Available online freely at www.isisn.org

Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

REVIEW ARTICLE BIOSCIENCE RESEARCH, 2021 18(SI-1): 10-24. **OPEN ACCESS**

Stem Cell Therapy: A Potential Therapeutic Modality against COVID-19

Madiha Mohaimin[1], Anam Bilal[1], Kulsum Iqbal[2], Hooriya zia[3], Fahad Kidwai[4*]and Asma Khurshid[5*]

[1]Institute of Dental Sciences, Sehora 181132, Jammu University, Jammu & Kashmir, **India.**
[2]School of Dental Medicine, Tufts University, Boston, MA 02111, **United States of America**
[3]College of Kinesiology, University of Saskatchewan, Saskatoon, Saskatchewan, **Canada**
[*4]Department of Health and Human Services, Craniofacial and Skeletal Diseases Branch, National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD 20892, **United States of America**
[*5]DOW Research Institute of Biotechnology and Biomedical Sciences, DOW University of Health Sciences, Ojha Campus, Karachi, **Pakistan**

***Correspondence:** asma.khurshid@duhs.edu.pk, fahad.kidwai@nih.gov, **Received 26-04-2021, Revised: 08-06-2021, Accepted: 30-06-2021 e-Published: 08-08-2021**

Coronavirus Disease 2019 caused by the Severe Acute Respiratory Syndrome Coronavirus 2 has completely crippled the health and economic sectors across the globe and turned out to be a major threat to human population. The potential role of virus has been considered as an originating cause of tissue injury by disrupting the renin-angiotensin system. However, hyperactive function of immune system also leads to inexorable tissue injury through cytokine storms. Therefore, improved therapeutic interventions have been devised by modulation of the response of immune system. Apart from current ongoing treatments efficacy and safety profile is still a big challenge. MSCs mostly isolated from human bone marrow (BM), in addition to umbilical cord (UC) and adipose tissue (AT) has a great potential for multi-potential differentiation and self-renewal. This manuscript aims to summarize the potential therapeutic applications of stem cell derived therapy with biomedical application in terms of immune-mediated pathophysiological conditions with associated challenges and future advancement.

Keywords: Coronavirus, 2019-nCoV, COVID-19, stem cell therapy, SARS-CoV-2, Mesenchymal stem/stromal cells (MSCs), transmission

INTRODUCTION

SARS-CoV2 is believed to spread through respiratory route via droplets or with direct contact with the affected person (Khurshid, Ammar Ahmed et al. 2020, Saldanha-Araujo, Melgaço Garcez et al. 2020). Due to the isolation of SARS-CoV-2 from fecal samples of severe pneumonia patients, alternative routes of transmission have been suggested (Zhang, Du et al. 2020). It has been found that COVID-19 infects the angiotensin I converting enzyme 2 (ACE2) receptor-positive cells. Along with lung and capillary endothelial cells, ACE2 is also expressed in heart, kidney, liver and digestive system. Hence, infection with COVID-19 virus can affect multiple organs and can have multiple presentations in organs and tissues which express ACE2. Infection with the virus leads to intense inflammation, edema and inflammatory cell migration locally. Local tissue damage is proportional to the viral load and is detectable on radiographs even before the symptoms of pneumonia arise (Hamming, Timens et al. 2004, Leng, Zhu et al. 2020, Saldanha-Araujo, Melgaço Garcez et al. 2020). Stem cells are defined as those cells of the body that have the ability to differentiate into any specific type of

cell of the body. These are undifferentiated or unspecialized cells and possess the capability of self- renewal (Biehl and Russell 2009, Zakrzewski, Dobrzynski et al. 2019, Faheem Anwar1 2021). Stem cells have unique characteristics as they can replicate again and again, producing daughter cells by undergoing cell division. They preserve the characteristics of the parent cell and at the same time differentiate into specialized cells according to specific signals (EL Barky AR 2017).

Types of Stem Cells:

The various types of stem cells based on their differentiation potential are totipotent, pluripotent, multi-potent, uni-potent and oligopotent (EL Barky AR 2017). Totipotent cells have the ability to differentiate into any type of cells in an organism. These cells have the highest differentiation potential amongst all the types of stem cells. For example, zygote that is formed after the fertilization of an egg is a totipotent cell and has the potential to develop into all the types of cells in the body (EL Barky AR 2017). Pluripotent cells can differentiate into almost all types of cells of the body. They can form cells of all the germ layers but cannot differentiate into cells of extra embryonic structures like placenta. For example, embryonic stem cells (Zakrzewski, Dobrzynski et al. 2019). Multi-potent stem cells are those that have the ability to differentiate only into the cells of the tissue from which they are derived (EL Barky AR 2017). They have a narrow range of differentiation and can form cells from a specific lineage. For example, hematopoietic stem cells give rise to various types of blood cells (Zakrzewski, Dobrzynski et al. 2019). Oligopotent stem cells can differentiate into a few types of cells. For example, lymphoid stem cells and myeloid stem cells (Biehl and Russell 2009). Unipotent stem cells have the narrowest differentiation range and can form only one type of cells. For example, muscle stem cells only develop into cells of their own type (Surat P 2019).

Sources of Stem Cells:

Stem cells can be derived from various sources like from the embryo, the fetus, from infants and from adults. Embryonic stem cells are pluripotent in nature and are derived from an early stage of embryo development known as blastocyst. They can be derived from human or mouse blastocysts. There are ethical and legal restrictions related to the use of embryonic stem cells for medical use. Mostly they are derived from eggs that have been fertilized in vitro (Yu and Silva 2008, Manuela Monti1* 2012, Zakrzewski, Dobrzynski et al. 2019). Fetal stem cells are derived from fetal organs and give rise to pluripotent and hematopoietic stem cells (Durand, Mallea et al. 2020). Infant stem cells can be derived from the umbilical cord or from Wharton's jelly. Stem cells derived from cord blood are multi-potent in nature whereas Wharton's jelly is a source of mesenchymal stem cells (Zhang, Du et al. 2020). Adult or somatic stem cells are derived from mature tissues. They have a narrow spectrum of differentiation. Their main function is healing and repair. Among many types, there are mesenchymal, hematopoietic, neural, gastrointestinal, epidermal and pancreatic stem cells (EL Barky AR 2017, Zakrzewski, Dobrzynski et al. 2019).

