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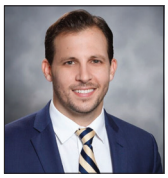
Mini-Review

Mesenchymal Stem Cells Therapy for Coronavirus COVID-19 Induced ARDS: A Promising Concept

Jorge Antonio Gonzalez[1], MD, Roger Rodolfo Gonzalez[2], BS, Laura Elisa Ayala[3], AA

[1]Department of Sports Medicine and Orthopedics, Orthopedic Specialty Institute, Fort Lauderdale, Florida, United States, [2]American University of Antigua College of Medicine, University Park Road, Coolidge, Antigua and Barbuda, [3]Department of Pre-Medicine, Florida International University, Miami, Florida, United States.



***Corresponding author:**
Jorge Antonio Gonzalez, MD
Department of Sports Medicine and Orthopedics, Orthopedic Specialty Institute, Fort Lauderdale 33308, Florida, United States.

jgonzalezmd1@gmail.com

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ABSTRACT

Novel coronavirus severe acute respiratory syndrome (SARS)-CoV-2 pandemic has devastated the world causing an enormous health and financial crisis like none seen before. As many physicians and scientists fight to find a cure and vaccine, the virus continues to spread unchecked with a high mortality rate. Pulmonary involvement and development of severe acute respiratory distress syndrome (ARDS) have been some of the main contributors of mortality and morbidity in SARS-CoV-2 infection. Mesenchymal stem cells (MSC) have gained clinical interest as a treatment option due to their immunomodulatory and antifibrotic properties. Due to the emerging need to find treatment options, multiple MSC clinical trials are undergoing. Cellular treatment may represent a viable option for the treatment of ARDS and coronavirus infection.

Keywords: Coronavirus, COVID-19, SARS-CoV-2, Mesenchymal stem cell, Stem cell therapy, Acute respiratory distress syndrome

INTRODUCTION

Toward the end of the year 2019, a rapidly spreading pulmonary illness was first reported in Wuhan, China. Fudan University first declared that the causative agent of this disease was a new coronavirus strain that has a 5% genetic association with severe acute respiratory syndrome (SARS) and a subset of Sarbecovirus.[1] During this time, the novel virus was named SARS-CoV-2, before the World Health Organization named the virus-associated disease COVID-19.[2]

The disease continues to spread throughout the world, affecting to date (May 2, 2020) over 3 million people with 240,490 deaths in 212 different countries.[3] While these numbers are expected to grow, scientists and clinicians continue to find innovative treatments to fight the infection.

The pathophysiology of SARS-CoV-2 is due to the recognition of angiotensin-converting enzyme two receptor (ACE-2) by its spike protein, which facilitates host cell entry and spread.[4-6] Because ACE-2 receptors are widely expressed in the lungs, infection of the respiratory system leads to a hyperproduction of inflammatory cytokines that have been associated with acute respiratory distress syndrome (ARDS) and cardiopulmonary collapse leading to death.[7,8] This hyperinflammatory response is called cytokine storm and proposed treatment with immunomodulation and immunosuppressant therapies is believed to be beneficial.[9]

ARDS AND MESENCHYMAL STEM CELLS (MSC)

ARDS is a clinical complication of acute lung injury (ALI). It is a devastating condition characterized by a dysfunction of the lung epithelial barrier, the capillary endothelium, causing diffuse alveolar damage, interstitial edema, leading to rapidly progressive acute respiratory hypoxia, failure, and death.[10-12] There have been many preclinical and clinical studies looking into MSC as a treatment option for ARDS [Table 1]. One of the hypothesized mechanisms of action of MSC in the treatment for ARDS is believed to be their anti-inflammatory,[13] anti-fibrotic,[14] and immunomodulatory[15] properties. When analyzing the preclinical and early clinical data, and taking into account the overall safety of these cellular therapies MSC seems like a promising option.[16-19]

