

Invited Mini Review

Immunomodulatory effect of mesenchymal stem cells and mesenchymal stem-cell-derived exosomes for COVID-19 treatment

Kaavya Jayaramayya^{1,2}, Iyer Mahalaxmi², Mohana Devi Subramaniam³, Neethu Raj¹, Ahmed Abdal Dayem⁴, Kyung Min Lim⁴, Se Jong Kim⁴, Jong Yub An⁴, Yoonjoo Lee⁴, Yujin Choi⁴, Arthi Kirubhakaran¹, Ssang-Goo Cho^{4,*} & Balachandar Vellingiri^{1,*}

¹Human Molecular Cytogenetics and Stem Cell Laboratory, Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641-046, ²Department of Zoology, Avinashilingam Institute for Home Science and Higher Education for Women, Coimbatore 641-043, ³SN ONGC Department of Genetics and Molecular Biology, Vision Research Foundation, Sankara Nethralaya campus, Chennai 600-006, India, ⁴Department of Stem Cell and Regenerative Biotechnology, Konkuk University, Seoul 05029, Korea

The world has witnessed unimaginable damage from the coronavirus disease-19 (COVID-19) pandemic. Because the pandemic is growing rapidly, it is important to consider diverse treatment options to effectively treat people worldwide. Since the immune system is at the hub of the infection, it is essential to regulate the dynamic balance in order to prevent the overexaggerated immune responses that subsequently result in multiorgan damage. The use of stem cells as treatment options has gained tremendous momentum in the past decade. The revolutionary measures in science have brought to the world mesenchymal stem cells (MSCs) and MSC-derived exosomes (MSC-Exo) as therapeutic opportunities for various diseases. The MSCs and MSC-Exos have immunomodulatory functions; they can be used as therapy to strike a balance in the immune cells of patients with COVID-19. In this review, we discuss the basics of the cytokine storm in COVID-19, MSCs, and MSC-derived exosomes and the potential and stem-cell-based ongoing clinical trials for COVID-19. [BMB Reports 2020; 53(8): 400-412]

INTRODUCTION

The world has been facing a dreadful situation due to the spread of the Severe Acute Respiratory Syndrome-Coronavirus-2

(SARS-CoV-2) (1). However, neither confirmed effective antiviral medications nor vaccines are available to deal with this emergency (2). Many reports have suggested that it is the cytokine storm in COVID-19 that leads to acute respiratory distress syndrome (ARDS) (3). The cytokine storm in COVID-19 refers to the fact that a variety of cytokines are rapidly produced after viral infections (4). In addition, such a cytokine storm induces hypoxia, and direct viral infection can cause cellular damage. Multiorgan damage and injury have been concomitant with COVID-19, and can be observed more in patients with a more severe form of the disease (5).

Stem cells are specialized cells that can renew themselves by means of cell division and can differentiate into multilineage cells. Mesenchymal stem cell (MSCs) have immunomodulatory features and secrete cytokines and immune receptors that regulate the microenvironment in the host tissue (6). In addition, it has been observed that the crucial role of MSCs in therapy has been mediated by exosomes released by the MSCs. These exosomes have exhibited immunomodulatory, antiviral, anti-fibrotic, and tissue-repair-related functions *in vivo*; similar effects have been observed *in vitro* (6).

COVID-19 AND THE IMMUNE SYSTEM

The dynamic equilibrium maintained by innate and adaptive immunity is essential for impeding the progression of COVID-19 (7). In patients infected with SARS-CoV-2, the plasma levels of IL-1 β , IL-1RA, IL-7, IL-8, IL-10, IFN- γ , monocyte chemoattractant peptide (MCP)-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, G-CSF, and TNF- α are significantly higher than in controls. The levels of these factors are also increased in patients who were admitted to ICUs (8). Similarly, reductions in the levels of T cells and NK cells have been observed in COVID-19 patients (9). The loss of such cells can impair the immune system (10). The levels of the helper T cells, cytotoxic suppressive T cells, and regulatory T cells are much lower in

*Corresponding authors. Balachandar Vellingiri, Tel: +91-422-2422514, +91-422-2422222; Fax: +91-422-2422387; E-mail: geneticbala@buc.edu.in, geneticbala@yahoo.co.in; Ssang-Goo Cho, Tel: +82-2-4504207; Fax: +82-2-444-4207; E-mail: ssangoo@konkuk.ac.kr, ssangoo33@gmail.com

<https://doi.org/10.5483/BMBRep.2020.53.8.121>

Received 5 June 2020

Keywords: COVID-19, Exosome, Immunomodulation, Mesenchymal stem cells (MSCs), Ongoing Clinical trials, Therapy

patients with COVID-19 than in their healthy and less severe counterparts. The decrease in the regulatory T cells may hamper their ability to inhibit the chronic inflammation (11). Interestingly, a remarkable increase is observed in the naïve T cells, whereas the memory T cells are reduced in infected patients (10). The reduced expression of memory cells may be a plausible explanation for the increased rates of reinfection by SARS-CoV-2.

THE CYTOKINE STORM

SARS-CoV-2 binds to the Angiotensin-converting enzyme 2 (ACE2) receptor and enters the host cell (1). During infection, the innate and adaptive immune systems work together to inactivate the virus. Since leukocytes and neutrophils are present in higher concentrations in COVID-19 individuals, these immune cells may result in the cytokine storm (10). After viral entry, the virus induces pyroptosis and cell death. The dead cells recruit macrophages to the site of injury that phagocytose them. The phagocytes then express damage-associated molecular patterns (DAMPs), which bind to the toll-like receptors (TLR) and induce nuclear factor kappa B (NF- κ B) signalling by means of the MyD88 pathway. NF- κ B enters the nucleus and catalyzes the transcription of pro-IL-1 β and procaspase-1. When additional signals are detected, the pro-IL-1 β and procaspase 1 are cleaved into IL-1 β and caspase 1 (12). The activated NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) recruits the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and pro-caspase-1 to form the NLRP3 inflammasome (13). In addition, the

phagocytosis releases ATP, which binds to the P2X purinoceptor 7 (P2RX7) and activates the inflammasome (14). The increased calcium levels caused by the viral proteins results in lysosomal damage, thereby releasing cathepsins that activate the inflammasome (15). Further, the binding of SARS-CoV-2 to the ACE2 reduces the available ACE2 receptors on the cell surface. This increases the levels of Angiotensin II (AngII) in the extracellular space, because ACE2 converts AngI and AngII into Ang 1-9 and Ang1-7, respectively. AngII increases the levels of TNF- α and IL-6 in the cell that upregulates NF- κ B, activating the inflammasome (12). The continuous activation of the inflammasome results in a cytokine storm, which recruits more immune cells, necrosis, and cell death. This inflammasome pathway further causes tissue injury in various organs (Fig. 1).

