MESENCHYMAL STEM CELLS VERSUS COVID-19. CAN THEY WIN THE BATTLE?

Amra Ramovic Hamzagic[1], Dragica Miloradovic[2], Dragana Miloradovic[2], Zeljko Ivosevic[2] and Biljana Ljujic[2*]

[1]*State University of Novi Pazar, Department of biomedical sciences, Novi Pazar, Serbia*
[2]*University of Kragujevac, Faculty of Medical Sciences, Department of Genetics, Kragujevac, Serbia*

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Corresponding author:

Biljana Ljujic

University of Kragujevac, Faculty of Medical Sciences, Department of Genetics, Svetozara Markovica 69, 34000 Kragujevac, Serbia

Tel.: +381604433223

E-mail: bljujic74@gmail.com

ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent stem cells with numerous features potentially useful in various pathologies. It has been shown that MSCs have regenerative potential due to modulation of immune system response, inflammation diminishing, trans differentiation into various types of cells, proangiogenetic and anti fibrotic influence. Besides all of these traits, MSCs posses anti viral capacity and have been further employed in clinical trails since last year. Here, we revised immunomodulatory, biological and antiviral traits of MSCs, but also pathogenesis of Covid-19 and it's impact on immune system. Conspicuously, there is a grow-ing number of studies examining effect of MSCs in patients suffer-ing from Covid-19 pneumonia and ARDS. Since MSCs are in theo-ry capable of healing lung injury and inflammation, here we dis-cuss hypothesis, pros and cons of MSCs treatment in Covid-19 pa-tients. Finally, we debate if MSCs based therapy can be promising tool for Covid-19 lung pathologies.

Keywords: *Mesenchymal stem cells, inflammation, covid-19, pneumonia, ARDS.*

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ABBREVIATIONS

ACE2 - Angiotensin-converting enzyme 2
AngII - Angiotensin 2 pathway
ARDS - Acute respiratory distress syndrome
AT-MSCs - Adipose tissue derived mesenchymal stem cells
BM-MSC - Bone marrow derived mesenchymal stem cells
CCL2 - C-C Motif Chemokine Ligand 2)
COPD - Chronic Obstructive Pulmonary Disease
CRP - C-reactive protein
CVDs - Cardiovascular disease
DCs- Dendritic cells
FGF7- Fibroblast Growth Factor 7
G-CSF - Alpha granulocyte-colony stimulating factor
GM-CSF- Granulocyte-macrophage colony-stimulating factor
GVHD - Graft- versus host disease
HCoV-19- Human coronavirus 2019
hESC - Human embryonic stem cell
HGF - Hepatic growth factor
hiPSC - Human induced pluripotent stem cells
HLA-G- Human leukocyte antigen-G
HO- Heterotopic ossification
HO-1- Hemeoxygenase-1
hWJCs - Wharton Jelly's MSCs
IDO - Indolamine 2,3-dioxygenase IL-10,
IFI6 - Interferon Alpha Inducible Protein 6
IFITM - Interferon-inducible transmembrane
IFNAR2 - Interferon Alpha And Beta Receptor Subunit 2
IL-1Ra - Interleukin 1 receptor antagonist
IL-6 Amp - Interleukin-6 amplifier
IL-6 - Interleukin-6
ISG - Interferon stimulated genes
KGF - Keratinocyte growth factor
LIF - Leukocyte inhibitory factor
MCP-1- Monocyte chemoattractant protein-1
MERS - Middle East respiratory syndrome
MIP1A - Macrophage inflammatory protein 1
MODS - Multiple organ dysfunction syndrome
MSC-EV- Mesenchymal stem cell derived extracellular vesicles
MSCs -Mesenchymal stem cells
MT1G -Metallothionein 1G
NETs -Neutrophil extracellular traps
NO - Nitric oxide
p21/CDKN1A - p21 Cyclin Dependent Kinase Inhibitor 1A
PD - programmed cell death
PGE2 - Prostaglandin E2
PMAIP1 - Phorbol-12-Myristate-13-Acetate-Induced Protein 1
SARS - Severe acute respiratory syndrome
SARS-CoV-2- SARS coronavirus 2
SAT- Spermidine/spermine N(1)-acetyltransferase
SERPINE1 - Serpin family E member 1
sIL-6Ra - Interleukin-6a
SARS-CoV-2S - spike glycoprotein
TGF-b - Transforming growth factor-b ,
TLRs - Toll like receptors
TMPRSS2 - Transmembrane protease serine 2
TNF-α - Tumor necrosis factor-α
Tregs - Regullatory T cells
TSG-6 - Tumor necrosis factor a-stimulated gene 6
UCB-MSCs - Umbilical chord blood derived mesenchymal stem cells
VEGF - Vascular endothelial growth factor
WHO -World Health Organization