In a study published in the journal of critical care medicine,[20] umbilical cord MSC was injected into rats with *Escherichia coli*-induced ARDS, and this group noticed improved oxygenation, prolonged survival linked to a reduction of inflammatory markers interleukin-6, tumor necrosis factor-α (TNF-α), and alveolar infiltration of neutrophils. Similar findings were reported by Mei *et al*. in lipopolysaccharide-induced ARDS. They also found that MSC genetically modified the vascular protective protein angiopoietin-1, which lead to a reversal of lung permeability.[21] The anti-inflammatory properties of MSC were also seen in bleomycin-induced murine ARDS animals.[22] An improvement in ALI and ARDS was seen in mouse models treated with MSCs, and a reduction in macrophage inflammatory protein-2 and TNF-α was seen in bronchoalveolar lavage after infusion.[23] The upregulation of vascular endothelial growth factors and hepatocyte growth factors due to MSC was crucial in preventing vascular permeability and downregulating endothelial cell apoptosis in rat models with ARDS.[24,25] Even in xenotransplantation of human-derived menstrual blood, MSCs into murine models

Table 1: Summary of preclinical and clinical trials.

Indication	Study design	Dose	Application route	Cell source	Result	References
ARDS - preclinical	*Escherichia coli* induced ARDS in rats	1×10^7 human MSCs/kg	i.v.	Human MSC's umbilical cord and bone marrow-derived	Reduced inflammatory markers, prolonged animal survival	[20]
ARDS - preclinical	LPS-induced ARDS in mice	2.5×10^5 MSCs	i.v.	Syngeneic murine MSCs	Reduced inflammation, reduced lung permeability	[21]
ARDS - preclinical	Bleomycin-induced ARDS in mice	5×10^5 MSCs	i.v.	Syngeneic murine MSCs	Prolonged animal survival, reduced	[22]
ARDS - preclinical	LPS-induced ARDS in mice	5×10^5 MSCs	i.t.	Human MSCs	Prolonged animal survival, reduced pulmonary edema	[23]
ARDS - preclinical	LPS-induced ARDS in mice	5×10^6 MSC	i.v.	Rat MSCs bone marrow-derived	Reduced inflammation, reduced lung permeability	[24]
ARDS - preclinical	LPS-induced ARDS in mice	5×10^6 MSC	i.v.	Rat MSCs bone marrow-derived	Reduced inflammation, reduced lung injury	[25]
ARDS - preclinical	LPS-induced ARDS in mice	1×10^6 cell	i.v.	Allogeneic human MSCs, menstrual blood-derived	Reduced inflammation, reduced lung permeability, Reduced lung injury	[26]
ARDS - Clinical	Phase 1, multicenter, open-label, dose-escalation study (n=9)	1×10^6, 5×10^6 or 10×10^6 MSCs/kg	i.v.	Allogeneic human MSC's bone marrow-derived	MSC treatment was safe, decrease inflammatory markers	[18]
ARDS - Clinical	Phase 1, randomized, placebo-controlled pilot study (n=12)	1×10^6 MSCs×kg	i.v.	Allogeneic human MSCs, adipose tissue-derived	MSC treatment was safe	[17]
ARDS - Clinical	Phase 2a, Double: blinded, randomized, Placebo-controlled (n=60)	1×10^6 MSCs×kg	i.v.	Allogeneic human MSC's bone marrow-derived	MSC treatment was safe	[19]

ARDS: Acute respiratory distress syndrome, MSC: Mesenchymal stem cells, LPS: Lipopolysaccharide

showed a reduction of inflammatory markers and repair of damaged lung tissue.[26]

The safety of MSC in human-clinical trials has thus far demonstrated an excellent safety profile.[17-19] Wilson *et al*. performed a single-dose allogeneic bone marrow-derived MSC escalation clinical study to assess safety parameters in moderate to severe ARDS patients. Nine patients were randomized to the three dose groups of 1, 5, and 10×10^6 MSC/kg. They reported no adverse events and also showed that the mean lung injury scores and the sequential organ failure assessment score improved in a dose-dependent manner but did not reach statistical significance.[18] The same group went onto perform a double-blinded, multicenter randomized clinical trial of a single-dose MSC infusion for moderate to severe ARDS.[19] They concluded that MSC treatment was safe, but mortality did not differ in treatment groups, which is possibly due to the wide MSC viability range of 36–85% that was reported in their study.