MSCs AND IMMUNOMODULATION

MSCs are predominantly isolated from the bone marrow, adipose tissue, dental pulp, umbilical cord, Wharton's jelly, placenta, synovial fluid, endometrium, and peripheral blood. These cells exhibit different cell-surface markers and can be used for a variety of treatment options (Table 1). MSCs can undergo *in vitro* amplification and self-renewal, and have low immunogenicity and immune-modulatory functions; the latter have attracted attention in clinical trials (16). MSCs have been widely used in various cellular therapies, such as pre-clinical studies, as well as in some clinical trials, because of their high safety and efficacy (17, 18). MSCs can exert immune-modulatory effects in the host cells of both the innate and the

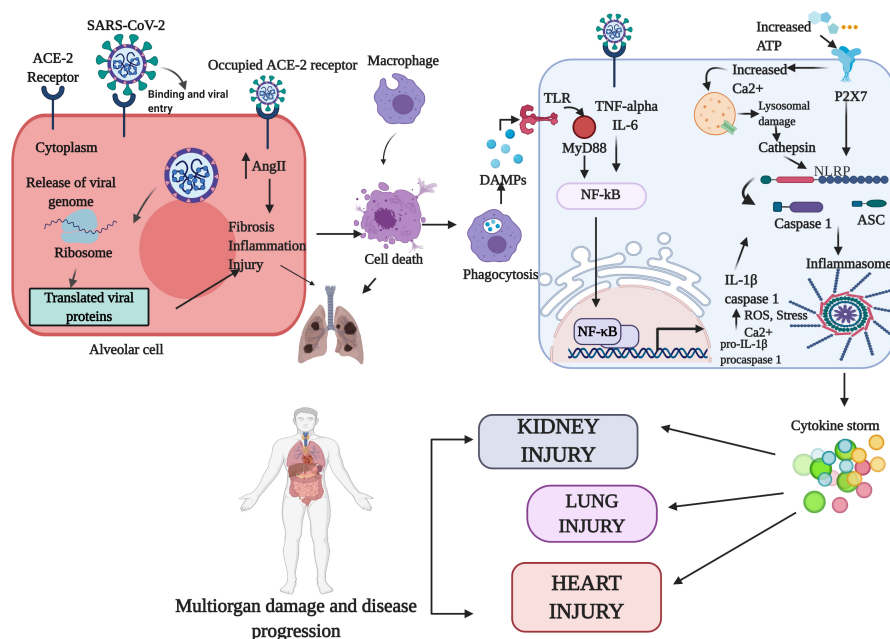


Fig. 1. Role of cytokine storm in COVID-19. When SARS-CoV-2 binds to the cell, the ACE2 receptors become occupied. This increases AngII which results in lung fibrosis, inflammation, and damage. The infected cell also undergoes cell death as a result of the viral infection. Macrophages engulf the dead cells and release DAMPs, which bind the TLR and activated NF- κ B by means of MyD88. Activated NF- κ B binding activates the inflammasome. Binding of the virus to the receptor also upregulates IL-6 and TNF- α , further activating NF- κ B. Increase in ATP binds the P2X7 receptor, which in turn increases Ca²⁺, which causes lysosomal damage and further activation of the inflammasome. Continuous activation of the inflammasome produces the cytokine storm, resulting in multiorgan damage.

Table 1. Commonly used sources of MSCs

S. No	Source	Extraction route	Purity level	Proliferation rate	Doubling time	MSCs Marker
1.	Bone Marrow	Bone Marrow Aspiration	High	Lowest	40 Hrs	Stro-1, CD271, SSEA-4, CD146
2.	Adipose Tissue	Liposuction, lipectomy	Medium	Higher	5 days	CD271, CD146
3.	Dental pulp	Tooth extraction or root canal	Low	High	30-40 Hrs	Stro-1, SSEA-4, CD146
4.	Umbilical Cord	After birth from umbilical cord	High	Medium	30 Hrs	CD146
5.	Wharton's jelly	After birth from umbilical cord	High	High	30 Hrs	CD73, CD90, CD105
6.	Placenta	Obtained after delivery	High	High	36 Hrs	SSEA-4, CD146
7.	Synovial Fluid	Synovium or synovial fluid	High	High	10 days	Stro-1, SSEA-4, CD146
8.	Endometrium	Endometrium biopsies or menstrual blood	High	High	18-36 Hrs	Stro-1, CD146
9.	Peripheral Blood	Density Gradient Centrifugation	Low	Low	95 Hrs	CD133

adaptive immune system. The direct or indirect interactions of MSCs with the immune cells make the MSCs activate the immunomodulatory responses (19). The immunomodulatory functions of MSCs depend on the environment of the host cells; based on the inflammatory status, the MSCs decide the type of immunoregulatory effect (20). MSCs represent pro-inflammatory immune reactions and anti-inflammatory reactions (21). MSCs regulate the immune system via the transforming growth factor β 1 (TGF β 1), which can trigger the proliferation of Tregs, induce IL-6, which prevents the proliferation of neutrophils, and stimulate the prostaglandin E2 (PGE2), which inhibits the antigen presentation by dendritic cells and proliferations of T-effector cells (22, 23). MSCs mediate these kinds of effects by direct contact, where it releases the regulatory cytokines, such as IFN- γ , indoleamine 2,3-dioxygenase, TGF β , IL-10, and PGE2 (24). Moreover, MSCs can hinder the proliferation and/or functions of the CD4+ Th1 and TH17 cells, CD8+ T cells, and the natural killer (NK) cells, mainly by secreting soluble factors, such as TGF β 1 and hepatocyte growth factor (HGF) (16).

MESENCHYMAL STEM CELLS (MSCs) AND MSC SECRETOME

It has currently become apparent that MSCs induce therapeutic characteristics by a paracrine pathway by releasing bioactive substances known as secretomes (25). MSC-secretomes are made of soluble proteins, including cytokines, chemokines, growth factors, and extracellular vesicles (EVs), which include micro-vesicles and exosomes (26). Stem cells release these secretomes by common secretory mechanisms. When the culture medium or secretome are injected into the patients, the neighboring cells assimilate the molecules by paracrine signalling (27). The exosomes themselves contain numerous bioactive molecules, which include microRNAs (miRNA), transfer RNAs (tRNA), long noncoding RNAs (lncRNA), growth factors, proteins, and lipids. The lipid content of the exosomes provide an added advantage by aiding in the infusion of the exosomes with the plasma membrane of the neighboring cells (28). The molecules

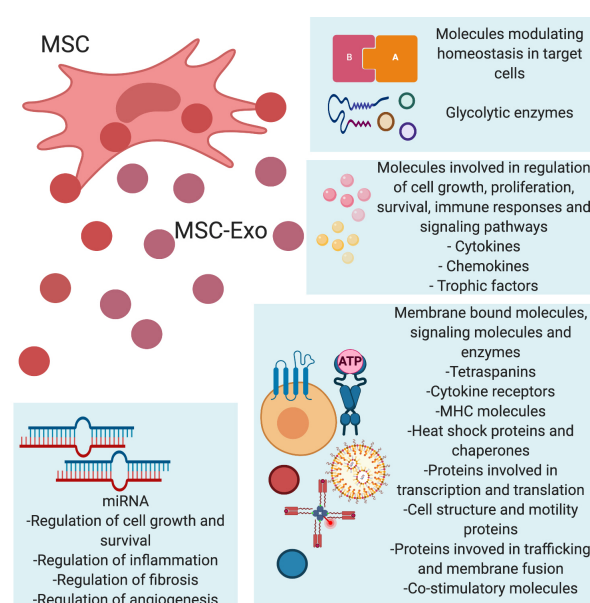


Fig. 2. Molecules released by MSC-Exos. MSC-Exos affect their targets by means of various molecules that they secrete. The MSC-Exos secrete molecules that maintain the homeostasis in the neighboring cells while also secreting glycolytic enzymes. Other molecules involved in cell growth, proliferation, and modulation of the immune response and signalling pathways are secreted by the MSC-Exos. Some membrane-bound molecules that aid in cell signalling and miRNAs with various functions are also released by MSC-Exos.

involved in regulation of cell growth, proliferation, survival, and immune responses are released by exosomes, are elaborately illustrated in Fig. 2. Upon internalization of the molecules in the secretome, the neighboring cells modulate various downstream pathways, including immunomodulation, suppression of apoptosis, prevention of fibrosis, and remodelling of the injured tissues (25).

