International Journal of Biomedicine 12(3) (2022) 329-338
http://dx.doi.org/10.21103/Article12(3)_RA1

REVIEW ARTICLE

INTERNATIONAL JOURNAL OF BIOMEDICINE

Mesenchymal Stem Cell Therapy and COVID-19

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Abstract

The coronavirus disease 2019 (COVID-19) caused by the novel, severe acute respiratory coronavirus 2 (SARS-CoV-2) has been spreading since late 2019 and has infected more than 360 million people worldwide. Infected individuals often develop severe illnesses, such as hypoxic respiratory failure and acute respiratory distress syndrome, which can lead to multiple organ failure. To manage the COVID-19 pandemic, vaccination programs have been conducted around the globe. In addition to supportive and antiviral medications, much attention has been focused on immunotherapies aimed at reducing pathological changes in the lungs. Currently, mesenchymal stem cells (MSCs) have received extensive attention as an option in treating COVID-19 because of their immunomodulatory, anti-inflammatory, and regenerative properties. This article discusses how MSCs play a major role in the battle against COVID-19, their pathological characteristics, their safety, and their possible effectiveness in treating the disease. (**International Journal of Biomedicine. 2022;12(3):329-338.**).

Keywords: COVID-19 • cytokine • mesenchymal stem cells • treatment

For citation: Rahman FBA. Mesenchymal Stem Cell Therapy and COVID-19. International Journal of Biomedicine. 2022;12(3):329-338. doi:10.21103/Article12(3)_RA1

Abbreviations

G-CSF, granulocyte colony-stimulating factor; **IP-10**, IFN-γ-inducible protein 10; **CP-1**, monocyte chemoattractant protein-1; **MSCs**, mesenchymal stem cells; **MIP-1α**, macrophage inflammatory protein-1 alpha.

Introduction

COVID-19, which appeared in December 2019, is caused by the novel SARS-CoV-2 and first appeared in Wuhan, China.[1] SARS-CoV-2 belongs to the beta coronavirus family.[2] As of May 24, 2022, a total of 6,280,424 deaths have occurred of the 526,707,203 COVID-19 cases worldwide (www. WHO.int).

The symptoms of COVID-19 vary among individuals and can range from asymptomatic infections to critical illnesses.[3] Studies report mild symptoms, such as fever, fatigue, and dry cough, with some individuals experiencing diarrhea and expectoration.[4,5] The more serious symptoms developed into dyspnea or hypoxemia within a week and, in severe cases, rapidly developed into ARDS, septic shock, metabolic acidosis, and coagulation dysfunction.[4,6,7]

Altogether 60.7% of the world's population, or 4,717,280,262 persons, have been fully vaccinated. Vaccinations have proven to be a good solution to this problem. However, vaccines are not considered as a treatment but more as prevention. Various treatments have been introduced for COVID-19, such as remdesivir, favipiravir, corticosteroids, tocilizumab, hydroxychloroquine, and convalescent plasma therapy.[8,9] Treating COVID-19 patients with stem cell therapy has been considered an option, and the few studies conducted show some degree of success.[4,10] Stem cell therapy treatments have been employed for various diseases, ranging from autoimmune diseases to hereditary and infectious diseases.[11-13]

COVID-19 and potential recipients of MSC treatment

Potential recipients of MSC treatment can be divided into 3 groups: 1) young patients who are critically ill, 2) old

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patients that are critically ill, and 3) patients with comorbidities having a high risk of infections.[14] The inclusion criteria for critically ill patients are categorized into oxygen saturation <93%, respiratory rates >30 times/min, and requiring ventilation.[15] The advantages of MSCs are that they can be obtained from various sources, such as bone marrow, adipose tissue, placenta, and dental sources. In addition, MSCs are multipotent and can be cryopreserved for multiple uses, thus making them readily available.[16] Their advantages are that they can proliferate and differentiate into trilineage differentiation, and their immunomodulatory properties make them a good source for stem cell treatment. In addition, MSCs possess extensive immunoregulatory abilities and can regulate both the innate and adaptive immune systems, making them the most promising cell-based therapy for COVID-19.[17,18] MSCs have no ethical issues and are available from various sources. A search at ClinicalTrials.gov on 27 May 2022 using the terms "mesenchymal stem cells" and "COVID-19" revealed about 97 clinical trials that had been registered (Table 1).

Some studies report that stem cells could reduce mortality rates and improve pulmonary functions and disease remission in patients with COVID-19.[7,10,19-22] However, a comprehensive analysis of this issue has not yet been performed. This study aimed to evaluate the safety and efficacy of stem cells in treating patients with COVID-19. Currently, a few studies have reported using stem cell therapy as one of the options for treating COVID-19.[23,24]

COVID-19 is usually associated with elevated levels of several inflammatory cytokines such IL-2, IL-6, IL-7, MCP-1, MIP-1α, G-CSF, TNF-α, and IP-10.[25-29] The association of COVID-19 with elevated levels of cytokines is known as a "cytokine storm."