Mesenchymal Stem Cells (MSCs) and COVID-19

Mesenchymal stem cell therapy has many beneficial results and as studies suggest is likely to emerge as an effective therapeutic option for the treatment of COVID-19 due to their potential of reducing inflammation produced by cytokine storm as a result of COVID-19 infection (Durand, Mallea et al. 2020, Iglesias, Butrón et al. 2021). However, as the disease is still in its initial stages and not much is known about its natural history, sufficient information regarding its pathogenesis and treatment is not available. Mesenchymal Stem Cells (MSC) have been safely and effectively used in various therapies, researches, clinical trials related to immune mediated diseases such as graft-versus-host disease (GvHD), inflammatory bowel disease, rheumatoid arthritis and acute respiratory distress syndrome (ARDS) etc (Iglesias, Butrón et al. 2021). The mesenchymal stem cells can alter both innate and adaptive immunity, help in immune modulation and differentiation and hence are effectively used in the treatment of inflammatory diseases (Leng, Zhu et al. 2020, Li, Niu et al. 2020, Liu, Peng et al. 2020, Hernandez, Beaty et al. 2021). The human umbilical cord (hUC-MSCs) derived mesenchymal stem cells possess immuno modulatory characteristics that leads its potential role in treatment of coronavirus disease 2019 (COVID-19) (Hernandez, Beaty et al. 2021). Currently, the integrated therapy of umbilical cord-derived mesenchymal stem cells for COVID-19 patients drowns to be successful and safe in phase 1 and 2 clinical trials (Maeurer, Ramalho et al. 2021).

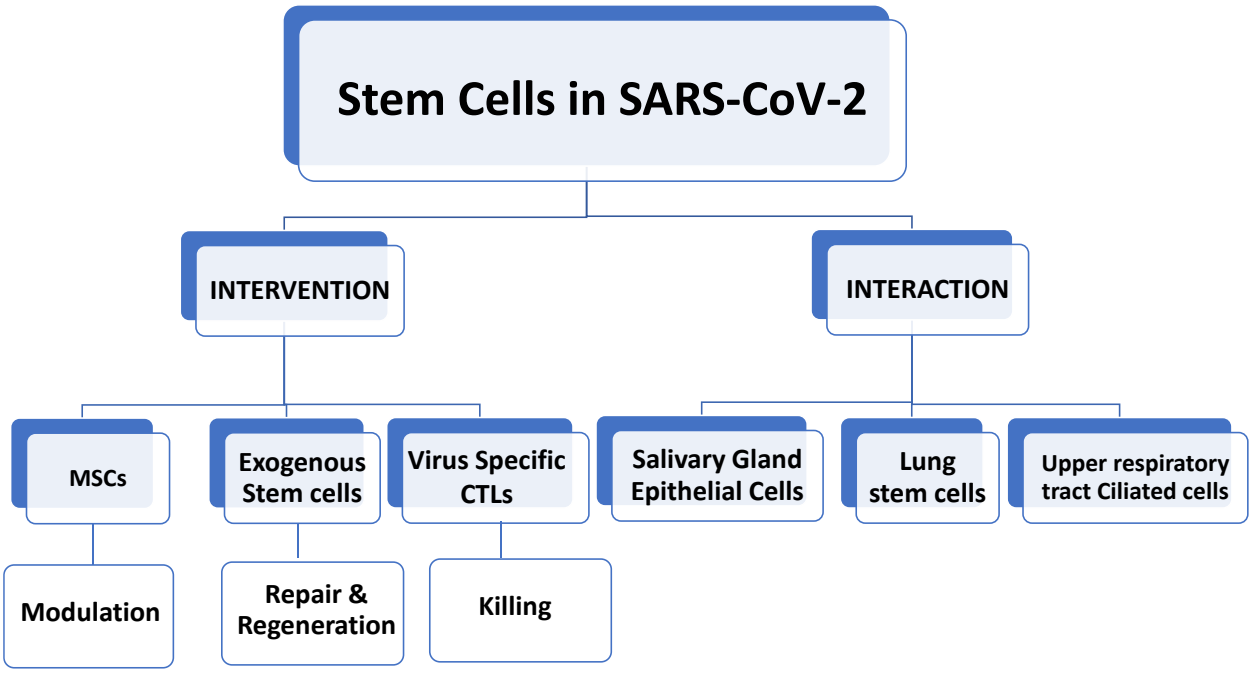

Figure 1: Potential applications of Stem Cell therapy in treatment of SARS-CoV-2
Schematic representation of potential application of Stem Cell as a therapeutic targeting of SARS-CoV-2 infection in terms of lung repair and regeneration.

Currently, combination of antivirals, steroids and supportive care in terms of ventilators and fluid replacement are being used for the treatment of COVID-19 patients but no pharmacological measure has been able to prevent the progress of the disease (Yu, Jia et al. 2020). The exaggerated inflammatory response caused by COVID-19 virus leads to hyper inflammation and cytokine storm of interleukin-2 (IL-2), IL-6, IP10, granulocyte colony stimulating factor, tumor necrosis factor (TNF), MCP1, and MIP1 which leads to multiorgan damage in severe cases. The role of stem cell therapy against the treatment of COVID-19 has been depicted in figure 1. Use of stem cell therapy has been reported to inhibit the over activation of the immune system and prevent cytokine storm. With stem cell therapy, healing and repair of the damaged tissues is promoted (Choudhery and Harris 2020, Leng, Zhu et al. 2020, Saldanha-Araujo, Melgaço Garcez et al. 2020). MSCs were found to be angiotensin-converting enzyme 2 (ACE2)- and Transmembrane protease serine 2 TMPRSS2-negative and in low expression respectively and hence are unlikely to be affected by the virus and hence can be used in the treatment of COVID-19 patients (Yu, Jia et al. 2020, Hernandez, Beaty et al. 2021). MSCs can be used in critically ill COVID-19 patients with comorbidities who are at higher risk of infection (Choudhery and Harris 2020). It has been found that on intravenous administration of MSC, part of MSCs get entrapped in the lungs. Increased local production of Angiotensin II upon injury in the lungs leads to MSC migration and retention at the site of lesion leading to immunomodulatory action such as release of anti-inflammatory cytokines and antimicrobial peptides which improves the lung environment and improves lung function by promoting tissue repair and regeneration and thereby improving the health of severe COVID-19 pneumonia patients (Leng, Zhu et al. 2020, Yu, Jia et al. 2020).