IMMUNOMODULATORY POTENTIAL OF MSC-EXOS

Exosomes are nanoparticles with a diameter of 40-150 nm. To generate and isolate the exosomes, MSCs can be conditioned to increase the release of exosomes by treatment with cytokines or by serum starvation or hypoxia (29). The exosomes are then purified and can be subsequently introduced into the body. MSC-Exos can inhibit CD4⁺ and CD8⁺ T cells and NK cells (30). They inhibited T cells expressing IL-17 and induced IL-10-expressing regulatory cells that are involved with suppression of inflammation. MSC-Exos also aid in suppressing the differentiation of CD4⁺ and CD8⁺ T cells by releasing molecules like TGF β and prevent inflammation *in vivo* (31). Similarly, treatment with MSC-Exos reduced the proliferation and activation of NK cells (32). MSC-Exos could shift macrophages from the M1 to the M2 phenotype, further suppressing pro-inflammatory states (33). Moreover, sepsis is an important lethal factor in COVID-19 patients, and treatments with MSC-Exos have increased the rate of survival in mice with sepsis (34). Concomitantly, MSC-Exos also suppressed release of the pro-inflammatory factors TNF- α , IFN- γ , IL-6, IL-17, and IL-1 β (35) and promoted release of anti-inflammatory factors, such as IL-4, IL-10 and TGF- β (36). Additionally, MSC-Exos also reduced the number of chemokines in the serum when injected (37). These immunomodulatory effects of MSC-Exos have also been attributed to their anti-inflammatory cargo, such as IDO, HLA-G, PD-L1 and galectin-1 (38, 39). These mechanisms are illustrated in Fig. 3.

MSC-EXOS THERAPY FOR COVID-19

In COVID-19, multiorgan damage has been seen in many-infected individuals. MSC-Exos is known to alleviate lung injury in asthmatic models and ARDS (40, 41). MSC-Exos may also be useful in the treatment of cardiovascular (42) and renal problems (43). Hence, they can be used to treat organ damage associated with COVID-19. Similarly, MSC-EVs have also exhibited inhibitory activity on the hemagglutination of avian, swine, and human influenza viruses (44). Likewise, MSC-Exos lowered the death rate in H7N9 patients without any toxic effects during follow-up examinations (45). In addition, these exosomes consist of adhesion molecules that accurately guide them to the injured site. The usage of the exosomes may be preferred to the MSCs, since they can easily cross the blood-brain barrier, are inexpensive, and cannot undergo independent self-renewal, hence preventing adverse consequences, such as tumor formation. In this pandemic situation, MSC-Exos may be considered as a good treatment option to alleviate the effect of SARS-CoV-2 infection.

CURRENT CLINICAL TRIALS OF STEM CELL-BASED THERAPY IN COVID-19

Of late, stem-cell-based studies in the treatment of COVID-19

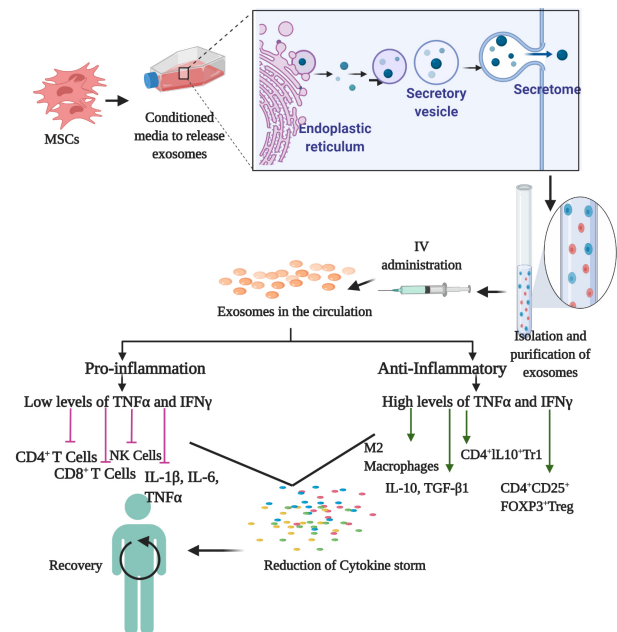


Fig. 3. MSC-Exos therapy for COVID-19. Isolated MSCs are conditioned in specialized media that induce release of exosomes. The MSCs identify the external signal and start to pack regulatory factors in secretory vesicles that are released into the culture medium. The exosomes are identified and isolated using specific markers, and are then administered intravenously the i.v. injection. The exosomes inhibit IL-1, IL-6, NK cells, CD4⁺, and CD8⁺. This results in suppression of the cytokine storm. Exosomes also activate IL-10, TGF-beta, M2 macrophages, and T and B regulatory cells to further suppress the immune system. This reduces the proinflammatory cytokines, alleviating symptoms and aiding in recovery of patients.

have been gaining momentum. The efficiency and safety of usage of exosomes that had been obtained from BM-MSCs was recently tested on 24 SARS-CoV-2 patients (46). These patients exhibited moderate to severe ARDS. When the exosomes were introduced into the patients, there were no side effects, and patients improved in clinical status and oxygenation (46). In a similar study, patients treated with MSCs showed a remarkable improvement in pulmonary function, higher levels of peripheral lymphocytes, and a reduction in the cells that trigger the cytokine storm. Interestingly, the MSCs did not exhibit ACE2 or TMPRSS2 expression, showing that they may not be infected with COVID-19 (47). Several clinical trials are in the pipeline for usage of stem cells for the treatment of COVID-19 (Table 2). Wharton's jelly-derived MSCs (WJ-MSCs), which have been used in various studies based on stem-cell therapy and trials, are in progress for their usage for COVID-19 treatment (48). Moreover, adipose tissue-derived AD-MSCs have been used in a few studies in various doses and protocols for COVID-19 therapy (49). Likewise, a novel trial includes inhalation of MSC-Exos for alleviation of symptoms (50). In addition, MSCs from dental pulp (51) and olfactory mucosa