The SARS-CoV-2 virus will replicate and attack the respiratory tract and pulmonary tissues, which can trigger over-reactive immune responses and induce tissue inflammation and damage during acute infections. The histological characteristics of lesions in the lungs are virus-induced and lead to diffused alveolar epithelial damage and inflammatory cell infiltration, as seen in autopsies on patients who suffered a critical illness. As a result, the damage shows alveolar destruction with alveolar linin cell necrosis, protein-rich exudates, hyaline membrane formation, and endothelial cell membrane destruction.[30] In addition, SARS-CoV-2 can cause severe thrombotic disorders.[31-33] In severe cases, high levels of cytokines and chemokines are detected as a result of overactivation and massive infiltration of immunocytes such as CD4+ and CD8+ T cells into the lungs.[34]

MSCs are seen as one of the options for treating COVID-19 patients as the disease can produce excessive inflammatory cytokines that result in the respiratory system being overwhelmed by a storm of such cytokines as IP-10, IL-2, IL-6, and TNF-α as a result of the infection.

The immune systems of COVID-19 patients seem to produce excessive amounts of cytokines and result in an inimical environment for the disease course.[4] MSCs are capable of secreting various types of soluble factors, such as nitric oxide, indoleamine 2,3-dioxygenase, prostaglandin E2, TGF-β, and IL-10 by paracrine secretion, as well as releasing extracellular vesicles and EXOs to suppress excessive immune responses.[35] They can also interact with immune cells such as B cells, lymphocytic T cells, macrophages, NK cells, and neutrophils in order to regulate and balance the immune response. In addition, MSCs can also make direct interactions with various immune cells, including lymphocytic T cells, B cells, macrophages, neutrophils, and NK cells, to regulate the intensity and balance of the immune response.[36] MSCs can be independent of interferons and can continuously activate many antiviral genes.

The prolonged condition of excessive amounts of cytokines can cause severe lung infections, leading to difficulty in breathing and eventually death. Excessive cytokines in COVID-19 patients can lead to organ failure followed by edema, cardiac failure, and acute respiratory distress syndrome. The role of MSCs is to prevent the over-production of cytokines, as any complete shutting down of the immune system will affect a patient's ability to fight infections.

COVID-19 patients have been successfully treated using anti-IL-6 receptor monoclonal antibodies. This was done by inhibiting the overactivation of the immune system and improving the endogenous repair of injured tissues.[10]

It was also found that the number of regulatory dendritic cells increased significantly after MSC transplantation.[10] MSC transplantation also decreased TNF-α levels and higher IL-10 levels in critically ill COVID-19 patients in the MSC treatment group, compared to the placebo control group.

Challenges and Perspective

Large-scale vaccination programs aimed at establishing herd immunity were initiated to check the spread of the SARS-CoV2 pandemic. However, there have been re-infections and post-vaccination breakthroughs in COVID-19 cases. MSCs may serve as an alternative immunotherapeutic option for severely affected individuals and contribute to the improvement of COVID-19 outcomes. However, the use of MSCs in treating COVID-19 patients is still at an early stage. Various factors need to be taken into account in order to maximize their therapeutic effects. These include the choice of a time window for treatment, identifying suitable-phase COVID-19 patients, dosages, and interval times, among others.[30] Although still in the experimental stage, some MSC treatments against COVID-19 have been completed. Notably, clinical application protocols will be required to maximize their therapeutic effect. In addition, the MSC characteristics of different production batches may vary, while biological activity and cell dryness may affect their efficacy. Also, MSCs derived from different sources could produce dissimilar therapeutic effects.

Some adverse effects of MSC treatment and infusions, such as low-grade fevers, facial flushing, headaches, and allergic rashes, have been reported.[30] The risk of thromboembolic events associated with high doses of intravenous MSC infusions should be taken into consideration.

MSCs have been suggested as a post-COVID-19 treatment for severe cases due to their anti-fibrotic and differentiation properties. In addition, both frozen and fresh MSCs have shown some proven efficacy in clinical applications, and it is noteworthy that dead or apoptotic MSCs found in MSC preparations exert the same immunomodulatory properties as living MSCs by releasing phosphatidylserine.[37]