Table 1: Summarizes the clinical trial data of stem cell therapy against COVID-19 (Medicine. 2021)

Row	Status	Study Title	Conditions	Interventions	Locations
1	Recruiting	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Use of Stem Cells for COVID-19 Treatment	Biological: WJ-MSCs	Stem Cells Arabia Amman, Jordan
2	Completed	Study Evaluating the Safety and Efficacy of Autologous Non-Hematopoietic Peripheral Blood Stem Cells in COVID-19	Coronavirus Disease 2019 (COVID-19)	Biological: Autologous Non-Hematopoietic Peripheral Blood Stem Cells (NHPBSC) Drug: COVID-19 standard care	Abu Dhabi Stem Cells Center Abu Dhabi, United Arab Emirates
3	Not yet recruiting	Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	COVID-19	Biological: autologous adipose-derived stem cells	-
4	Recruiting	Mesenchymal Stem Cell Infusion for COVID-19 Infection	COVID-19	Drug: Mesenchymal stem cells Other: Placebo	NIBMT Rawalpindi, Punjab, Pakistan
5	Recruiting	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19	COVID-19	Biological: Infusion IV of Mesenchymal Stem cells	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán Mexico City, Mexico
6	Completed	Mesenchymal Stem Cells Therapy in Patients With COVID-19 Pneumonia	Coronavirus Disease 2019 (COVID-19) Pneumonia	Other: Mesenchymal stem cells	University of Health Sciences Istanbul, Turkey
7	Recruiting	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	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
8	Recruiting	Study of Intravenous Administration of Allogeneic Adipose Stem Cells for COVID-19	COVID-19	Biological: PSC-04	Fresno Community Hospital Fresno, California, United States
9	Recruiting	Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome	COVID-19 Infection COVID-19-Associated Acute Respiratory Distress Syndrome	Other: Best Practice Biological: Mesenchymal Stem Cell	M D Anderson Cancer Center Houston, Texas, United States
10	Not yet recruiting	Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia	COVID-19	Biological: Umbilical cord derived mesenchymal stem cells Biological: Placebo	-
11	Recruiting	Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia	COVID-19 Cytokine Storm	Biological: Injection of Secretome-MSCs Drug: Standard treatment of COVID-19	Sultan Imanuddin Hospital Kalimantan, Central Borneo, Indonesia Charlie Hospital Kendal, Central Java, Indonesia RS PKU Muhammadiyah Yogyakarta Yogyakarta, Central Java, Indonesia (and 3 more...)
12	Active, not recruiting	Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19	ARDS, Human COVID-19	Biological: Mesenchymal Stem Cells derived from Wharton Jelly of Umbilical cords	Instituto de Medicina Regenerativa Tijuana, Baja California, Mexico

13	Not yet recruiting	NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia	COVID-19 Pneumonia	Biological: NestaCell® Biological: Placebo	Hospital Vera Cruz Campinas, São Paulo, Brazil, Hospital de Barueri São Paulo, Brazil, IncCOR São Paulo, Brazil, UNIFESP São Paulo, Brazil
14	Active, not recruiting	Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded Adipose Tissue in Patients. With Severe Pneumonia Due to COVID-19	SARS-CoV-2	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, (and 3 more...)
15	Not yet recruiting	Impact of COVID-19 After Autologous Hematopoietic Stem Cell Transplantation in Sweden	COVID-19 Myeloma Multiple Malignant Lymphoma, (and 2 more...)	Other: Autologous stem cell transplantation	-
16	Active, not recruiting	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	COVID-19	Drug: HB-adMSCs Drug: Placebos	Hope Biosciences Stem Cell Research Foundation Sugar Land, Texas, United States
17	Recruiting	Mesenchymal Stem Cells in Patients Diagnosed With COVID-19	COVID-19	Biological: MSC Drug: Control	Hospital Regional Lic Adolfo Lopez Mateos Mexico City, Ciudad De Mexico CDMX (Mexico City), Mexico
18	Not yet recruiting	Efficacy of Infusions of MSC From Wharton Jelly in the SARS-Cov-2 (COVID-19) Related Acute Respiratory Distress Syndrome	COVID-19 ARDS	Biological: Ex vivo expanded Wharton's Jelly Mesenchymal Stem Cells Biological: Placebo	-
19	Recruiting	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19	COVID-19	Biological: MSCs	Beijing 302 Military Hospital of China Beijing, China
20	Not yet recruiting	In the Treatment of Severe COVID-19 study of Human Umbilical Cord Mesenchymal Stem Cells	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
21	Not yet recruiting	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients. With Coronavirus Disease 2019 (COVID-19)	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
22	Recruiting	Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (RECOVER)	ARDS, Human COVID-19	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
23	Completed	Treatment with Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	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