Table 2. Ongoing stem cell based clinical trials in COVID-19

Study title	Intervention	Study size	Description	Status	Country	Reference
Treatment of COVID-19 patients using Wharton's Jelly- Mesenchymal Stem Cells	WJ-MSCs	5	Dose: 3 IV doses of 1×10^6 /kg Time: 3 days apart	Phase 1	Jordan	55
Safety and Efficacy study of Allogenic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	Allogenic Human Dental Pulp MSCs Placebo: Intravenous Saline	20	Dose: IV of 3.0×10^7 human dental pulp stem cell solution (30 ml) on day 1, day 4 and day 7 IV of 3 ml of 0.9% saline at the same interval	Phase 2	China	56
NestCell Mesenchymal Stem Cells to Treat Patients with Severe COVID-19 Pneumonia	NestCell	66	Dose: 2×10^7 cells (20 million cells) Time: days 1, 3 and 5 in addition to standard care. On day 7, cells will only be administered if necessary	Phase 1	Brazil	57
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	HB-adMSCs	100	3 groups of patients, will receive five IVs at 200, 100 and 50 million cells/dose Infusions will occur at week 0, 2, 6, 10 and 14. Placebo is saline	Phase 2	USA	58
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	Allogenic expanded adMSCs	26	Two doses of 80 million adipose-tissue derived mesenchymal stem cells	Phase 2	Spain	59
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	HB-adMSCs	56	Dose: five IV infusions Time: follow-up inflammatory data will be obtained at 6, 14, 26 weeks; and PHQ-9 Questionnaires at weeks 2, 6, 10, 14, 18, 22, 26	Phase 2	USA	60
Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem cells	Dental pulp MSCs	24	Dose: 1.0×10^6 cells/kg The injection of dental mesenchymal stem cells will be increased on day 1, 3 and 7	Early Phase 1	China	51
Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19	MSCs	20			China	61
Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	MSCs Saline containing 1% Human serum albumin (solution of MSC)	90	3 times of MSCs (3.0×10^7 MSCs intravenously at Day 0, Day 3, Day 6)	Phase 1	China	62
Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)	BM-MSCs	20	Participants will receive conventional treatment plus BM-MSCs (1×10^6 /kg body weight intravenously at Day 1)	Phase 2	China	63
Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19	UC-MSCs	48	4 times of UC-MSCs (0.5×10^6 UC-MSCs/kg body weight intravenously at Day 1, Day 3, Day 5, Day 7)	Not yet recruiting	China	64

Table 2. Continued

Study title	Intervention	Study size	Description	Status	Country	Reference
Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	Drug: Oseltamivir and hormones MSCs	60	Umbilical cord mesenchymal stem cells were given at 106/kg body weight/time, once every 4 days for a total of 4 times. Peripheral intravenous infusion was given within 3 days of first admission	Early Phase 1	China	53
Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	UC-MSCs	30	1*10E6 UC-MSCs/kg suspended in 100 ml saline	Phase 2	China	65
Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	Cell therapy	60	Protocol 1 (n = 20): Two doses of MSCs 100 × 10E6 (± 10%) at Day 0 and Day 2 plus Conventional treatment Protocol 2: Two doses of MSCs 100 × 10E6 (± 10%) at Day 0 and Day 2, intravenously plus two doses of EVs at Day 4 and Day 6 plus conventional treatment	Phase 3	Iran	66
Role of Immune and Inflammatory Response in Recipients of Allogeneic Haematopoietic Stem Cell Transplantation (SCT) Affected by Severe COVID19	No intervention	40	Comparison of biomarkers	Active, not recruiting	United Kingdom	67
Use of UC-MSCs for COVID-19 Patients	UC- MSCs	24	UC-MSC will be administered at 100 × 10 ⁶ cells/infusion administered intravenously in addition to the standard of care treatment	Phase 2	USA	68
Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19	Stem Cell Educator-Treated Mononuclear Cells Apheresis	20	SCE therapy circulates a patient's blood through a blood cell separator, briefly cocultures the patient's immune cells with adherent CB-SC in vitro, and returns the autologous immune cells to the patient's circulation	Phase 2	USA	69
Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19	Drug: HB-and MSC Drug: Placebo Drug: HC Drug: AZ	110	Dose: 4 IV of HB-adMSCs at 100 million cells/dose + hydroxychloroquine and azithromycin HB-adMSC infusions will occur at day 0, 3, 7, and 10 Placebo: similar intervals without the HB-adMSCs	Phase 2	USA	54
Therapy for Pneumonia Patients Infected by 2019 Novel Coronavirus	Biological: UC-MSCs	N.A	0.5*10E6 UC-MSCs/kg body weight suspended in 100 ml saline containing 1% human albumin intravenously at Day 1, Day 3, Day 5, Day 7	With-drawn	China	70
Battle Against COVID-19 Using Mesenchymal Stromal Cells	Allogeneic and expanded adipose tissue-derived MSCs	100	Two serial doses of 1.5 million adipose-tissue derived mesenchymal stem cells/kg	Phase 2	Madrid	71
Safety and Efficacy of CAStem for Severe COVID-19 Associated With/Without ARDS	CAStem	9	A dose-escalation with 3 cohorts with 3 patients/cohort who receive doses of 3, 5 or 10 million cells/kg	Phase 2	China	72

Table 2. Continued 2

Study title	Intervention	Study size	Description	Status	Country	Reference
ASC Therapy for Patients With Severe Respiratory COVID-19	Stem Cell Product	40	100 million allogeneic adipose-derived mesenchymal stromal cells diluted in 100 ml saline	Phase 2	Denmark	73
Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS)	MSC	40	Infusion of allogeneic bone marrow-derived human mesenchymal stem (stromal) cells	Phase 2	Germany	74
Unilateral Cord(UO)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus (nCoV) Pneumonia	UC-MSCs	10	UC-MSCs infusion intravenously on day 1, day 3, day 5, and day 7	Phase 2	China	75
A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	MSCs-derived exosomes	30	5 times aerosol inhalation of MSCs-derived exosomes (2.0*10E8 nano vesicles/3 ml at Day 1, Day 2, Day 3, Day 4, Day 5)	Phase 1	China	50
MultiStem Administration for COVID-19 Induced ARDS (MACoVIA)	MultiStem	400	IV infusion of MultiStem	Phase 3	USA	76
Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS	UC Wharton's jelly-derived human Platebo: NaCl 0.9% Mesenchymal Stromal Cells	60	Dose: 1 million/kg through an intravenous route	Phase 2	France	48
Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV)	Mesenchymal Stromal Cells	24	IV injection of 1 million MSV cells/Kg diluted in 100 ml saline	Phase 2	Spain	77
Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease) Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19)	Remestemcel-L	300	Dose: 1 × 10 ⁸ MSCs through IV Administered twice during the first week, with the second infusion at 4 days following the first injection (± 1 day)	Early Phase 1	USA	78
Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	Allogenic pooled olfactory mucosa-derived MSCs	40	IV injection	Phase 3	USA	79
Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	Autologous adMSCs	200	3 doses of 200 million cells through IV every 3 days	Phase 2	Minsk	52
Mesenchymal Stem Cell Infusion for COVID-19 Infection	MSCs	20	Dose: 2 × 10 ⁶ cells/kg, administered on day 1, 7 in addition to supportive care	Phase 2	USA	49
Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia (CELMA)	UC-MSCs	30	Dose: 1 *10 ⁶ cells/Kg	Phase 2	Pakistan	80
Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (COVID-19)	MSC	10	Dose: 1 million/Kg	Phase 2	USA	81
NestaCell [®] Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE)	NestaCell [®]	90	Dose : 2 × 10 ⁷ cells on days 1, 3, 5 and 7	Phase 2	Mexico	82
				Phase 2	Brazil	83