Table 1. ClinicalTrials.gov Search Results 06/14/2022

	Title	Status	Study Results	Conditions	Interventions	Locations
1	Mesenchymal Stem Cell Infusion for COVID-19 Infection	Unknown status	No Results Available	• COVID-19	• Drug: Mesenchymal stem cells • Other: Placebo	• NIBMT, Rawalpindi, Punjab, Pakistan
2	Mesenchymal Stem Cell Secretome In Severe Cases of COVID-19	Completed	No Results Available	• COVID-19	• Biological: Injection of secretome -mesenchymal stem cell • Other: Placebo • Drug: Standard treatment of Covid-19	• RSUPN Dr. Cipto Mangunkusumo, Jakarta Pusat, DKI Jakarta, Indonesia • RSUP Fatmawati, Jakarta, DKI Jakarta, Indonesia • RSUP Persahabatan, Jakarta, DKI Jakarta, Indonesia • Rumah Sakit Universitas Indonesia, Depok, Jawa Barat, Indonesia
3	Mesenchymal Stem Cells Therapy in Patients With COVID-19 Pneumonia	Completed	No Results Available	• Coronavirus Disease 2019 (COVID-19) Pneumonia	• Other: Mesenchymal stem cells	• University of Health Sciences, Istanbul, Turkey
4	Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia	Unknown status	No Results Available	• COVID-19	• Biological: Umbilical cord derived mesenchymal stem cells • Biological: Placebo	
5	A Proof of Concept Study for the DNA Repair Driven by the Mesenchymal Stem Cells in Critical COVID-19 Patients	Completed	No Results Available	• COVID-19 Pneumonia	• Biological: Mesenchymal Stem Cells Transplantation	• Istinye University, Istanbul, Turkey • SBÜ Dr. Sadi Konuk E#itim ve Ara#t#rma Hastanesi, Istanbul, Turkey
6	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	Unknown status	No Results Available	• COVID-19	• Biological: Dental pulp mesenchymal stem cells	
7	NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia	Unknown status	No Results Available	• COVID-19 Pneumonia	• Biological: NestaCell® • Biological: Placebo	• Hospital Vera Cruz, Campinas, São Paulo, Brazil • Hospital de Barueri, São Paulo, Brazil • IncCOR, São Paulo, Brazil
8	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19	Unknown status	No Results Available	• Covid 19	• Biological: Infusion IV of Mesenchymal Stem cells	• Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
9	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Unknown status	No Results Available	• Use of Stem Cells for COVID-19 Treatment	• Biological: WJ-MSCs	• Stem Cells Arabia, Amman, Jordan
10	Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19	Withdrawn	No Results Available	• COVID	• Biological: Mesenchymal cells • Drug: Standard of care	• Hospital Universitario de Getafe, Getafe, Madrid, Spain • Hospital Universitario de Cruces, Barakaldo, Spain • Hospital Universitario de La Princesa, Madrid, Spain • Hospital Infantil Universitario Niño Jesus, Madrid, Spain •Hospital Ramón Y Cajal, Madrid, Spain • Complejo Universitario La Paz, Madrid, Spain
11	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19	Unknown status	No Results Available	• COVID-19	• Biological: MSCs	• Beijing 302 Military Hospital of China, Beijing, China
12	Mesenchymal Stem Cells in Patients Diagnosed With COVID-19	Recruiting	No Results Available	• Covid19	• Biological: MSC • Drug: Control	• Hospital Regional Lic Adolfo Lopez Mateos, Mexico City, Ciudad De Mexico CDMX (Mexico City), Mexico
13	Bone Marrow Mesenchymal Stem Cell Derived Extra-cellular Vesicles Infusion Treatment for Mild-to-Moderate COVID-19: A Phase II Clinical Trial	Not yet recruiting	No Results Available	• COVID-19	• Drug: ExoFlo	• Direct Biologics, Austin, Texas, United States
14	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	Recruiting	No Results Available	• COVID-19	• Biological: allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC) •Other: Intravenous saline injection (Placebo)	• Renmin Hospital of Wuhan University (East Campus), Wuhan, Hubei, China
15	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	Active, not recruiting	No Results Available	• COVID-19 Pneumonia	• Drug: Oseltamivir • Drug: hormones • Device: oxygen therapy • Procedure: mesenchymal stem cells	• Fuzhou General Hospital, Fuzhou, Fujian, China
16	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)	Unknown status	No Results Available	• Coronavirus Disease 2019 COVID-19)	• Biological: BM-MSCs • Biological: Placebo	• Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China
17	When to Apply to Which Patient in MSC?	Recruiting	No Results Available	• COVID-19 Acute Respiratory Distress Syndrome	• Drug: Mesenchymal Stem Cell Antigen-1, Human	• Trabzon Kanuni Training and Research Hospital, University of Healthy Sciences, Trabzon, Yomra, Turkey
18	Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19	Unknown status	No Results Available	• ARDS, Human • Covid-19	• Biological: Mesenchymal Stem Cells derived from Wharton Jelly of Umbilical cords	• Instituto de Medicina Regenerativa, Tijuana, Baja California, Mexico