24	Recruiting	Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients	Corona Virus Infection	Biological: Intravenous Infusions of Stem Cells	Jinnah Hospital Lahore, Punjab, Pakistan
25	Enrolling by invitation	Treatment of COVID-19 Associated Pneumonia with Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	COVID-19, Coronavirus (and 4 more...)	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
26	Available	Expanded Access Protocol on Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicle Infusion Treatment for Patients With COVID-19 Associated ARDS	Covid19, ARDS, Hypoxia, Cytokine Storm	Biological: Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicles Infusion Treatment	-
27	Active, not recruiting	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	COVID-19	Drug: HB-adMSCs	Sherry Diers Sugar Land, Texas, United States
28	Completed	Mesenchymal Stem Cells for the Treatment of COVID-19	COVID-19, Prophylaxis	Biological: PrimePro. Other: Placebo	Southern California Hospital at Culver City / Southern California Hospital at Hollywood Culver City, California, United States
29	Not ye t recruiting	Study to Evaluate the Efficacy and Safety of AstroStem-V in Treatment of COVID-19 Pneumonia	COVID-19, Pneumonia	Drug: AstroStem-V	-
30	Recruiting	Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS	COVID-19, Corona Virus Infection, SARS-CoV Infection, (and 2 more...)	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
31	Active, not recruiting	Role of Immune and Inflammatory Response in Recipients of Allogeneic Hematopoietic Stem Cell Transplantation (SCT) Affected by Severe COVID-19	COVID-19	Other: no intervention	Great Ormond Street Hospital NHS Foundation Trust London, United Kingdom
32	Recruiting	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	COVID-19	Biological: Cell therapy protocol 1, Biological: Cell therapy protocol 2	Royan Institute Tehran, Iran, Islamic Republic of
33	Not yet recruiting	Study of Intravenous Administration of Allogeneic Adipose-Derived Mesenchymal Stem Cells for COVID-19-Induced Acute Respiratory Distress	COVID-19 ARDS	Drug: COVI-MSC, Drug: Placebo	Fresno Community Hospital, Fresno, California, United States
34	Not yet recruiting	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	COVID-19	Biological: Dental pulp mesenchymal stem cells	-
35	Recruiting	Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients	COVID-19, 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.
36	Recruiting	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	COVID-19	Biological: UC-MSCs, Other: Placebo	Puren Hospital Affiliated to Wuhan University of Science and Technology Wuhan, Hubei, China
37	Not yet recruiting	Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19	COVID-19, Acute Respiratory Distress Syndrome, Corona Virus Infection	Biological: UCMSCs, Other: Placebo	University of Miami, Miami, Florida, United States
39	No longe r available	Intermediate Size Expanded Access Protocol Evaluating HB-adMSC's for the Treatment of Post-COVID-19 Syndrome	Post COVID - 19 Syndrome	Biological: Autologous HB-adMSC's	Hope Biosciences Stem Cell Research Foundation Sugar Land, Texas, United States.
40	Completed	Use of UC-MSCs for COVID-19 Patients	Corona Virus Infection, ADRS, ARDS, Human, (and 2 more...)	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
41	Not yet recruiting	Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19	Severe Acute Respiratory Syndrome (SARS) Pneumonia	Combination Product: Stem Cell Educator-Treated Mononuclear Cells Apheresis	
42	Active, not recruiting	Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19	COVID-19	Drug: HB-adMSC, Drug: Placebo	River Oaks Hospital and Clinics Houston, Texas, United States. United Memorial Medical Center Houston, Texas, United States.
43	Completed	An Exploratory Study of ADR-001 in Patients with Severe Pneumonia Caused by SARS-CoV-2 Infection	Severe Acute Respiratory Syndrome Coronavirus 2	Biological: Mesenchymal stem cell	Osaka University Hospital Suita, Osaka, Japan
44	Active, not recruiting	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	COVID-19 Pneumonia	Drug: Oseltamivir, Drug: hormones, Device: oxygen therapy, Procedure: mesenchymal stem cells	Fuzhou General Hospital, Fuzhou, Fujian, China.
45	Recruiting	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID-19	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
46	Recruiting	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs	COVID-19 Pneumonia	Procedure: Placenta-Derived MMSCs; Cryopreserved Placenta-Derived Multipotent Mesenchymal Stromal Cells, Drug: Antibiotics, Drug: Hormones, (and 2 more...)	Institute of Cell Therapy, Kyiv, Ukraine
47	Suspended	BAttLe Against COVID-19 Using MesenchYmal Stromal Cells	COVID-19, Respiratory Distress Syndrome	Drug: Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells	Fundacion Jimenez Diaz, Madrid, Spain

48	Not yet recruiting	Convalescent Plasma for COVID-19 Patients (CPCP)	COVID-19	Biological: Convalescent Plasma as Therapy for COVID-19 patients	Vinmec Research Institute of Stem Cell and Gene Technology, Hanoi, Vietnam
49	Completed	Therapeutic Study to Evaluate the Safety profile and efficacy of DW-MSC in COVID-19 Patients	COVID-19, Corona Virus Infection, SAR	Drug: allogeneic mesenchymal stem cell, Other: Placebo	Site 550: University of Hassanudin/ Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia
50	Not yet recruiting	Heart Patch for Myocardial Infarction COVID-19	Myocardial Infarction, Heart Diseases	Device: Heart patch seeded with autologous cardio myocytes and amnion epithelial stem cells	-
51	Withdrawn	Therapy for Pneumonia Patients infected by 2019 Novel Coronavirus	COVID-19	Biological: UC-MSCs, Other: Placebo	Puren Hospital Affiliated to Wuhan University of Science and Technology Wuhan, Hubei, China
52	Recruiting	Pediatrics HOT COVID-19 Database in NY Tristate	Pediatric Cancer, Immune System Disorder, COVID-19 , Hemoglobinopathies		Connecticut Children's Hospital, Hartford, Connecticut, United States. Yale New Haven Children's Hospital, New Haven, Connecticut, United States. Hackensack Meridian Health, Hackensack, New Jersey, United States (and 14 more...)
53	Recruiting	Using PRP and Cord Blood in Treatment of Covid -19	Virus	Combination Product: stem cells	Aljazeera (Al Gazeera) hospital, Giza, Egypt
54	Enrolling by invitation	Convalescent Plasma for COVID-19 Patients	COVID-19	Biological: Convalescent COVID-19 Plasma	Vinmec Research Institute of Stem cell and Gene Technology, Hanoi, Vietnam
55	Recruiting	Study of the Safety of Therapeutic Tx with Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	COVID-19	Biological: BM-Allo.MSC, Biological: Placebo	St. Francis Medical Center, Lynwood, California, United States
56	Not yet recruiting	Use of hUC-MSC Product (BX-U001) for the Treatment of COVID-19 With ARDS	COVID-19, ADRS, Acute Respiratory Distress Syndrome	Biological: Human umbilical cord mesenchymal stem cells + best supportive care, Other : Placebo control + best supportive care	-
57	Active, not recruiting	Mesenchymal Stromal Cell Therapy for the Treatment of Acute Respiratory Distress Syndrome	ARDS, Human, COVID-19	Drug: Mesenchymal Stromal Stem Cells - KI-MSC-PL-205	Uppsala University Hospital, Uppsala, Sweden
58	Recruiting	Response to SARS-CoV-2 Vaccine in Stem Cell Transplant and Cellular Therapy Patients	Hematologic Disorders and Bone Marrow Failure, Hematopoietic Stem Cell Transplantation (HSCT) or Cellular Therapy (CART)	Diagnostic Test: COVID-19 serology IgG	Henry Ford Health System Detroit, Michigan, United States
59	Completed	Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan	COVID-19, Cytokine Release Syndrome, Critical Illness, ARDS	Procedure: Therapeutic Plasma exchange, Biological: Convalescent Plasma, Drug: Tocilizumab, (and 2 more...)	Pak Emirates Military Hospital, Rawalpindi, Punjab, Pakistan
60	Recruiting	A Phase II Study in Patients with Moderate to Severe ARDS Due to COVID-19	COVID-19	Biological: hMSC	Providence Saint John's Health Center - Saint John's Cancer Institute, Santa Monica, California, United States. PRX Research, Dallas Regional Medical Center, Mesquite, Texas,