Table 2. Continued 3

Study title	Intervention	Study size	Description	Status	Country	Reference
Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	UC-MSCs	100	Dose: 3 of 4.0*10E7 cells at Day 0, Day 3, Day 6	Phase 2	China	84
Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients	MSCs	20	IV injection of Cultured stem cells at days 1, 3 and 5	Phase 2	Turkey	85
Clinical Use of Stem Cells for the Treatment of Covid-19	MSCs	30	Dose: 3 million cells/kg on days 0, 3 and 6	Phase 2	Turkey	86
Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19	WJ-MSCs	40	2 doses	Phase 2	Colombia	87
MSCs in COVID-19 ARDS	Remestemcel-L	300	Twice in the first week with a gap of 4 days between the injections	Phase 3	USA	88
Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 (COVIDMES)	WJ-MSCs	30	Administration along with standard care	Phase 2	Spain	89
Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome - Vanguard (CIRCA-19)	MSCs	9	IV administration	Phase 1	Canada	90
ACT-20 in Patients With Severe COVID-19 Pneumonia	Allogenic UC-MSCs	70	1 million cells/kg body weight in 100 ml in conditioned media	Phase 2		91
Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	Allogenic BM-MSC	45	IV administration	Phase 1	USA	92
Double-Blind, Multicenter, Study to Evaluate the Efficacy of PLX PAD for the Treatment of COVID-19	MSCs	140	15 IM injections (1 ml each). Twice with an interval of 1 week	Phase 2	USA	93
A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy	MSCs and a plasmapheresis device	24	Administered through integration into a Continuous Renal Replacement Therapy circuit	Phase 2		94

WJ: Wharton's Jelly; MSC: Mesenchymal stem cells; adMSCs: adipose derived MSCs; UC: Umbilical cord; IV: Intravenous; BM: Bone marrow; HC: hydroxychloroquine; AZ: azithromycin.

(52) were administered in various doses. MSCs in the clinical trials are predominantly administered intravenously; i.v. injection and, in some studies, MSCs have been given as adjuvant therapy in addition to drugs like oseltamivir, hormones, hydroxychloroquine, and azithromycin (53, 54). These trials reveal promising new routes for the battle against COVID-19 (55-94).

FUTURE DIRECTIONS

Stem cells have been studied extensively for their ability to regenerate and for the treatment of various diseases. Recently, we devised an improved protocol for the isolation of urine-derived stem cells and their further differentiation into immune cells (95). Moreover, our research group promoted the hematopoietic differentiation of hiPSCs using a novel small molecule (96). At the advent of COVID-19, it has become mandatory to discover therapeutic strategies that are easily reproducible and cost effective. Drugs currently available for the treatment of COVID-19 include ones that target viral replication. These drugs include camostat mesylate, which is involved in the inhibition of viral fusion to the cell membrane, and favipiravir and remdesivir, which are anti-viral drugs. However, because the cytokine storm is found predominantly in COVID-19 patients, it is essential to consider drugs that inhibit viral replication while treating the cytokine storm. Hence, MSC-Exos may be appropriate therapeutic agents for COVID-19 (97). MSCs can be more advantageous than other anti-inflammatory agents, because they can provide immunomodulatory effects based on the host cells. In addition to these effects, MSCs can prevent fibrosis of tissues, enable reversal of lung dysfunction, and aid in the regeneration of damaged tissue, which can be significantly beneficial for COVID-19-associated organ damage (98, 99). Because the healing properties of the MSCs can be primarily attributed to the secretomes or exosomes, using them may be more effective than using MSCs themselves. Exosomes can be mass-produced, administered systematically with minimal toxicity, and be able to reach the cell targets more efficiently. In addition to their inherent immunomodulatory potential, the MSC-Exos can also be used as a drug-delivery system (100). MSC-Exos can be modified *in vivo* to release exosomes that have a higher immunomodulatory potential (101) and can be cultured using various cytokines to exhibit an anti-inflammatory state (102). Although MSC-Exos appear to be promising therapeutic agents for COVID-19, more experimental research is necessary for them to be used clinically. Moreover, it is essential to optimize the protocols for storage and isolation of MSC-Exos for the treatment of COVID-19. It is also imperative to do experiments to understand the underlying mechanisms of COVID-19 in order to optimize MSC-Exo therapy for treatment (97). Further, it is also essential to find the optimum dosage, route of administration, and treatment schedule for MSC-Exos. Hence, since MSCs are more widely studied in these aspects than are MSC-Exos, they are predominantly preferred in clinical

trials for COVID-19 (103).

CONCLUDING REMARKS

COVID-19 has invoked frenzy in individuals worldwide. The unceasing increase of infection and death has halted the lives of the citizens of countries everywhere. Hence, it is important to discover novel therapeutic platforms and productive measures without further delay (104). The therapies produced must be easily reproducible and available in large quantities so that enough bioactive molecules will be available for all individuals who have succumbed to COVID-19. MSCs and MSC-Exos can be used for their immunomodulatory effects in individuals with COVID-19.

ACKNOWLEDGEMENTS

The author Dr. VB would like to thank Bharathiar University for providing the necessary infrastructure facility and Project funded and supported by MHRD-RUSA 2.0 – BEICH to carry out this manuscript of diagnostic and therapeutic approaches (Ref No. BU/RUSA/BEICH/2019/65).

Dr. SMD would like to thank the Science and Engineering Research Board (SERB) (ECR/2018/000718), Government of India, New Delhi, for providing necessary help in carrying out this review process. The study was supported by a grant from the National Research Foundation (NRF) funded by the Korean government (Grant no: 2019M3A9H1030682).

CONFLICTS OF INTEREST

The authors have no conflicting interest.

REFERENCES

1. Vellingiri B, Jayaramayya K, Iyer M et al (2020) COVID-19: A promising cure for the global panic. *Sci Total Environ* 725, 138277
2. Iyer M, Jayaramayya K, Subramaniam MD et al (2020) COVID-19: an update on diagnostic and therapeutic approaches. *BMB Rep* 53, 191-205
3. Grasselli G, Zangrillo A, Zanella A et al (2020) Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 323, 1574-1581
4. Sun X, Wang T, Cai D et al (2020) Cytokine storm intervention in the early stages of COVID-19 pneumonia. *Cytokine Growth Factor Rev*. doi: 10.1016/j.cytogfr.2020.04.002
5. Balachandar V, Mahalaxmi I, Devi SM et al (2020) Follow-up studies in COVID-19 recovered patients-is it mandatory? *Sci Total Environ* 729, 139021
6. Taghavi-farahabadi, M, Mahmoudi M, Soudi S and Hashemi SM (2020) Hypothesis for the management and treatment of the COVID-19-induced acute respiratory distress syndrome and lung injury using mesenchymal stem cell-