19	Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	Completed	No Results Available	• Corona Virus Disease 2019(COVID-19)	• Biological: UC-MSCs • Biological: Saline containing 1% Human serum albumin#solution without UC-MSCs#	• General Hospital of Central Theater Command, Wuhan, Hubei, China • Maternal and Child Hospital of Hubei Province, Wuhan, Hubei, China • Wuhan Huoshenshan Hospital, Wuhan, Hubei, China
20	Study of Allogeneic Adipose-Derived Mesenchymal Stem Cells to Treat Post COVID-19 "Long Haul" Pulmonary Compromise	Withdrawn	No Results Available	• Covid19	• Biological: COVI-MSC	
21	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	Completed	No Results Available	• COVID-19	• Biological: HB-adMSCs	• Hope Biosciences Stem Cell Research Foundation, Sugar Land, Texas, United States
22	Study of Allogeneic Adipose-Derived Mesenchymal Stem Cells for Treatment of COVID-19 Acute Respiratory Distress	Recruiting	No Results Available	• Covid19	• Biological: COVI-MSC • Drug: Placebo	• Teradan Clinical Trials LLC, Brandon, Florida, United States • Sarasota Memorial Health Care System (SMH), Sarasota, Florida, United States • St Luke's Research, Boise, Idaho, United States • St. Luke's Boise, Boise, Idaho, United States • Ascension St. John, Tulsa, Oklahoma, United States • PRX Research/Dallas Regional Medical Center, Mesquite, Texas, United States
23	Efficacy of Infusions of MSC From Wharton Jelly in the SARS-Cov-2 (COVID-19) Related Acute Respiratory Distress Syndrome	Completed	No Results Available	• COVID19 ARDS	• Biological: Ex vivo expanded Wharton's Jelly Mesenchymal Stem Cells • Biological: Placebo	• Nancy University Hospital, Vandœuvre-lès-Nancy, France
24	A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19	Completed	No Results Available	• COVID-19	• Biological: HB-adMSCs • Other: Placebos	• Hope Biosciences Stem Cell Research Foundation, Sugar Land, Texas, United States
25	Study of Allogeneic Adipose-Derived Mesenchymal Stem Cells to Treat Post COVID-19 "Long Haul" Pulmonary Compromise	Not yet recruiting	No Results Available	• Covid19	• Biological: COVI-MSC • Biological: Placebo	
26	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19	Unknown status	No Results Available	• 2019 Novel Coronavirus Pneumonia • COVID-19	• Biological: UC-MSCs • Drug: Placebo	• Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China
27	Clinical Study for Subjects With COVID-19 Using Allogeneic Adipose Tissue-Derived Mesenchymal Stem Cells	Not yet recruiting	No Results Available	• Corona Virus Infection • Covid19	• Biological: Allogeneic adipose-derived stem cells	
28	Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia	Recruiting	No Results Available	• Covid-19 • Cytokine Storm	• Biological: Injection of Secretome-MSCs • Drug: Standard treatment of Covid-19	• RSUD Bantul, Bantul, Central Java, Indonesia • RS PKU Muhammadiyah Gamping, Yogyakarta, Central Java, Indonesia • RS Primaya Bekasi Timur, Bekasi, Jakarta, Indonesia • Bhayangkara Hospital, Makassar, South Celebes, Indonesia • Gatot Soebroto Army Hospital, Jakarta, Indonesia • Dr. Esnawan Antariksa Air Force Hospital, Jakarta, Indonesia
29	A Global Expanded Access Protocol on Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicle Infusion Treatment for Patients With COVID-19 Associated ARDS	Available	No Results Available	• Covid19 • ARDS • Hypoxia • Cytokine Storm	• Biological: Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicles Infusion Treatment	
30	Study of Intravenous Administration of Allogeneic Adipose-Derived Mesenchymal Stem Cells for COVID-19-Induced Acute Respiratory Distress	Withdrawn	No Results Available	• Covid19 • ARDS	• Drug: COVI-MSC • Drug: Placebo	• Fresno Community Hospital, Fresno, California, United States
31	Study to Evaluate the Efficacy and Safety of AstroStem-V in Treatment of COVID-19 Pneumonia	Not yet recruiting	No Results Available	• Covid19 Pneumonia	• Drug: AstroStem-V	
32	Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients	Recruiting	No Results Available	• COVID • Pulmonary Infection • Sars-CoV2	• Drug: Oseltamivir • Drug: Azithromycin • Biological: Umbilical Cord Mesenchymal Stem Cells	• Cipto Mangunkusumo General Hospital, Jakarta Pusat, DKI Jakarta, Indonesia • Persahabatan General Hospital, Jakarta, DKI Jakarta, Indonesia • Sulianti Saroso Center for Infectious Disease, Jakarta, DKI Jakarta, Indonesia • Universitas Indonesia Hospital, Depok, West Java, Indonesia
33	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	Unknown status	No Results Available	• COVID-19	• Biological: UC-MSCs • Other: Placebo	• Puren Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China
34	Clinical Trial to Assess the Safety and Efficacy of Intravenous Admi-nistration of Allogeneic Adult Mesenchymal Stem Cells ofExpanded Adipose Tissue in Patients With Severe Pneumonia Due to COVID-19	Completed	No Results Available	• Sars-CoV2	• Drug: ALLOGENEIC AND EXPANDED ADIPOSE TISSUE-DERIVED MESENCHYMAL STEM CELLS	• Hospital Universitario de Jerez de la Frontera, Jerez de la Frontera, Cádiz, Spain • Hospital Reina Sofía, Córdoba, Spain • Hospital Universitario Virgen de las Nieves, Granada, Spain • Hospital Universitario Virgen Macarena, Sevilla, Spain • Hospital Unversitario Virgen del Rocío, Sevilla, Spain • Hospital Nuestra Señora de Valme, Sevilla, Spain