					United States.
61	Recruiting	Safety and Efficacy of CA Stem for Severe COVID-19 Associated With/Without ARDS	COVID-19, Acute Respiratory Distress Syndrome, Virus; Pneumonia, Acute Lung Injury	Biological: CAStem	Beijing YouAn Hospital, Capital Medical University. Beijing, Beijing, China, China
62	Not yet recruiting	Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS)	ARDS, COVID-19	Biological: MSC	University Hospital Tuebingen. Tuebingen, Germany
63	Withdrawn	ASC Therapy for Patients with Severe Respiratory COVID-19	Respiratory Tract Diseases	Drug: Stem Cell Product	2014 Department of Cardiology, The Heart Centre, University Hospital Rigshospitalet. Copenhagen, Denmark
64	Recruiting	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	SARS-CoV-2, Acute Respiratory Distress Syndrome, COVID-19,	Biological: Mesenchymal Stromal Cells, Other: Supportive Care	Houston Methodist Hospital. Houston, Texas, United States
65	Recruiting	For the Treatment of Patients Safety and efficacy Evaluation of Mesenchymal Stem Cells with Respiratory Distress caused by COVID-19	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, (and 2 more...)
66	Not yet recruiting	The Use of Exosomes for the Treatment of Acute Respiratory Distress Syndrome or Novel Coronavirus Pneumonia Caused by COVID-19	COVID-19, 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
67	Recruiting	Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome	Acute Respiratory Distress Syndrome, COVID-19	Biological: Mesenchymal Stromal Cells	The Ottawa Hospital, Ottawa. Ontario, Canada+F288
68	Not yet recruiting	ACT-20 in Patients with Severe COVID-19 Pneumonia	COVID-19 Pneumonia	Biological: ACT-20-MSC, Biological: ACT-20-CM, Biological: CYP-001, Biological: Placebo	-
69	Recruiting	The Mesenchymal COVID-19 Trial: A Pilot Study to Investigate Early Efficacy of MSCs in Adults with COVID-19	COVID-19, Acute Respiratory Distress Syndrome	-	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
70	Recruiting	Natural Killer Cell (CYNK-001) Infusions in Adults With COVID-19	Coronavirus, Coronavirus Infection, Severe Acute Respiratory Syndrome Coronavirus 2, (and 17 more...)	Biological: CYNK-001	Banner University Medical Center Phoenix. Phoenix, Arizona, United States. University of Arkansas. Little Rock, Arkansas, United States. UC Irvine. Irvine, California, United States. (and 6 more...)
71	Not yet recruiting	Safety and Feasibility of Allogenic MSC in the Treatment of COVID-19	COVID-19, SARS-CoV2	Biological: Mesenchymal Stromal Cells infusion	-
72	Recruiting	Repair of Acute Respiratory Distress Syndrome	Acute Respiratory Distress	Biological: Human umbilical	Belfast Health and Social Care Trust, Royal

		by Stromal Cell Administration (REALIST) (COVID-19)	Syndrome	cord derived CD362 enriched MSCs, Biological: Placebo (Plasma-Lyte 148)	Hospitals. Belfast, Northern Ireland, United Kingdom
73	Recruiting	Treatment of Severe COVID-19 Pneumonia with Allogeneic Mesenchymal Stromal Cells (COVID_MSV)	COVID-19 Pneumonia	Biological: Mesenchymal Stromal Cells, Other: Placebo	Hospital Universitario Rio Hortega, Valladolid, Spain
74	Recruiting	Umbilical Cord (UC)-Derived Mesenchymal Stem Cells (MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia	Pneumonia, Viral. Pneumonia, Ventilator-Associated	Biological: UC-MSCs	Zhongnan Hospital of Wuhan University. Wuhan, Hubei, China
75	Recruiting	COVID-19 in Hematological Malignancies	COVID-19 Infection in Hematological Malignancies Patients	-	ASST-Spedali Civili. Brescia, Italy. AOU Policlinico Federico II. Napoli, Italy. Fondazione Policlinico A. Gemelli IRCCS. Rome, Italy. (and 3 more...)
76	Enrolling by invitation	Safety and Efficiency of Method of Exosome Inhalation in COVID-19 Associated Pneumonia	Covid19, SARS-CoV-2 PNEUMONIA, COVID-19	Drug: EXO 1 inhalation, Drug: EXO 2 inhalation, Drug: Placebo inhalation	Medical Centre Dinasty. Samara, Russian Federation
77	Active, not recruiting	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS	Severe Acute Respiratory Syndrome Coronavirus 2, Severe Acute Respiratory Distress Syndrome	Biological: Umbilical cord Wharton's jelly-derived human, v	Hôpital Pitié-Salpêtrière - APHP. Paris, France. Hôpital Européen Georges Pompidou - APHP. Paris, France.
78	Recruiting, NEW	Assessment of Immunogenicity of Coronavirus Disease 2019 (COVID-19) Vaccine in Cancer Patients Receiving Cancer Treatment	Breast Cancer, Lung Cancer, Melanoma (Skin)	Biological: COVID-19 Vaccine	. Kansas City, Kansas, United States
79	Active , not recruiting	MSCs in COVID-19 ARDS	Mesenchymal Stromal Cells, Remestemcel-L, Acute Respiratory Distress Syndrome, COVID-19	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. (and 18 more...)
80	Completed, Has Results	Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia.	COVID-19, SARS-CoV-2 PNEUMONIA, COVID-19,	Drug: EXO 1 inhalation, Drug: EXO 2 inhalation, Drug: Placebo inhalation	Medical Centre Dinasty. Samara, Russian Federation
81	Recruiting	COVID-19 Vaccine Response in Immunocompromised Haematology Patients	Haematological Disorders, Immune Suppression	Procedure: Blood test	University Hospitals of North Midlands NHS Trust, Stoke-on-Trent, United Kingdom
82	Not ye t recruiting, NEW	A Trial of the Safety and Immunogenicity of the COVID-19 Vaccine (mRNA-1273) in Participants with Hematologic Malignancies and Various Regimens of Immunosuppression, and in Participants with Solid Tumors on PD1/PDL1 Inhibitor Therapy	Solid Tumor Malignancy, Hematologic Malignancy, Leukemia, (and 2 more...)	Biological: mRNA-1273	National Institutes of Health Clinical Center. Bethesda, Maryland, United States