INTRODUCTION

Mesenchymal stem cells (MSCs) are adult multipotent stem cells with ability to self renew and can be isolated from various tissues (1). MSCs are defined by three norms- adherence to culture flasks; expression of cluster of differentiation CD105, CD73 and CD90 but also absence of CD45, CD34, CD11b, CD14, CD79a, CD31 and MHC class II molecule. Additionally, MSCs can differentiate into different types of tissues (2) therefore representing an excellent tool for regenerative medicine. MSCs can migrate to the sites of injury and modulate immune response (3). This trait, among others, makes MSCs an excellent choice for immune-mediated diseases. Immediately after engraftment, MSCs interact with both, innate and adaptive immune system in two ways; by paracrine manner and by PD receptor interaction. Paracrine manner includes release of numerous soluble factors- transforming growth factor-b (TGF-b), hepatic growth factor (HGF), nitric oxide (NO), indolamine 2,3-dioxygenase (IDO), IL-10, IL-6, leukocyte inhibitory factor (LIF), IL-1 receptor antagonist (IL-1Ra), galectins, tumor necrosis factor a-stimulated gene 6 (TSG-6), human leukocyte antigen-G (HLA-G), hemeoxygenase-1 (HO-1), and prostaglandin E2 (PGE2) hence emphasizing it's immunosupressive potential. MSCs influence immune response by interaction with crucial inflammatory cells, specifically, MSCs abolish production and spur of pro-inflammatory M1 macrophages and provoke their alteration in M2 phenotype (4). Also, MSCs can negatively impact dendritic cells DCs in terms of their growth and secretion of various cytokines, which eventually leads to diminished inflammation due to T cells inhibition (5-7). MSCs can diminish generation of Th1 and Th17 cytokines, but also enhance Th2 cytokines generation (19–21). Proliferation of Th1 and Th17 cells can be suppressed by MSCs, but also,

MSCs can add to the number of Tregs, and in that manner can have immunosupressive and anti-inflammatory effect (8). In spite of that, MSCs can adopt pro-inflammatory phenotype as well, which is determined by the environmental conditions (9). Actually, low levels of pro inflammatory cytokines promote pro-inflammatory phenotype of MSCs and vice versa (9). This balance of MSCs' phenotype is determined by Toll like receptors (TLRs) (10) that also represent main receptor for virus recognition (11-13). Important element of MSCs mediated immunomodulation are exosomes (14,15) and various secretomes (16,17). For instance, Let-7, miR-34a, miR-146a and miR200b/c are known to be involved in proinflammatory metabolic pathways (18,19). Let-7 has been involved in the suppression of posttranscriptional regulation of IL-6 secretion and downregulates TLR4 signal (20-22). Also, miR-34a and miR-146 turns out to have a critical role in regulation of NF-kB cascade, possibly aiming upstream elements at the time of T cell stimulation (23,24). Eventually, miR-200b/c presumably diminishes complement tentative cytolysis, induced by C5b-9 coupling, since suppression of miR-200c increased MSC demise (25). These outcomes propose the anti inflammatory and cytoprotective features of miRNAs from MSC-EV, confirming that MSCs secretomes promote tissue regeneration by neoangiogenesis, apoptosis inhibition and fibrosis inhibition (26-32), which can be beneficial in numerous pathologies especially those with inflammatory component in pathogenesis.

MSCs sources

Bone marrow, adipose tissue, umbilical cord and dental pulp are suggested as convenient sources of MSCs, yet it is not completely elucidated which source of MSCs is optimal (38, 39). BM-MSCs are characterized by easy acquisition, rapid expansion *in vitro*, minimum immunologic rejection, protracted standing post-transplatationally in the host, preservation of capacity to differentiate subsequently to repetitive passages as well as simplicity of transplantation (40,41). Anyway, the acquisition of BM-MSCs is complicated process and also, size and longevity of BM-MSCs diminishes by ageing (42,43). So, to bypass such obstacles, alternative sources for MSCs isolation are implied (12,13). Umbilical cord blood and adipose tissue have been proposed as an alternate source for isolation and therapeutic employment of MSCs regarding its larger proliferative potential, high cell yields and ease of harvesting (44,45). BM-MSCs, UCB-MSCs and AT-MSCs all have similar morphological as well as operational traits (11). In the context of current pandemic Covid-19, and the entire inflammatory response caused by cytokine storm, as it will be further elaborated in this review, adequate MSCs source should be discussed so that optimal MSCs could be employed in therapy. Since the virus enters the cells through target ACE2 receptor, it is crucial to decide whether MSCs from any of these sources express ACE2 receptor, and therefore is susceptible to Covid-19 infection. Recent study showed that ACE2 is highly expressed in adult bone marrow, adipose tissue or umbilical cord-derived MSC. Distinguishing from placental derived MSCs together with human embryonic stem cell (hESC) or human induced pluripotent stem cells (hiPSC) that express low levels of ACE2 receptor (46). These outcomes should be further taken into consideration when determining on the optimal source of MSC therapy.