35	Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	Not yet recruiting	No Results Available	• COVID-19	• Biological: autologous adipose-derived stem cells	
36	Allogenic UCMSCs as Adjuvant Therapy for Severe COVID-19 Patients	Recruiting	No Results Available	• Covid 19	• Biological: Normoxic Allogenic UCMSC • Other: Normal saline solution	• Dr. Moewardi General Hospital, Surakarta, Central Java, Indonesia • Dr. Hasan Sadikin, Bandung, West Java, Indonesia • Dr. Sardjito General Hospital, Yogyakarta, Indonesia
37	Adipose Mesenchymal Cells for Abatement of SARS-CoV-2 Respiratory Compromise in COVID-19 Disease	Not yet recruiting	No Results Available	• Covid-19 Pneumonia • Cyotokine Storm	• Biological: Autologous Adipose MSC's	
38	Mesenchymal Stem Cells for the Treatment of COVID-19	Completed	No Results Available	• Covid19 • Prophylaxis	• Biological: PrimePro • Other: Placebo	• Southern California Hospital at Culver City / Southern California Hospital at Hollywood, Culver City, California, United States
39	Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	Completed	No Results Available	• COVID • Covid-19 • Coronavirus • Pneumonia • Pneumonia, Viral • Pneumonia, Interstitial • Sars-CoV2	• Biological: Allogenic pooled olfactory mucosa-derived mesenchymal stem cells • Other: Standard treatment according to the Clinical protocols	• Institute of Biophysics and Cell Engineering of National Academy of Sciences of Belarus, Minsk, Belarus
40	ExoFlo™ Infusion for Post-Acute COVID-19 and Chronic Post-COVID-19 Syndrome	Not yet recruiting	No Results Available	• Covid19 • Postviral Syndrome • Dyspnea	• Biological: Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicles • Other: Saline	
41	Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicles as Early Goal Directed Therapy for COVID-19 Moderate-to-Severe Acute Respiratory Distress Syndrome (ARDS): A Phase III Clinical Trial	Not yet recruiting	No Results Available	• COVID-19 Acute Respiratory Distress Syndrome	• Drug: EXOFLO	
42	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	Unknown status	No Results Available	• Covid-19	•Biological: Cell therapy protocol 1 •Biological: Cell therapy protocol 2	•Royan Institute, Tehran, Iran
43	Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19	Withdrawn	No Results Available	• COVID-19 • Acute Respiratory Distress Syndrome • Corona Virus Infection	• Biological: UCMSCs • Other: Placebo	
44	Use of UC-MSCs for COVID-19 Patients	Completed	Has Results	• Corona Virus Infection • ARDS •ARDS, Human • Acute Respiratory Distress Syndrome • COVID-19	• Biological: Umbilical Cord Mesenchymal Stem Cells + Heparin along with best supportive care. •Other: Vehicle + Heparin along with best supportive care	• Diabetes Research Institute, University of Miami Miller School of Medicine, Miami, Florida, United States
45	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs	Unknown status	No Results Available	• COVID-19 Pneumonia	• Procedure: Placenta-Derived MMSCs;Cryopreserved Placenta-Derived Multipotent Mesenchymal Stromal Cells • Drug: Antibiotics • Drug: Hormones • Drug: Anticoagulant Therapy • Device: #xygen therapy	• Institute of Cell Therapy, Kyiv, Ukraine
46	A Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection (COVID-19)	Recruiting	No Results Available	• SARS-CoV-2 Infection (COVID-19)	• Biological: Mesenchymal stem cell • Biological: Placebo	• Osaka University Hospital, Suita, Osaka, Japan
47	Safety and Effectiveness of Placental Derived Exosomes and Umbilical Cord Mesenchymal Stem Cells in Moderate to Severe Acute Respiratory Distress Syndrome (ARDS) ssociated With the Novel Corona Virus Infection (COVID-19)	Recruiting	No Results Available	• COVID-19 Acute Respiratory Distress Syndrome •Respiratory Distress Syndrome	• Drug: EV-Pure™ and WJ-Pure™ • Drug: Placebo	• Kit Bartalos, Liberty, Missouri, United States
48	Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19	Terminated	No Results Available	• COVID-19	• Biological: HB-adMSC • Other: Placebo	• River Oaks Hospital and Clinics, Houston, Texas, United States • United Memorial Medical Center, Houston, Texas, United States
49	Efficacy and Safety of EXOSOME-MSC Therapy to Reduce Hyper-inflammation In Moderate COVID-19 Patients	Recruiting	No Results Available	• SARS-CoV2 Infection	• Drug: Exosome-MSC Intravenous injection • Drug: Placebo Intravenous Injection • Drug: COVID-19 Standard Treatment	• RSPAD Gatot Soebroto, Jakarta, DKI Jakarta, Indonesia • RSUP Dr. M. Jamil, Padang, West Sumatra, Indonesia • RSUP Dr. Sardjito, Yogyakarta, Indonesia
50	An Exploratory Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection	Completed	No Results Available	• Severe Acute Respiratory Syndrome Coronavirus 2	• Biological: Mesenchymal stem cell	• Osaka University Hospital, Suita, Osaka, Japan