83	Recruiting	Analysis of the Inflammatory Response and the Development of Humoral and Cellular Immunity in Patients With COVID-19	SARS-CoV-2	Other: Active COVID-19 disease	UMAE Hospital de Especialidades del Centro Médico Nacional Siglo XXI, IMSS. México, Ciudad De México, Mexico
84	Recruiting	MultiStem Administration for COVID-19 Induced ARDS (MACoVIA)	ARDS	Biological: MultiStem, Biological: Placebo	Athersys Investigational Site 107. Chicago, Illinois, United States. Athersys Investigational Site 103. Akron, Ohio, United States. Athersys Investigational Site 101. Cleveland, Ohio, United States. Athersys Investigational Site 102. Cleveland, Ohio, United States
85	Recruiting	Study of Descartes-30 in Acute Respiratory Distress Syndrome	Acute Respiratory Distress Syndrome, COVID-19	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. (and 3 more...)
86	Recruiting	SARS-CoV-2 Donor-Recipient Immunity Transfer	Accelerated Phase CML, BCR-ABL1 Positive, Acute Lymphoblastic Leukemia,Acute Myeloid Leukemia, (and 10 more...)	Procedure: Biospecimen Collection, Other: Diagnostic Laboratory Biomarker Analysis, Other: Electronic Health Record Review, Other: Questionnaire Administration	City of Hope Medical Center. Duarte, California, United States
87	Recruiting	A Study of Cell Therapy in COVID-19 Subjects. With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy	COVID-19, Acute Kidney Injury	Biological: SBI-101	University of New Mexico School of Medicine, Albuquerque, New Mexico, United States
88	Recruiting	COVID-19 Vaccination of Immunodeficient Persons (COVAXID)	COVID-19	Biological: Comirnaty (COVID-19, mRNA vaccine)	Karolinska University Hospital. Stockholm, Huddinge, Sweden
89	Completed	Clinical Characteristics of Patients with Leukemia and COVID-19	Leukemia, Acute. Covid19, Leukemia, Lymphoblastic	-	Hospital Regional de Alta Especialidad de Ixtapaluca. Ixtapaluca, State of Mexico, Mexico. Hospital General de México "Dr. Eduardo Liceaga". Mexico City, Mexico
90	Active, not recruiting	Multiple Dosing of Mesenchymal Stromal Cells in Patients with ARDS (COVID-19)	Acute Respiratory Distress Syndrome, ARDS (Moderate or Severe), COVID-19 Pneumonia	Biological: Mesenchymal stroma l cells, Other: Placebo	University of Minnesota. Minneapolis, Minnesota, United States. University of Pittsburgh. Pittsburgh, Pennsylvania, United States
91	Recruiting	COVID19-hematological Malignancies: the Italian Hematology Alliance	SARS-CoV-2 Infection, Hematological Malignancies	-	SC Ematologia Ospedale SS Antonio e Biagio e Cesare Arrigo. Alessandria, Italy. UOC Ematologia, Ospedali Riuniti. Ancona, Italy. UOC Ematologia e Terapia Cellulare, Ospedale Mazzoni. Ascoli Piceno, Italy. F423 (and 78 more...)
92	Recruiting	MRG-001 as an Immunoregulatory and Regenerative Therapy for COVID-19 Patients	COVID-19	Drug: MRG-001, Drug: Placebo	ICON Early Phase Services, San Antonio, Texas, United States
93	Completed	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating	Coronavirus	Biological: MSCs-derived exosomes	Ruijin Hospital Shanghai Jiao Tong University School of Medicine. Shanghai, Shanghai, China

		Severe Novel Coronavirus Pneumonia			
94	Recruiting	A Study on the Immune-response to COVID-19 Vaccination in Cancer Patients - the IOSI-COVID-19-001 Study	COVID-19, Cancer	Procedure: Blood sample	Oncology Institute of Southern Switzerland, Bellinzona, Switzerland
95	Not yet recruiting, NEW	COVID-19 Vaccine Cohort in Specific Populations	Immune Deficiency	Biological: COVID-19 vaccine	-
96	Recruiting	Use of Mesenchymal Stem cells against various Chronic and Acute Conditions	Autoimmune Diseases, Cardiovascular Disorders, Diabetes Complications, (and 8 more...)	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
97	Recruiting	COVID-19 Patients Characterization, Biobank, Treatment Response and Outcome Predictor	Coronavirus Infections	Other: Observational Study	Autoimmunity and Vascular Inflammation Unit, Division of Regenerative Medicine, Stem Cells and Gene Therapy - IRCCS San Raffaele Scientific Institute. Milan, Lombardy, Italy. AIDS Immunopathogenesis Unit - IRCCS San Raffaele Scientific Institute. Milan, Lombardy, Italy. Department of Infection Diseases - IRCCS San Raffaele Scientific Institute -. Milan, Lombardy, Italy. (and 10 more...)
98	Not yet recruiting	A Study to Collect Bone Marrow for Process Development and Production of BM-MSC for the treatment of critical COVID-19 Pneumonitis	Healthy Volunteers for Bone Marrow Donation	Procedure: Bone Marrow Harvest	Cambridge University Hospitals NHS Foundation Trust, Cambridge, Cambridgeshire, United Kingdom
99	Recruiting	During COVID-19 Infection Changes in cellular Immune Profile	COVID-19, SARS-CoV-2	Other: Leukapheresis	Seraph Research Institute, Los Angeles, California, United States