- derived exosomes. *Med Hypotheses* 144, 109865
7. Li G, Fan Y, Lai Y et al (2020) Coronavirus infections and immune responses. *J Med Virol* 92, 424-432
8. Qin C, Zhou L, Hu Z et al (2020) Dysregulation of immune response in patients with COVID-19 in Wuhan, China. *Clin Infect Dis*. doi: 10.1093/cid/ciaa248
9. Wang W, He J and Wu S (2020) The definition and risks of cytokine release syndrome-like in 11 COVID-19-infected pneumonia critically ill patients: disease characteristics and retrospective analysis. doi: <https://doi.org/10.1101/2020.02.26.20026989>
10. Tufan A, Güler AA and Matucci-Cerinic M (2020) COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. *Turk J Med Sci* 50, 620-632
11. Sakaguchi S, Miyara M, Costantino CM and Hafler DA (2010) FOXP3⁺ regulatory T cells in the human immune system. *Nat Rev Immunol* 10, 490-500
12. Zbinden-Foncea H, Francaux M, Deldicque L and Hawley JA (2020) Does high cardiorespiratory fitness confer some protection against pro-inflammatory responses after infection by SARS-CoV-2? *Obesity*. doi: 10.1002/oby.22849
13. Shneider A, Kudriavtsev A and Vakhrusheva A (2020) Can melatonin reduce the severity of COVID-19 pandemic? *Int Rev Immunol* 39, 153-162
14. Guo J, Huang Z, Lin L and Lv J (2020) Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease: A viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. *J Am Heart Assoc* 9, e016219
15. Conti P, Ronconi G, Caraffa A et al (2020) Induction of pro-inflammatory cytokines (IL-1 and IL-6) and lung inflammation by Coronavirus-19 (COVI-19 or SARS-CoV-2): anti-inflammatory strategies. *J Biol Regul Homeost Agents* 34, 1
16. Zhao Q, Ren H and Han Z (2016) Mesenchymal stem cells: Immunomodulatory capability and clinical potential in immune diseases. *J Cell Immunother* 2, 3-20
17. Prockop DJ (2017) The exciting prospects of new therapies with mesenchymal stromal cells. *Cytotherapy* 19, 1-8
18. Wilson JG, Liu KD, Zhuo H et al (2015) Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *Lancet Respir Med* 3, 24-32
19. Uccelli A, Moretta L and Pistoia V (2008) Mesenchymal stem cells in health and disease. *Nat Rev Immunol* 8, 726-736
20. Ren G, Zhang L, Zhao X et al (2008) Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. *Cell Stem Cell* 2, 141-150
21. Waterman RS, Tomchuck SL, Henkle SL and Betancourt AM (2010) A new mesenchymal stem cell (MSC) paradigm: polarization into a pro-inflammatory MSC1 or an immunosuppressive MSC2 phenotype. *PLoS One* 5, e10088
22. Patel SA, Meyer JR, Greco SJ, Corcoran KE and Bryan M, Rameshwar P (2010) Mesenchymal stem cells protect breast cancer cells through regulatory T cells: role of mesenchymal stem cell-derived TGF- β . *J Immunol* 184, 5885-5894
23. Raffaghello L, Bianchi G, Bertolotto M et al (2008) Human mesenchymal stem cells inhibit neutrophil apoptosis: a model for neutrophil preservation in the bone marrow niche. *Stem Cells* 26, 151-162
24. Thanunchai M, Hongeng S and Thitithanyanont A (2015) Mesenchymal stromal cells and viral infection. *Stem Cells Int* 2015, 860950
25. Bari E, Ferrarotti I, Saracino L, Perteghella S, Torre ML and Corsico AG (2020) Mesenchymal stromal cell secretome for severe COVID-19 infections: Premises for the therapeutic use. *Cells* 9, 924
26. Crivelli B, Chlapanidas T, Perteghella S et al (2017) Mesenchymal stem/stromal cell extracellular vesicles: From active principle to next generation drug delivery system. *J Controlled Release* 262, 104-117
27. Deffune E, Prudenciatti A and Moroz A (2020) Mesenchymal stem cell (MSC) secretome: a possible therapeutic strategy for intensive-care COVID-19 patients. *Med Hypotheses* 142, 109769
28. Keshtkar S, Azarpira N and Ghahremani MH (2018) Mesenchymal stem cell-derived extracellular vesicles: novel frontiers in regenerative medicine. *Stem Cell Res Ther* 9, 63
29. Lou G, Chen Z, Zheng M and Liu Y (2017) Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. *Exp Mol Med* 49, e346-e346
30. Lai P, Chen X, Guo L et al (2018) A potent immunomodulatory role of exosomes derived from mesenchymal stromal cells in preventing cGVHD. *J Hematol Oncol* 11, 135
31. Álvarez V, Sánchez-Margallo FM, Macías-García B et al (2018) The immunomodulatory activity of extracellular vesicles derived from endometrial mesenchymal stem cells on CD4⁺ T cells is partially mediated by TGF β . *J Tissue Eng Regen Med* 12, 2088-2098
32. Fan Y, Herr F, Vernochet A, Mennesson B, Oberlin E and Durrbach A (2019) Human fetal liver mesenchymal stem cell-derived exosome impair natural killer cell function. *Stem Cells Dev* 28, 44-55
33. Domenis R, Cifù A, Quaglia S et al (2018) Pro inflammatory stimuli enhance the immunosuppressive functions of adipose mesenchymal stem cells-derived exosomes. *Sci Rep* 8, 13325
34. Song Y, Dou H, Li X et al (2017) Exosomal miR-146a contributes to the enhanced therapeutic efficacy of interleukin-1 β -primed mesenchymal stem cells against sepsis. *Stem Cells* 35, 1208-1221
35. Chen W, Huang Y, Han J et al (2016) Immunomodulatory effects of mesenchymal stromal cells-derived exosome. *Immunol Res* 64, 831-840
36. Ji L, Bao L, Gu Z et al (2019) Comparison of immunomodulatory properties of exosomes derived from bone marrow mesenchymal stem cells and dental pulp stem cells. *Immunol Res* 67, 432-442
37. He Ping (2019) AB0291E the effect of human umbilical cord mesenchymal stem cells-derived exosomes on chemokines in collagen-induced arthritis rats. *BMJ* 1606-1606
38. Mardpour S, Hamidieh AA, Taleahmad S, Sharifzad F,