51	Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients	Completed	No Results Available	• Covid19 • Corona Virus Infection • SAR	• Drug: allogeneic mesenchymal stem cell • Other: Placebo	• Site 550: University of Hassanudin/ Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia
52	Study of Intravenous COVI-MSC for Treatment of COVID-19- Induced Acute Respiratory Distress	Recruiting	No Results Available	• Covid19	• Biological: COVI-MSC • Drug: Placebo	• Hospital São Rafael S.A. - Instituto D'Or de Pesquisa e Ensino, Salvador, BA, Brazil • Santa Casa de Misericórdia da Bahia (Hospital Santa Izabel),Salvador, BA, Brazil • Saraiva & Berlinger Ltda. - EPP (IPECC), Campinas, SP, Brazil • CECIP JAU - Centro de Estudos Clínicos do Interior Paulista Ltda., Jaú, SP, Brazil • CEMEC - Centro Multidisciplinar de Estudos Clínicos Ltda. -EPP, São Bernardo Do Campo, SP, Brazil • Impar Serviços Hospitalares S/A(Hospital Nove de Julho), São Paulo, SP, Brazil
53	Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome	Recruiting	No Results Available	• COVID-19 Infection • COVID-19-Associated Acute Respiratory Distress Syndrome • Hematopoietic and Lymphoid Cell Neoplasm • Malignant SolidNeoplasm • Symptomatic COVID-19 Infection Laboratory-Confirmed	• Other: Best Practice • Biological: Mesenchymal Stem Cell	• M D Anderson Cancer Center, Houston, Texas, United States
54	Therapy for Pneumonia Patients Infected by 2019 Novel Coronavirus	Withdrawn	No Results Available	• COVID-19	• Biological: UC-MSCs • Other: Placebo	• Puren Hospital Affiliated to Wuhan University of Science and Technology, Wuhan, Hubei, China
55	BAttLe Against COVID-19 Using MesenchYmal Stromal Cells	Suspended	No Results Available	• COVID • Respiratory Distress Syndrome	• Drug: Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells	• Fundacion Jimenez Diaz, Madrid, Spain
56	Extracellular Vesicle Infusion Treatment for COVID-19 Associated ARDS	Completed	No Results Available	• Covid19 • ARDS • Pneumonia, Viral	• Biological: DB-001 • Other: Intravenous normal saline	• Helen Keller Hospital, Sheffield, Alabama, United States • St. Joseph Hospital Heritage, Fullerton, California, United States • Donald Guthrie Foundation/ Robert Packer Hospital, Sayre, Pennsylvania, United States • Covenant Health, Lubbock, Texas, United States • PRX Research, Mesquite, Texas, United States
57	Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Lomecel-B (RECOVER	Recruiting	No Results Available	• ARDS, Human • Covid19	• Biological: Longeveron Mesenchymal Stem Cells (LMSCs) • Other: Placebo	• Miami VA Healthcare System, Miami, Florida, United States • University of Maryland Medical Center, Baltimore, Maryland, United States • Wake Forest Baptist Medical Center, Winston-Salem, North Carolina, United States
58	Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS)	Not yet recruiting	No Results Available	• ARDS • COVID-19	• Biological: MSC	• University Hospital Tuebingen,Tuebingen, Germany
59	Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	Active, not recruiting	No Results Available	• COVID	• Biological: BM-Allo.MSC • Biological: Placebo	• St. Francis Medical Center, Lynwood, California, United States
60	Immune Modulation by Exosomes in COVID-19	Recruiting	No Results Available	• COVID-19 • Critical Illness • Hypercytokinemia • Lung Fibrosis	• Biological: Application of exosomes in a whole blood assay	• Ulm University Hospital, Clinic of Anesthesiology and Intensive Care Medicine, Ulm, Germany
61	Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS	Recruiting	No Results Available	• Covid19 • Corona Virus Infection • SARS-CoV Infection • ARDS • Coronavirus	• Biological: Umbilical Cord Lining Stem Cells (ULSC) • Other: Placebo (carrier control)	• Miami Baptist Hospital, Miami, Florida, United States • Sanford Research, Sioux Falls, South Dakota, United States
62	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	Completed	No Results Available	• Coronavirus	• Biological: MSCs-derived exosomes	• Ruijin Hospital Shanghai Jiao Tong University School ofMedicine, Shanghai, Shanghai, China