Clinical trials of Stem cell on COVID-19 patients:

Due to the novelty of this disease limited data is available supporting the use of stem cell therapy in the treatment of this disease (Golchin, Seyedjafari et al. 2020). Clinical trials evaluating the efficacy and safety of mesenchymal stem cells use in COVID-19 patients are underway at different clinical phases (Li, Zhao et al. 2020). We conducted a search using terms “COVID-19” and “stem cells” on clinical trial data base and found 99 registered clinical trials details are mentioned in table 1 (Medicine. 2021). Majority of these studies are being conducted in USA, Europe, China. In the trials conducted so far it has been found that the systemic administration of the MSC in COVID-19 patients led an overall improvement in these patients seen as an increase in the number of peripheral lymphocytes and decrease in C- reactive protein (CRP) levels. There has also been seen a decline in the tumor Necrosis Factor TNF-α levels, a pro inflammatory cytokine and increase in IL-10 promoting immune modulation (Rajarshi, Chatterjee et al. 2020, Medicine. 2021).

Challenges and Limitations:

Mesenchymal stem cell therapy has shown good results as a treatment option for some diseases because of the immuno modulatory traits of stem cells (Esquivel, Mishra et al. 2021). Although stem cell therapy has shown promising results in animal studies, the same cannot be said about human stem cell therapy (Maeurer, Ramalho et al. 2021). Despite numerous clinical trials and many research papers published, the data generated is not enough and we are still far from having stem cell therapy for prevention or treatment of COVID-19. According to the International Society for Stem Cell Research there has been no approved stem cell-based treatment for COVID-19 till date (Choudhery and Harris 2020). Although stem cell therapy seems likely to have a promising future in the treatment of COVID-19, there are certain challenges that need immediate attention in order to develop a safe and effective stem cell-based approach for the same (Yu, Jia et al. 2020). First, since the disease is still in its infancy, it is not quite possible to predict the long-term effects of stem cell therapy on COVID-19 patients. The trials need to have adequate randomization with large sample sizes and long-term follow ups in order to correctly ascertain the effects of this treatment method (Choudhery and Harris 2020). Second, it is important to assess the fate of mesenchymal stem cells once they are administered systemically in the body. Mesenchymal stem cells have a short life span. They may cause emboli formation that can initiate an innate immune attack known as Instant Blood Mediated Inflammatory Reaction, hence the need to carefully plan and monitor their usage. Also, these are to be used on critically ill patients, possibly on ventilator support, so immense precautions must be taken at every step (Choudhery and Harris 2020, Li, Zhao et al. 2020).

Third, it is a challenge to produce sufficient number of stem cells as it a time-consuming process to obtain a clinically relevant amount. Mesenchymal stem cells are scanty in the primary tissues from where they are obtained. In vitro expansion of the same is required and the process requires a lot of time in order to produce enough to be used as an effective therapeutic dose. This is not a practical solution for an emergency situation like the COVID-19 pandemic. Unavailability of proper facilities that comply with Good Manufacturing Practice (GMP) for the production of stem cells and cost management are other problems that are being faced, especially by the developing and underdeveloped countries (Choudhery and Harris 2020). Fourth, extensive toxicology studies must be undertaken in order to exclude the possibility of tumor forming potential of the mesenchymal stem cells and establish the safety and efficiency of the therapeutic approach (O'Brien 2009, Golchin, Seyedjafari et al. 2020).

Lastly, it is important to consider that some studies suggest that mesenchymal stem cells may lead to drug resistance. Also, because of the non-specific immunosuppression caused by these cells, there is greater risk of contracting other infections in immuno-compromised COVID-19 patients. Overall stem cell therapy is an expensive affair and not many people can afford it. If proven to be a successful treatment option, offering the same to the patients is a major challenge for the concerned governments.

CONCLUSION

As the pandemic is still ongoing, data regarding the number of cases and mortality rate is also dynamic and keeps on changing each passing day. Because of this lack of solid data, no proper conclusion regarding stem cell therapy for COVID-19 can be drawn from the ongoing researches. Currently stem cell therapy is only being used to treat cytokine storm in critically ill

COVID-19 patients. There is an urgent need for fast-track initiation of new and expansion of ongoing investigations regarding the safety and efficacy of stem cell therapies for COVID-19 so as to obtain strong scientific evidence in order to expand the spectrum of its therapeutic benefit. More research in long term outcome of the treatment needs to be done. With the preliminary data that is available it seems that mesenchymal stem cell therapy has promising results towards COVID-19 patients with acute disease. Certain factors like cost and time for preparation of the therapy need to be evaluated.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conceptualization, A.K.; methodology, A.K. and M.M.; funding acquisition, F.K.; resources, A.K., A.B., K.I. and H.Z.; data curation, A.K. and M.M.; visualization, A.K.; supervision, A.K.; project administration, A.K. and M.M.; writing—original draft preparation, A.K., M.M. and A.B.; writing—review and editing, A.K. and F.K. All authors have read and agreed to the published version of the manuscript.

REFERENCES

Biehl, J. K. and B. Russell (2009). "Introduction to Stem Cell Therapy." 24(2): 98-103.

Choudhery, M. S. and D. T. Harris (2020). "Stem cell therapy for COVID-19: Possibilities and challenges." Cell Biol Int 44(11): 2182-2191.

Durand, N., J. Mallea and A. C. Zubair (2020). "Insights into the use of mesenchymal stem cells in COVID-19 mediated acute respiratory failure." NPJ Regen Med 5(1): 17.

EL Barky AR, A. E., Mohamed TM (2017). "Stem Cells, Classifi cations and their Clinical Applications." Am J Pharmacol Ther 1(1): 001-007.