- Taghikhani A and Baharvand H (2019) Interaction between mesenchymal stromal cell-derived extracellular vesicles and immune cells by distinct protein content. *J Cellular Physiol* 234, 8249-8258
39. Baharloo H, Azimi M, Salehi Z and Izad M (2020) Mesenchymal stem cell-derived exosomes: A Promising therapeutic ace card to address autoimmune diseases. *Int J Stem Cells* 13, 13-23
40. Du Y, Zhuansun Y, Chen R, Lin L, Lin Y and Li J (2018) Mesenchymal stem cell exosomes promote immunosuppression of regulatory T cells in asthma. *Exp Cell Res* 363, 114-120
41. Fujita Y, Kosaka N, Araya J, Kuwano K and Ochiya T (2015) Extracellular vesicles in lung microenvironment and pathogenesis. *Trends Mol Med* 21, 533-542
42. Barani B, Rajasingh S and Rajasingh J (2017) Exosomes: Outlook for future cell-free cardiovascular disease therapy. *Adv Exp Med Biol* 2017, 285-307
43. Tsuji K, Kitamura S and Wada J (2018) Secretomes from mesenchymal stem cells against acute kidney injury: possible heterogeneity. *Stem Cells Int* 2018, 8693137
44. Khatri M, Richardson LA and Meulia T (2018) Mesenchymal stem cell-derived extracellular vesicles attenuate influenza virus-induced acute lung injury in a pig model. *Stem Cell Res Ther* 9, 17
45. Chen J, Hu C, Chen L et al (2020) Clinical study of mesenchymal stem cell treating acute respiratory distress syndrome induced by epidemic Influenza A (H7N9) infection, a hint for COVID-19 treatment. *Engineering*. <https://doi.org/10.1016/j.eng.2020.02.006>
46. Vikram S, Sascha S, Angel L et al (2020) Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19. *Stem Cells Dev* 29, 747-754
47. Leng Z, Zhu R, Hou W et al (2020) Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis* 11, 216-228
48. Clinicaltrials.gov. Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS (STROMA-CoV2) ClinicalTrials.gov Identifier: NCT04333368. <https://clinicaltrials.gov/ct2/show/NCT04333368?term=Wharton&results?cond=COVIDcovid-19&draw=2&rank=2.term=stem+cell&cntry=&state=&city=&dist=.> Accessed on 26th June 2020
49. Clinicaltrials.gov. Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19. ClinicalTrials.gov Identifier: NCT04428801. <https://clinicaltrials.gov/ct2/show/NCT04428801>. Accessed on 26th June 2020
50. Clinicaltrials.gov. A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia. ClinicalTrials.gov Identifier: NCT04276987. <https://clinicaltrials.gov/ct2/show/NCT04276987>. Accessed on 26th June 2020. Accessed on 26th June 2020
51. Clinicaltrials.gov. Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells. ClinicalTrials.gov Identifier: NCT04302519. <https://clinicaltrials.gov/ct2/show/NCT04302519>. Accessed on 26th June 2020
52. Clinicaltrials.gov. Treatment of Covid-19 Associated Pneumonia with Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells. ClinicalTrials.gov Identifier: NCT04382547. <https://clinicaltrials.gov/ct2/show/NCT04382547>. Accessed on 26th June 2020
53. Clinicaltrials.gov. Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019. ClinicalTrials.gov Identifier: NCT04371601. <https://clinicaltrials.gov/ct2/show/NCT04371601>. Accessed on 26th June 2020
54. Clinicaltrials.gov. Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19. ClinicalTrials.gov Identifier: NCT04362189. <https://clinicaltrials.gov/ct2/show/NCT04362189>. Accessed on 26th June 2020
55. Clinicaltrials.gov. Treatment of COVID-19 patients using Wharton's Jelly- Mesenchymal Stem Cells. ClinicalTrials.gov Identifier: NCT04313322. <https://clinicaltrials.gov/ct2/show/NCT04313322>. Accessed on 16th July 2020
56. Clinicaltrials.gov. Safety and Efficacy study of Allogenic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients. ClinicalTrials.gov Identifier: NCT04336254. <https://clinicaltrials.gov/ct2/show/NCT04336254>. Accessed on 16th July 2020. Accessed on 16th July 2020
57. Clinicaltrials.gov. NestCell Mesenchymal Stem Cells to Treat Patients with Severe COVID-19 Pneumonia. ClinicalTrials.gov Identifier: NCT04315987. <https://clinicaltrials.gov/ct2/show/NCT04315987>. Accessed on 16th July 2020
58. Clinicaltrials.gov. 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. ClinicalTrials.gov Identifier: NCT04348435. <https://clinicaltrials.gov/ct2/show/NCT04348435>. Accessed on 16th July 2020
59. Clinicaltrials.gov. 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. ClinicalTrials.gov Identifier: NCT04366323. <https://clinicaltrials.gov/ct2/show/NCT04366323>. Accessed on 16th July 2020
60. Clinicaltrials.gov. 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. ClinicalTrials.gov Identifier: NCT04349631. <https://clinicaltrials.gov/ct2/show/NCT04349631>. Accessed on 16th July 2020
61. Clinicaltrials.gov. Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19. ClinicalTrials.gov Identifier: NCT04252118. <https://clinicaltrials.gov/ct2/show/NCT04252118>. Accessed on 16th July 2020
62. Clinicaltrials.gov. Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19) ClinicalTrials.gov Identifier: NCT04288102. <https://clinicaltrials.gov/ct2/show/NCT04288102?term=Treatment+With+Mesenchymal+Stem+Cells++for+Severe+Corona+Virus+Disease+2019+%28COVID-19%29&draw=2&rank=1>. Accessed on 16th July 2020
63. Clinicaltrials.gov. Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19) ClinicalTrials.gov Identifier:

