involved in immune regulation, including IL-6, IL-1β, and TNF-α. These properties should make MSCs very attractive for cell-based therapy [38].

6. Novel clinical trial using MSCs

This section will discuss four novel studies on the use of MSC-based therapies (via administration by intravenous route) and their potential mode of action in ARDS-induced infection in COVID-19 patients. One research was by [28] in China, the second by [16] in the United States, the third was done by Reza et al. (2021) in Iran, and the fourth was conducted by [47]) in the United States. The conclusions of these studies are very promising, and they lay the foundation for more research on testing the efficacy of MSCs.

A Study on MSCs in China

The study by [28] was about administration of MSCs in COVID-19 patients who had ARDS, and it was conducted at YouAn Hospital in Beijing. The study consisted of 7 patients who had differing levels of severity: critically severe (n = 1), severe (n = 4), and “common type,” i.e. mild or moderate disease (n = 2). Three of the “severe” categorized patients received the placebo treatment. Patients were followed for 14 days after MSC or placebo administration. No serious adverse effects (SAEs) were observed. All patients demonstrated clinical improvements within 2–4 days after MSC administration, including resolution of clinical symptoms (cough, fever, elevated respiratory rate), and improvements in oxygen saturation. Data in the clinically severe and severe patients demonstrated a decrease in the levels of circulating CXCR3+CD4, CD8, and natural killer cells – after six days. These significant conclusions weren't observed, however, in the “common type” patients.

In light of these limitations, little sample size, and because of the limited amount of information on the placebo control patients, it is difficult to tell for sure the clinical outcome of MSC administration over the long term. The authors have acknowledged the need for more critical parameters in future clinical trials, but this study highlights the potential of MSCs of attenuating the cytokine storm and the need to treat it as a potential therapeutic approach.

B Study on UC-MSCs (double-blind study)

The study by [16] was a double-blind randomized controlled trial at UHealth System/Jackson Health Systems (UHS/JHS), in Miami, Florida on 24 subjects for the purpose of testing the safety and efficacy of allogenic UC-MSCs in patient with COVID-19 and ARDS. The subjects were randomized 1:1 to either US-MSC treatment (n = 12) or the control group (n = 12).

Of the subjects, 11 subjects were receiving invasive mechanical ventilation and 13 were on high flow oxygen therapy via noninvasive ventilation. Subjects in the treatment group received two intravenous infusions of $100 \pm 20 \times 10^6$ UC-MSCs at days 0 and 3. No SAEs were observed related to UC-MSC infusions and the infusions were found to be safe. By day 6, subjects in the treatment group had significantly reduced levels of inflammatory cytokinins, in the concentrations of GM-CSF, IFN-γ, IL-5, IL-6, IL-7, TNF-α, TNF-β, PDGF-BB, and RANTES ($P < 0.05$). At 28 days after the last infusion, UC-MSC treatment was associated with significantly improved patient

survival (91% vs. 42%, $P = 0.015$), due to having a reduction in inflammatory cell types and cytokines, and an increase in anti-inflammatory cytokines, such as IL-10. The mitigation of inflammation in lung tissue would result in protecting alveolar epithelial cells and reverse lung dysfunction, by normalizing the pulmonary microenvironment and preventing pulmonary fibrosis [23].

What this study showed is that UC-MSCs can modulate immune responses and alter the immunopathogenic cytokine storm [16]. The authors of the study highlight the efficacy results but do understand that there are limitations to inferences based on their study, specifically sample size. However, the effect observed in UC-MSC treated group is remarkable and provides a reason for other researchers to carry out further investigations in a large, stratified clinical trial. Synergistic combination strategies could be explored, like dexamethastone [51] and convalescent plasma [31]. The reduction in levels of PDGF-BB in the treatment group adds another layer of significance because PDGF-BB stimulates mesenchymal cell activation, airway smooth muscle cell proliferation, and lung fibroblast cytokine production [21, 48]. It can thus be concluded that the administration of allogenic MSCs may accelerate tissue repair in the lungs, decreasing the need for further mesenchymal cell activation.

C Study on MSCs in Iran

This study, by Reza et al. (2020), was done on 11 patients diagnosed with COVID-19-induced ARDS, whose mean age was 53.8 years and who were admitted into intensive care units (ICUs). The purpose was to test the safety and potential adverse events following transplantation of prenatal MSCs in the subjects. Before the administration of MSCs, the subjects were critically ill, dyspneic, and required mechanical ventilation. They received three intravenous infusions (200×10^6 cells) every day for a total of 600×10^6 UC-MSCs (in 6 cases) and placental-MSCs (in 5 cases). After 48–96 h from the first infusion, there was reduced dyspnea and increased SpO_2 in seven patients. From the total of 11 patients, six were discharged from the ICU – with significant improvements – within 2–7 days of infusion. However, five cases died 4–19 days after the first cell infusion.