Cytokine storm in Covid-19

In December 2019, non typical infectious respiratory syndrome of idiopathic cause was recognised in Wuhan, China. Having already met with manifestations of (SARS) in 2003, Chinese scientific and medical department could identify a new coronavirus, SARS coronavirus 2 (SARS-CoV-2) as the pathogen (47). SARS-CoV-2 was easily and quickly spread all across the globe, leading to high morbidity and mortality. In order to prevent further spread of the virus, lock-down and other quarantine measures were enforced. Ease of spreading, high morbidity and mortality rate, changed the portrait of this pathogen, so on March 11, 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic. The COVID-19 is clinically heterogeneous, patients may be asymptomatic or have light, moderate, severe or critical clinical traits. Symptoms of COVID-19 may vary, but most common include fever, headache, malaise, cough, bone pain, myalgias, anosmia, impaired taste and respiratory distress. Similar to SARS in 2003, this infectious disease leads to a high probability of ICU admission and mortality (48, 49). The pathogenesis of SARS-CoV-2 has been explained by the interaction and binding of the virus spike glycoprotein (SARS-CoV-2S) to the angiotensin-converting enzyme-related carboxypeptidase (ACE2) on the target cell surface. After binding, spike protein is activated by the cellular transmembrane protease serine 2 (TMPRSS2) which enables the virus to enter the host cell (50), leading to complex over activated inflammation and immune response, known as cytokine storm. The term "cytokine storm" was first established in 1993. to depict a graft versus host disease, and defines as the rapid and sudden efflux of a large number of cytokines that happens as a result of the immune system′s overactivation by some stimuli (infection, drugs, etc.), begin locally and disseminate systemically, triggering collateral detriment in tissues (51,52). It is elucidated that cytokine storm is linked with the exacerbation of various infectious diseases, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and with the severity of COVID-19 (53). However, it was reported that cytokine storm is one of the main causes of a severe form of the disease in COVID-19 patients and dying, and is associated with thrombosis, massive mononuclear cell infiltration in multiple organs, and high levels of circulating cytokines (54). Notwithstanding that the specific dysregulated molecular causes are still not understood, it is assumed that cytokine storm is caused by disbalance in the regulation of the immune system (i.e., increment in immune cell activation via TLR or another mechanism, decreasing in anti-inflammatory response, etc.) (51). The immune response is being provoked by SARS-CoV-2 entering respiratory epithelial cells and is accompanied by inflammatory cytokine production and weak interferon (IFN) response. Cytokine storm occurs as a result of activation of pro-inflammatory Th1 cells and intermediate CD14+ CD16+ monocytes, macrophages, and neutrophils infiltration into the

lung tissue (54). Specifically, pathogenic Th1 cells that produce pro-inflammatory cytokines, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 (IL-6) can be activated by SARS-CoV-2 very fast. After that, GM-CSF further activates CD14+ CD16+ inflammatory monocytes to secrete immense amounts of IL-6 and tumor necrosis factor-α (TNF-α) (55). Neutrophil extracellular traps (NETs), weak IFN-γ induction, and membrane-bound immune receptors (e.g., Fc and Toll-like receptors), might be some of the causes for massive cytokine release (53,54). One of the possible mechanisms of the cytokine storm is induced by the angiotensin 2 (AngII) pathway, where SARS-CoV-2 triggers NF-κB. ACE2 on the cell surface is occupied by SARS-CoV-2, which results in decreasing in ACE2 expression and an increase in AngII. Also, AngII-angiotensin receptor type 1 (AngII-AT1R) axis can induce TNF-α and the soluble form of IL-6Ra (sIL-6Ra). IL-6 binds to sIL-6R through gp130 to form the IL-6-sIL-6R complex, which can trigger STAT3 in non-immune cells. Both NF-κB and STAT3 are able for activation of the IL-6 amplifier (IL-6 Amp) to induce various pro-inflammatory cytokines and chemokines, such as IL-8, and IL-6, vascular endothelial growth factor (VEGF), monocyte chemoattractant protein-1 (MCP-1) (56, 57). Some studies have been demonstrated that levels of IL-1β, IL-2, IL-6, IL-7, IL-8, IL-12, inducible protein 10 (IP-10), MCP-1, TNF-α, macrophage inflammatory protein 1 alpha (MIP1A), granulocyte-colony stimulating factor (G-CSF), and IFN-γ were increased, though levels of the Th2 cytokine IL-4 were low in patients with severe COVID-19 (58, 59,60). Other studies showed that the level of CD4＋cells and CD8＋ cells was reduced constantly, but neutrophil counts were elevated in patients with a severe form of COVID-19 comparing with mild patients (60). Because of the rapid evolution of the cytokine storm, critically ill COVID-19 patients develop acute respiratory distress syndrome (ARDS) (61). ARDS is described as a multi-factorial syndrome of severe lung injury whose main characteristics are: hypoxemia, pulmonary oedema, diffuse alveolar damage and multiple organ failure. Lungs are not able to provide sufficient oxygen saturation to the alveolar spaces and respiratory support may be required (62). Yet, there are paradoxical outcomes in terms of SARS-CoV-2 positive Chronic Obstructive Pulmonary Disease (COPD) patients. Actually, most of COPD patients did not develop critical symptoms, which is contradictory, due to the fact that pulmonary co morbidity elevates chances of ARDS development and fatal outcome (63, 64). It is assumed that key role in this “protection” plays IL-6. Covid-19-related pneumonia is caused by inflammasomes activation and secretion of IL-1, TNF and IL-6, making IL-6 crucial in ARDS development. IL-6 coordinates the cytokine storm resulting in an immune hyper-reaction and in the inflammatory injury of the pulmonary tissue (65). This is in line with a *meta*-analysis that emphasized high levels IL-6 in the severe forms of Covid-19 (66). Moderately-elevated concentrations of IL-6 found in moderate COPD patients has protective roles against the decay of Covid-19, explaining therefore their better prognosis. Eventually, the drug Tocilizumab, a monoclonal antibody that blocks the IL-6 receptor, is currently used to treat Covid-19 in hospitals (67). These outcomes, lead to conclusion that Tocilizumab must be utilised only in patients with an current cytokine storm, or else, it’s usage may be damaging.