- NCT04346368. <https://clinicaltrials.gov/ct2/show/NCT04346368>. Accessed on 16th July 2020
64. Clinicaltrials.gov. Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19. ClinicalTrials.gov Identifier: NCT04273646. <https://clinicaltrials.gov/ct2/show/NCT04273646>. Accessed on 16th July 2020
65. Clinicaltrials.gov. Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia. ClinicalTrials.gov Identifier: NCT04339660. <https://clinicaltrials.gov/ct2/show/NCT04339660>. Accessed on 16th July 2020
66. Clinicaltrials.gov. Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome. ClinicalTrials.gov Identifier: NCT04366063. <https://clinicaltrials.gov/ct2/show/NCT04366063>. Accessed on 16th July 2020
67. Clinicaltrials.gov. Role of Immune and Inflammatory Response in Recipients of Allogeneic Haematopoietic Stem Cell Transplantation (SCT) Affected by Severe COVID19. ClinicalTrials.gov Identifier: NCT04349540. <https://clinicaltrials.gov/ct2/show/NCT04349540>. Accessed on 16th July 2020
68. Clinicaltrials.gov. Use of UC-MSCs for COVID-19 Patients. ClinicalTrials.gov Identifier: NCT04355728. <https://clinicaltrials.gov/ct2/show/NCT04355728>. Accessed on 16th July 2020
69. Clinicaltrials.gov. Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19. ClinicalTrials.gov Identifier: NCT04299152. <https://clinicaltrials.gov/ct2/show/NCT04299152>. Accessed on 16th July 2020
70. Clinicaltrials.gov. Therapy for Pneumonia Patients Infected by 2019 Novel Coronavirus ClinicalTrials.gov Identifier: NCT04293692. <https://clinicaltrials.gov/ct2/show/NCT04293692>. Accessed on 16th July 2020
71. Clinicaltrials.gov. Battle Against COVID-19 Using Mesenchymal Stromal Cells. ClinicalTrials.gov Identifier: NCT04348461. <https://clinicaltrials.gov/ct2/show/NCT04348461>. Accessed on 16th July 2020
72. Clinicaltrials.gov. Safety and Efficacy of CAsTem for Severe COVID-19 Associated With/Without ARDS ClinicalTrials.gov Identifier: NCT04331613. <https://clinicaltrials.gov/ct2/show/NCT04331613>. Accessed on 16th July 2020
73. Clinicaltrials.gov. ASC Therapy for Patients With Severe Respiratory COVID-19. ClinicalTrials.gov Identifier: NCT04341610. <https://clinicaltrials.gov/ct2/show/NCT04341610>. Accessed on 16th July 2020
74. Clinicaltrials.gov. Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS). ClinicalTrials.gov Identifier: NCT04377334. <https://clinicaltrials.gov/ct2/show/NCT04377334>. Accessed on 16th July 2020
75. Clinicaltrials.gov. Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus (nCoV) Pneumonia. ClinicalTrials.gov Identifier: NCT04269525. <https://clinicaltrials.gov/ct2/show/NCT04269525>. Accessed on 16th July 2020
76. Clinicaltrials.gov. MultiStem Administration for COVID-19 Induced ARDS (MACoVIA) ClinicalTrials.gov Identifier: NCT04367077. <https://clinicaltrials.gov/ct2/show/NCT04367077>. Accessed on 16th July 2020
77. Clinicaltrials.gov. Treatment of Severe COVID-19 Pneumonia with Allogeneic Mesenchymal Stromal Cells (COVID_MSV) ClinicalTrials.gov Identifier: NCT04361942. <https://clinicaltrials.gov/ct2/show/NCT04361942>. Accessed on 16th July 2020
78. Clinicaltrials.gov. Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease). ClinicalTrials.gov Identifier: NCT04345601. <https://clinicaltrials.gov/ct2/show/NCT04345601>. Accessed on 16th July 2020
79. Clinicaltrials.gov. Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) ClinicalTrials.gov Identifier: NCT03042143. <https://clinicaltrials.gov/ct2/show/NCT03042143>. Accessed on 16th July 2020
80. Clinicaltrials.gov. Mesenchymal Stem Cell Infusion for COVID-19 Infection. ClinicalTrials.gov Identifier: NCT04444271. <https://clinicaltrials.gov/ct2/show/NCT04444271>. Accessed on 16th July 2020
81. Clinicaltrials.gov. Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia (CELMA). ClinicalTrials.gov Identifier: NCT04429763. <https://clinicaltrials.gov/ct2/show/NCT04429763>. Accessed on 16th July 2020
82. Clinicaltrials.gov. Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (COVID-19). ClinicalTrials.gov Identifier: NCT04416139. <https://clinicaltrials.gov/ct2/show/NCT04416139>. Accessed on 16th July 2020
83. Clinicaltrials.gov. NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE). ClinicalTrials.gov Identifier: NCT04315987. <https://clinicaltrials.gov/ct2/show/NCT04315987>. Accessed on 16th July 2020
84. Clinicaltrials.gov. Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19). ClinicalTrials.gov Identifier: NCT04288102. <https://clinicaltrials.gov/ct2/show/NCT04288102>. Accessed on 16th July 2020
85. Clinicaltrials.gov. Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients . ClinicalTrials.gov Identifier: NCT04437823. <https://clinicaltrials.gov/ct2/show/NCT04437823>. Accessed on 16th July 2020
86. Clinicaltrials.gov. Clinical Use of Stem Cells for the Treatment of Covid-19. ClinicalTrials.gov Identifier: NCT04392778. <https://clinicaltrials.gov/ct2/show/NCT04392778>. Accessed on 16th July 2020
87. Clinicaltrials.gov. Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19. ClinicalTrials.gov Identifier: NCT04390152. <https://clinicaltrials.gov/ct2/show/NCT04390152>. Accessed on 16th July 2020
88. Clinicaltrials.gov. MSCs in COVID-19 ARDS .ClinicalTrials.gov Identifier: NCT04371393 <https://clinicaltrials.gov/ct2/show/NCT04371393>. Accessed on 16th July 2020
89. Clinicaltrials.gov. Efficacy and Safety Evaluation of Mesen-

- chymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 (COVIDMES). ClinicalTrials.gov Identifier: NCT04390139. <https://clinicaltrials.gov/ct2/show/NCT04390139>. Accessed on 16th July 2020
90. Clinicaltrials.gov. Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome - Vanguard (CIRCA-19). ClinicalTrials.gov Identifier: NCT04400032. <https://clinicaltrials.gov/ct2/show/NCT04400032>. Accessed on 16th July 2020
91. Clinicaltrials.gov. ACT-20 in Patients With Severe COVID-19 Pneumonia. ClinicalTrials.gov Identifier: NCT04398303. <https://clinicaltrials.gov/ct2/show/NCT04398303>. Accessed on 16th July 2020
92. Clinicaltrials.gov. Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation ClinicalTrials.gov Identifier: NCT04397796. <https://clinicaltrials.gov/ct2/show/NCT04397796>. Accessed on 16th July 2020
93. Clinicaltrials.gov. Double-Blind, Multicenter, Study to Evaluate the Efficacy of PLX PAD for the Treatment of COVID-19 ClinicalTrials.gov Identifier: NCT04389450. <https://clinicaltrials.gov/ct2/show/NCT04389450>. Accessed on 16th July 2020
94. Clinicaltrials.gov. A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy. ClinicalTrials.gov Identifier: NCT04445220 <https://clinicaltrials.gov/ct2/show/NCT04445220>. Accessed on 16th July 2020
95. Kim K, Gil M, Dayem AA et al (2020) Improved isolation and culture of urine-derived stem cells (USCs) and enhanced production of immune cells from the USC-derived induced pluripotent stem cells. *J Clin Med* 9, 827
96. Kim K, Abdal Dayem A, Gil M et al (2020) 3,2'-Dihydroxyflavone Improves the proliferation and survival of human pluripotent stem cells and their differentiation into hematopoietic progenitor cells. *J Clin Med* 9, 669
97. Tsuchiya A, Takeuchi S, Iwasawa T et al (2020) Therapeutic potential of mesenchymal stem cells and their exosomes in severe novel coronavirus disease 2019 (COVID-19) cases. *Inflammation and Regeneration* 40, 1-6
98. Akkoc T (2020) COVID-19 and mesenchymal stem cell treatment; mystery or not. *Adv Exp Med Biol*. 1-10 https://doi.org/10.1007/5584_2020_557
99. Pinky, Gupta S, Krishnakumar V et al (2020) Mesenchymal stem cell derived exosomes: a nano platform for therapeutics and drug delivery in combating COVID-19. *Stem Cell Rev Rep* 1-11 doi: 10.1007/s12015-020-10002-z
100. Muraca M, Pessina A, Pozzobon M et al (2020) Mesenchymal stromal cells and their secreted extracellular vesicles as therapeutic tools for COVID-19 pneumonia?. *J Control Release* 325, 135-140
101. O'Driscoll L (2020) Extracellular vesicles from mesenchymal stem cells as a Covid-19 treatment. *Drug Discovery Today*. S1359-6446(20)30170-7. <https://doi.org/10.1016/j.drudis.2020.04.022>
102. Sleem A and Saleh F (2020) Mesenchymal stem cells in the fight against viruses: Face to face with the invisible enemy. *Curr Res Transl Med* S2452-3186(20)30031-3. doi: 10.1016/j.retram.2020.04.003
103. Harrell CR, Jovicic N, Djonov V et al (2020) Therapeutic Use of Mesenchymal Stem Cell-Derived Exosomes: From Basic Science to Clinics. *Pharmaceutics* 12, 474
104. Balachandar V, Mahalaxmi I, Kaavya J et al (2020) COVID-19: emerging protective measures. *Eur Rev Med Pharmacol Sci* 24, 3422-3425