63	Use of hUC-MSC Product (BX-U001) for the Treatment of COVID-19 With ARDS	Not yet recruiting	No Results Available	• COVID-19 • ARDS • Acute Respiratory Distress Syndrome	• Biological: Human umbilical cord mesenchymal stem cells + best supportive care • Other: Placebo control + best supportive care	
64	A Phase II Study in Patients With Moderate to Severe ARDS Due to COVID-19	Recruiting	No Results Available	• Covid19	• Biological: hMSC	• Providence Medical Foundation, Fullerton, California, UnitedStates • Providence Saint John's Health Center - Saint John's Cancer Institute, Santa Monica, California, United States
65	Study of Allogeneic Adipose-Derived Mesenchymal Stem Cells for Non-COVID-19 Acute Respiratory Distress Syndrome	Withdrawn	No Results Available	• Acute Respiratory Distress Syndrome • Ards	• Biological: COVI-MSC • Drug: Placebo	
66	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19	Recruiting	No Results Available	• Acute Respiratory Distress Syndrome	• Drug: Wharton's jelly derived Mesenchymal stem cells. • Drug: Hydroxychloroquine, lopinavir/ ritonavir or azithromycin and placebo (standard therapy)	• BioXcellerator, Medellin, Antioquia-CO, Colombia • Clinical Somer, Rionegro, Antioquia, Colombia
67	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	Recruiting	No Results Available	• Sars-CoV2 • Acute Respiratory Distress Syndrome • COVID-19	• Biological: Mesenchymal Stromal Cells • Other: Supportive Care	• Houston Methodist Hospital, Houston, Texas, United States
68	Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan	Completed	No Results Available	• Covid19 • Cytokine Release Syndrome • Critical Illness • ARDS	• Procedure: Therapeutic Plasma exchange • Biological: Convalescent Plasma • Drug: Tocilizumab • Drug: Remdesivir • Biological: Mesenchymal stem cell therapy	• Pak Emirates Military Hospital, Rawalpindi, Punjab, Pakistan
69	Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19	Active, not recruiting	No Results Available	• COVID-19 • SARS-CoV 2 • Adult Respiratory Distress Syndrome	• Drug: XCEL-UMC-BETA • Other: Placebo	• Hospital de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain • Mútua de Terrassa, Terrassa, Barcelona, Spain • Hospital del Mar, Barcelona, Spain • Hospital Vall d'Hebron, Barcelona, Spain • Hospital Clínic de Barcelona, Barcelona, Spain
70	Randomized Double-Blind Phase 2 Study of Allogeneic HB-adMSCs for the Treatment of Chronic Post-COVID-19 Syndrome	Recruiting	No Results Available	• Post COVID-19 Syndrome	• Biological: HB-adMSCs (allogeneic) • Other: Placebo	• Hope Biosciences Stem Cell Research Foundation, Sugar Land, Texas, United States
71	The Use of Exosomes for the Treatment of Acute Respiratory Distress Syndrome or Novel Coronavirus Pneumonia Caused by COVID-19	Not yet recruiting	No Results Available	• Covid19 • Novel Coronavirus Pneumonia • Acute Respiratory Distress Syndrome	• Drug: MSC-exosomes delivered intravenously every other day on an escalating dose: (2:4:8) • Drug: MSC-exosomes delivered intravenously every other day on an escalating dose (8:4:8) • Drug: MSC-exosomes delivered intravenously every other day (8:8:8)	• Mission Community Hospital, Panorama City, California, United States
72	Clinical Use of Stem Cells for the Treatment of Covid-19	Completed	No Results Available	• Covid19 • Pneumonia • Multiple Organ Failure • Corona Virus Infection	• Biological: MSC Treatment • Biological: Saline Control	• Istinye University, Istanbul, Turkey •SBÜ Dr. Sadi Konuk E#itim ve Ara#t#rma Hastanesi, Istanbul, Turkey
73	Safety and Feasibility of Allogenic MSC in the Treatment of COVID-19	Not yet recruiting	No Results Available	• COVID-19 • Sars-CoV2	• Biological: Mesenchymal Stromal Cells infusion	
74	HBPCOV01:"Intermediate Size Expanded Access Protocol for the Treatment of Post-COVID-19 Syndrome" HBPD05: "Intermediate Size Patient Population Expanded Access IND for the Treatment of Patients With Parkinson's Disease"	Available	No Results Available	• Post COVID-19 Syndrome • Parkinson Disease	• Biological: HB-adMSCs	• Hope Biosciences Stem Cell Research Foundation, Sugar Land, Texas, United States
75	ACT-20 in Patients With Severe COVID-19 Pneumonia	Unknown status	No Results Available	• COVID-19 Pneumonia	• Biological: ACT-20-MSC • Biological: ACT-20-CM • Biological: Placebo	
76	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV)	Completed	No Results Available	• COVID-19 Pneumonia	• Biological: Mesenchymal Stromal Cells • Other: Placebo	• Hospital Universitario Rio Hortega, Valladolid, Spain
77	Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients	Unknown status	No Results Available	• Corona Virus Infection	• Biological: Intravenous Infusions of Stem Cells	• Jinnah Hospital, Lahore, Punjab, Pakistan