In the 6 patients who survived the ICU discharge, it was observed that there were significant reductions in pro-inflammatory biomarkers, of TNF-α ($P < 0.01$), IL-8 ($P = 0.02$), and C-reactive protein ($P = 0.01$). Serum IL-6 levels decreased in five patients ($P = 0.06$) and INF-γ levels decreased in four patient ($P = 0.14$). The findings of the study do support the conclusion that intravenous injection of prenatal MSCs is safe, tolerable, and can improve respiratory symptoms in some critically ill COVID-19 patients.

This study does have limitation, however, due to the low number of patients. In addition, there was a lack of a case-matched control group, which limited the researchers' ability to compare the ICU course and mortality of the MSC-treated cases with similar patients who had COVID-19-induced ARDS. One more limitation was that there wasn't data regarding the reduction in C-reactive protein and pro-inflammatory cytokines in non-survivor subjects. There is a need for large, randomized controlled trials to fill in the gap of knowledge about the therapeutic potential of MSCs for the treatment of this disease.

D Study on Exosomes Derived From BM-MSCs

The researchers in this study administrated exosomes that were derived from BM-MSCs, intravenously, to COVID-19 patients. What these exosomes contain are several chemokines, growth factors, microRNAs, and mRNA that can exert paracrine and endocrine anti-inflammatory, regenerative, and immunomodulatory effects [57]. Before this study, exosomes were an unexplored treatment option for COVID-19, but preclinical studies of these bone-derived exosomes were done intravenously in animal models who suffered from acute lung injury, ARDS, asthma, and other inflammatory diseases, with successful results of edema clearance and sequelae of cytokine storm [22]. In the study by [47], the first clinical study to date using BM-MSCs-derived exosomes as treatment for a disease in an inpatient setting, 24 patients with COVID-19 were given exosomes delivered at single intravenous dose. They were followed and evaluated for safety from days 1–14 post-treatment. After 14 days, 17 patients recovered, but 3 of the patients remained critically ill and the other 4 passed away for reasons unrelated to the treatment.

In subjects who made it to recovery, oxygenation was restored with an improvement of the average pressure of arterial O_2 to a fraction of inspired oxygen ratio (increase of 192%; $P < 0.001$). There were also significant reductions in neutrophil count, along with statistically significant increases in lymphocyte count. This study demonstrated significant reversal of hypoxia, along with immune system downregulation and a reduction of the cytokine storm in patients, after just a single dose, placing them as a promising potential to be implemented. This study, like others before it, does have weaknesses in the absence of randomization, blinding, and limited sample size. Further clinical studies are warranted to investigate safety and efficacy of this treatment.

7. Conclusion

COVID-19 pandemic has become a global public health crisis. The vaccine is currently available, but that doesn't eliminate the need for the search for other therapeutic approaches. The dysfunction in lung tissue as a result of SARS-CoV-2 infection is due to a cytokine storm and ARDS. Decline of patient condition, multiple organ failure, and death can happen afterwards. Stem cells have always been the focus in regenerative medicine and cellular therapies, with the attention being on MSCs in particular. MSCs have immunomodulatory abilities and have been tapped as a potential therapeutic approach.

Four novel studies in assessing the safety, feasibility, and tolerability of a high dose of allogenic and prenatal MSCs were presented, and the implications were discussed. The results give hope that MSCs can immunomodulate COVID-19 related pulmonary disease by causing a significant reduction in the major inflammatory biomarkers of IL-1α, IL-1β, IL-6, IFN-γ, and TFN-α, and by stimulating an increase in anti-inflammatory cytokines such as IL-4, IL-5, and IL-10. These actions bring down the health complications of a COVID-19 infection. While no studies have been registered for the use of MSCs derived from the amniotic membrane, these cells have outstanding abilities to improve several lung injuries, as the review shows, opening up the field for their use in therapy of pulmonary diseases caused by COVID-19. The information presented in this review article was obtained after studying and investigating the results of [59] references. Still, in a scientific community, there is still a need for larger patient cohorts and randomized clinical trials in investigating the work of MSCs, and in the search for an effective cure against COVID-19.

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