Esquivel, D., R. Mishra, P. Soni, R. Seetharaman, A. Mahmood and A. Srivastava (2021). "Stem Cells Therapy as a Possible Therapeutic Option in Treating COVID-19 Patients." Stem Cell Rev Rep 17(1): 144-152.

Faheem Anwar1, M. K., Naumana Rehman3, Fazal Akbar4, Sohail Ahmad1, Muhammad Yousaf5, Ihteshamul Haq1, Fazli Zahir6, Zeeshan Shahzad1, Farzeen Khan7, Shumaila Bakht8, Maharij Haroon Jadoon9, Fatima Syed10, Muhammad Zeeshan11 (2021). "Review and forecasting on COVID-19 outbreak; An insight to in silico candidate drug discovery." BIOSCIENCE RESEARCH 18(2): 1198-1210. .

Golchin, A., E. Seyedjafari and A. Ardeshirylajimi (2020). "Mesenchymal Stem Cell Therapy for COVID-19: Present or Future." Stem Cell Rev Rep 16(3): 427-433.

Hamming, I., W. Timens, M. L. Bulthuis, A. T. Lely, G. Navis and H. van Goor (2004). "Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis." J Pathol 203(2): 631-637.

Hernandez, J. J., D. E. Beaty, L. L. Fruhwirth, A. P. Lopes Chaves and N. H. Riordan (2021). "Dodging COVID-19 infection: low expression and localization of ACE2 and TMPRSS2 in multiple donor-derived lines of human umbilical cord-derived mesenchymal stem cells." J Transl Med 19(1): 149.

Iglesias, M., P. Butrón, I. Torre-Villalvazo, E. A. Torre-Anaya, J. Sierra-Madero, J. J. Rodriguez-Andoney, A. R. Tovar-Palacio, A. Zentella-Dehesa, G. Domínguez-Cherit, T. S. Rodriguez-Reyna, J. Granados-Arriola, V. Espisosa-Cruz, F. P. Téllez-Pallares, A. Lozada-Estrada, C. A. Zepeda Carrillo, A. J. Vázquez-Mézquita and H. F. Nario-Chaidez (2021). "Mesenchymal Stem Cells for the Compassionate Treatment of Severe Acute Respiratory Distress Syndrome Due to COVID 19." Aging Dis 12(2): 360-370.

Khurshid, A., M. Ammar Ahmed, A. Aziz and R. Amin (2020). "Living with Coronavirus (COVID-19): a brief report." Eur Rev Med Pharmacol Sci 24(20): 10902-10912.

Leng, Z., R. Zhu, W. Hou, Y. Feng, Y. Yang, Q. Han, G. Shan, F. Meng, D. Du, S. Wang, J. Fan, W. Wang, L. Deng, H. Shi, H. Li, Z. Hu, F. Zhang, J. Gao, H. Liu, X. Li, Y. Zhao, K.

Yin, X. He, Z. Gao, Y. Wang, B. Yang, R. Jin, I. Stambler, L. W. Lim, H. Su, A. Moskalev, A. Cano, S. Chakrabarti, K. J. Min, G. Ellison-Hughes, C. Caruso, K. Jin and R. C. Zhao (2020). "Transplantation of ACE2(-) Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia." Aging Dis 11(2): 216-228.

Li, C., H. Zhao and B. Wang (2020). "Challenges for Mesenchymal Stem Cell-Based Therapy for COVID-19." Drug Des Devel Ther 14: 3995-4001.

Li, Z., S. Niu, B. Guo, T. Gao, L. Wang, Y. Wang, L. Wang, Y. Tan, J. Wu and J. Hao (2020). "Stem cell therapy for COVID-19, ARDS and pulmonary fibrosis." Cell Prolif 53(12): e12939.

Liu, S., D. Peng, H. Qiu, K. Yang, Z. Fu and L. Zou (2020). "Mesenchymal stem cells as a potential therapy for COVID-19." Stem Cell Res Ther 11(1): 169.

Maeurer, M., R. Ramalho, F. S. Wang and A. Zumla (2021). "Host-directed therapies for COVID-19." Curr Opin Pulm Med 27(3): 205-209.

Manuela Monti1*, C. P., Claudia Del Fante2, Marila Cervio2, Carlo Alberto Redi1 Fondazione IRCCS Policlinico San Matteo, Pavia (Italia) (2012). "Stem cells: sources and therapies." Biol Res 45(3): 207-214.

Medicine., U. S. N. L. o. (2021). "ClinicalTrials.gov." Retrieved 22 April 2021, 2021, from https://clinicaltrials.gov/.

O'Brien, T., & Barry, F. P. (2009). "Stem Cell Therapy and Regenerative Medicine." Mayo Clinic proceedings 84(10): 859-861.

Rajarshi, K., A. Chatterjee and S. Ray (2020). "Combating COVID-19 with mesenchymal stem cell therapy." Biotechnol Rep (Amst) 26: e00467.

Saldanha-Araujo, F., E. Melgaço Garcez, A. E. Silva-Carvalho and J. L. Carvalho (2020). "Mesenchymal Stem Cells: A New Piece in the Puzzle of COVID-19 Treatment." Front Immunol 11: 1563.

Surat P. (2019, Jul 1, 2019). "Stem Cell Sources, Types, and Uses in Research." Retrieved 30 March, 2021, from https://www.news-medical.net/life-sciences/Stem-Cell-Sources-Types-and-Uses-in-Research.aspx.

Yu, D. and G. A. Silva (2008). "Stem cell sources and therapeutic approaches for central nervous system and neural retinal disorders." Neurosurg Focus 24(3-4): E11.

Yu, F., R. Jia, Y. Tang, J. Liu and B. Wei (2020). "SARS-CoV-2 infection and stem cells: Interaction and intervention." Stem Cell Res 46: 101859.

Zakrzewski, W., M. Dobrzynski, M. Szymonowicz and Z. Rybak (2019). "Stem cells: past, present, and future." Stem Cell Res Ther 10(1): 68.

Zhang, W., R. H. Du, B. Li, X. S. Zheng, X. L. Yang, B. Hu, Y. Y. Wang, G. F. Xiao, B. Yan, Z. L. Shi and P. Zhou (2020). "Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes." Emerg Microbes Infect 9(1): 386-389.