78	The MEseNchymal coviD-19 Trial: MSCs in Adults With Respiratory Failure Due to COVID-19 or Another Underlying Cause	Recruiting	No Results Available	• Covid19 • Acute Respiratory Distress Syndrome	• Biological: CYP-001	• Nepean Hospital, Kingswood, New South Wales, Australia • Westmead Hospital, Westmead, New South Wales, Australia • Footscray Hospital, Footscray, Victoria, Australia • Sunshine Hospital, Saint Albans, Victoria, Australia
79	Safety and Efficiency of Method of Exosome Inhalation in COVID-19 Associated Pneumonia	Enrolling by invitation	No Results Available	• Covid19 • SARS-CoV-2 PNEUMONIA • COVID-19	• Drug: EXO 1 inhalation • Drug: EXO 2 inhalation • Drug: Placebo inhalation	• Medical Centre Dinasty, Samara, Russian Federation
80	Is Fetal Hemoglobin a Key for Improvement of Hypoxia and Saving Last Breath in COVID-19 Patient?. A Pilot Study.	Not yet recruiting	No Results Available	• COVID-19 Acute Respiratory Distress Syndrome	• Procedure: fetal blood transfusion	
81	Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia.	Completed	Has Results	• Covid19 • SARS-CoV-2 PNEUMONIA • COVID-19	• Drug: EXO 1 inhalation • Drug: EXO 2 inhalation • Drug: Placebo inhalation	• Medical Centre Dinasty, Samara, Russian Federation
82	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(nCOV) Pneumonia	Unknown status	No Results Available	• Pneumonia, Viral • Pneumonia, Ventilator-Associated	• Biological: UC-MSCs	• Zhongnan Hospital of Wuhan University, Wuhan, Hubei, China
83	Mesenchymal Stromal Cell Therapy For The Treatment Of Acute Respiratory Distress Syndrome	Active, not recruiting	No Results Available	• ARDS, Human • COVID	• Drug: Mesenchymal Stromal Stem Cells - KI-MSC-PL-205	• Uppsala University Hospital, Uppsala, Sweden
84	MSCs in COVID-19 ARDS	Terminated	No Results Available	• Mesenchymal Stromal Cells • Remes-temcel-L • Acute Respiratory Distress Syndrome • COVID	• Biological: Remestemcel-L • Drug: Placebo	• Dignity Health, Gilbert, Arizona, United States • University of Southern California, Los Angeles, California, United States • Stanford University, Stanford, California, United States • Emory University, Atlanta, Georgia, United States • Lutheran Hospital, Fort Wayne, Indiana, United States • Ochsner Clinic, New Orleans, Louisiana, United States • Maine Medical Center, Portland, Maine United States • University of Maryland, Baltimore, Maryland, United States • Brigham and Women's Hospital, Boston, Massachusetts, United States • University of Michigan, Ann Arbor, Michigan, United States • and 11 more
85	Menstrual Blood Stem Cells in Severe Covid-19	Completed	No Results Available	• Covid19 • Cytokine Storm	• Biological: Allogeneic human enstrual blood stem cells secretome • Other: Intravenous saline injection	• Avicenna Research Institute, Tehran, Iran
86	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS	Completed	No Results Available	• Severe Acute Respiratory Syndrome Coronavirus 2 • Severe Acute Respiratory Distress Syndrome	• Biological: Umbilical cord Wharton's jelly-derived human • Other: NaCl 0.9%	• Hôpital Pitié-Salpêtrière - APHP, Paris, France • Hôpital Européen Georges Pompidou - APHP, Paris, France
87	Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19	Not yet recruiting	No Results Available	• Severe Acute Respiratory Syndrome (SARS) Pneumonia	• Combination Product: Stem Cell Educator- Treated Mononuclear Cells Apheresis	
88	Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis	Recruiting	No Results Available	• SARS-Cov-2 Induced Pulmonary Fibrosis	• Drug: Nintedanib 150 MG [Ofev] • Other: Placebo	• Pneumologie, Paris, France
89	Study of Descartes-30 in Acute Respiratory Distress Syndrome	Recruiting	No Results Available	• Acute Respiratory Distress Syndrome • Covid19	• Biological: Descartes 30	• University of Alabama at Birmingham, Birmingham, Alabama, United States • University of California-Irvine, Irvine, California, United States • University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States • University of Maryland Medical Center Medical Center, Baltimore, Maryland, United States • Brigham and Women's Hospital, Boston, Massachusetts, United States • University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, United States

90	Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19)	Active, not recruiting	No Results Available	• Acute Respiratory Distress Syndrome • ARDS (Moderate or Severe) • COVID-19 Pneumonia	• Biological: Mesenchymal stromal cells • Other: Placebo	• University of Minnesota, Minneapolis, Minnesota, United States • University of Pittsburgh, Pittsburgh, Pennsylvania, United States
91	A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy	Active, not recruiting	No Results Available	• COVID-19 • Acute Kidney Injury • Sepsis	• Biological: SBI-101	• University of New Mexico School of Medicine, Albuquerque, New Mexico, United States • Medical University of South Carolina, Charleston, South Carolina, United States
92	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST)	Recruiting	No Results Available	• Acute Respiratory Distress Syndrome	• Biological: Human umbilical cord derived CD362 enriched MSCs • Biological: Placebo (Plasma-Lyte 148)	• Belfast Health and Social Care Trust, Royal Hospitals, Belfast,,Northern Ireland, United Kingdom
93	ASC Therapy for Patients With Severe Respiratory COVID-19	Withdrawn	No Results Available	• Respiratory Tract Diseases	• Drug: Stem Cell Product	• 2014 Department of Cardiology, The Heart Centre, University Hospital Rigshospitalet, Copenhagen, Denmark
94	Cellular Immuno-Therapy for COVID-19 Acute Respiratory	Completed	No Results Available	• Acute Respiratory Distress Syndrome • Covid19	• Biological: Mesenchymal Stromal Cells	• The Ottawa Hospital, Ottawa, Ontario, Canada
95	Mesenchymal Stem Cells for the Treatment of Various Chronic and Acute Conditions	Recruiting	No Results Available	• Autoimmune Diseases • Cardiovascular Disorders • Diabetes Complications • Integumentary Disease • Musculoskeletal Disorders • Neurodegenerative Disorders • Neurologic Disorders • Pulmonary Disorders • Sexual Dysfunction • Urologic Disorders • Viral Illness	• Biological: PrimePro™/ PrimeMSK™	• Southern California Hospital at Culver City / Southern California Hospital at Hollywood / Multiple US-based Sub-Investigator Sites, Culver City, California, United States
96	Mesenchymal Stromal Cells for COVID-19 and Viral Pneumonias	Recruiting	No Results Available	• COVID-19 Pneumonia • Viral Pneumonia	• Biological: Allogeneic Mesenchymal Stromal Cells	• Medical University of South Carolina, Charleston, South Carolina, United States
97	A First-In-Human Phase 1b Study of AmnioPul-02 in COVID-19	Not yet recruiting	No Results Available	• COVID-19	• Drug: AmnioPul-02	

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Overall, although clinical research on treating COVID-19 with MSCs is still in its infancy, the continuing exploration and mining of data show that such therapy has far-reaching significance and prospects for broad clinical application. We also hope that with continued improvements in stem cell therapies more lives and patients with severe cases of COVID-19 can be saved.

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