A small randomized placebo-controlled pilot study using allogeneic adipose-derived MSC in 12 patients showed short-term safety profile as well.[17] More randomized controlled trials (RCT) are needed to further assess clinical benefit of MSC treatment in ARDS.

COVID-19 AND MSC

While many pharmaceutical and biotechnology companies throughout the world are working on therapeutics or vaccine options to combat SARS-CoV-2 and COVID-19, doctors and scientists are taking a special interest in cellular treatments. Over a dozen cell-based clinical studies have submitted investigational new drug application applications to the FDA and are in the process of gathering data.[27]

A study published in Beijing, looked at the clinical efficacy of MSC for ARDS due to the epidemic influenza A (H7N9) infection.[28] ARDS, pneumonia, and respiratory failure were the major contributors to mortality and morbidity seen in the Influenza A pandemic in 2013.[28] A single-center open-label clinical trial was performed in China, where 17 patients with H7N9 viral-induced ARDS were treated with allogenic menstrual blood-derived MSC. This study also included a 44 patient control group with similar clinical findings. The study showed lower mortality in the treatment group, which had 17.6% mortality when compared to 54.5 % mortality in the control group.[28] Due to the similarities in viral pathogenesis between Influenza A (H7N9) and SARS-CoV-2 with ARDS, it is believed that MSC treatment for COVID-19 can be beneficial.

Some early cases and small RCT have been reported, with many more expected in the near future. Liang *et al*. reported a case of a 65-year-old patient with severe ARDS due to COVID-19. After the patient continued to deteriorate despite the experimental treatment of antiviral, antibiotics, IFN-α, methylprednisolone, and immunoglobulin, patient needed intubation. Companionate use of MSC with and without α1 thymosin was given; 5×10^7 cells were injected intravenously.[29] Continued observation of this case showed gradual normalization of inflammatory markers with clinical improvement after the second infusion. Progressive improvement was reported, and the patient was extubated and ultimately discharged from the ICU 2 days after the last MSC treatment.[29]

Another self-reported outcome was published in Israel.[30] After the utilization of a placenta based MSC product, there was a reported 100% survival rate in seven patients with a 66% improvement in respiratory parameters. This company plans on starting a multinational clinical study.

A small randomized control trial published in again and disease treated seven patients with COVID-19 pneumonia with MSC. The study reported improvement in mortality as well as normalization of inflammatory parameters when compared to the three patient control group.[4]

In April, a hospital in New York reported data while using Remestemcel-L in COVID-19 induced ARDS. The allogeneic MSC product had already been accepted for priority review by the FDA for acute graph versus host disease. The results in the companionate use showed an 83% survival rate of the 12 patients treated. Although this was not an RCT, the authors compared their treatment group's survival rate with the 12% survival rate reported by other New York hospitals in the same time frame.[31] This company has since partnered with Cardiothoracic Surgical Trials Network to participate in a 240 patient RCT .[31]

CONCLUSION

Death and financial struggle due to coronavirus led to a worldwide crisis, as no vaccine or therapeutic options were available. Innovative treatments are being looked into as potential answers for the pandemic. As physicians and researchers battle the novel virus, it is important to understand the treatment options that are being utilized while vaccines are being developed. The disease continues to attack the lungs, and mortality is high for those patients that develop COVID-19 induced ARDS. Cell-based treatment has surfaced as a potential option due to its safety profile and early preclinical evidence. Multiple MSC trials have been registered on clinicaltrials.gov to evaluate clinical safety and efficacy for COVID-19 induced ARDS treatment. It is important to mention that although cellular-based treatment is a promising option to treat COVID-19 infections; these are non-approved treatments in the USA at the moment. Clinic-based treatment and marketing without an investigational new drug application and FDA clinical

approval are considered unlawful by the FTC/FDA.[32,33] The scientific community must continue to work together in an evidence-based approach to find safe and efficacious treatment options for SARS-CoV-2.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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