MSCs’ antiviral traits against Covid-19

Luckily, MSCs are insusceptible to virus infections due to IFN-stimulated genes (ISG), that can impact every of step of viral cycle (68-70). Specifically, PMAIP1, ISG15, IFI6, IFITM, SAT1, p21/CDKN1A, SERPINE1 and CCL2 are ISGs that being expressed in MSCs are shown to halt numerous viral pathogens, but most importantly SARS (69). Team of researches made a list of ISGs constitutively expressed by human MSC and afterwards set up by IFITM1, IFI6, CCL2, ISG15, SAT1 and PMAIP1. In attendance of IFN-γ there was an induction of non-constitutive ISGs, as well as MT1G, CD74, SERPING1, IFNAR2 and MT1X (68). MSCs have this great ability to switch to non-constitutive ISGs up regulation in order to better fight viruses, which can be advantageous in regards to respiratory infections (68). One of the most crucial ISGs is IDO, which not just that have immunomodulatory properties, but also inhibits viral protein bio synthesis (71). These anti viral features, besides familiar MSCs’ immunomodulatory, antiinflammatory, neoangiogenic, regenerative and multipotent potential, definitely make MSCs potent and competent player in a harsh battle against Covid-19.

MSCs as a tool for Therapeutic Applications in Covid-19

Since SARS-CoV-2 and COVID-19 first and foremost affect lungs, leading to ARDS, pneumonia and MODS consecutively, plus the fact that MSCs entrap in lungs, traits of MSCs residing in lungs should be thoroughly observed as therapeutic tool for SARS-CoV-2. It is shown that lung residing MSCs promote regeneration and tissue repair (72). Lung residing MSCs are positioned perivasculary and express CD73 which in turn promotes expression of anti-inflammatory genes in MF and vice versa (72). Again, exhibition of this marker is flexible and differ depending on the cell surrounding conditions, and testify how MSCs are sensitive to inflammatory response (73). MSCs respond by production of soluble factors, specifically when in lungs- MSCs secrete FGF7 (or KGF) leading to normalization of alveolar clearance (74). Various proteomic and transcriptomic analyses displayed that lung MSCs affect signal pathways in regards to up regulation of Wnt/β-catenin and down-regulation of NF-κB signaling, leading to diminished TNF-α production and eventually to fibrosis reduction (75, 76, 77). MSCs displayed remedial effect in model of ARDS by stimulating surfactant secretion, differentiating into pulmonary endothelial cells and alveolar epithelial cells (78). Hence, most important are exactly these effect in regards to SARS-CoV-2-cytokine storm and ARDS (79, 80), which has already been elaborated in preclinical and clinical studies (81, 82).

Clinical applications of MSCs in COVID-19

Most recent study revised outcomes of MSCs applied in patients with ARDS and Covid-19 related conditions (83).

When it comes to ARDS, highlights should be noted; patients with ARDS received BM-MSCs in dose of 10 million cells/kg. It is found no MSCs related adverse effects, except for, three patients who died in next weeks after treatment. Yet, for one who died from multiple spleen, brain and kidney embolic infarctions, it is confirmed by MRI that these changes were present prior to MSC administration (84) suggesting MSCs administration as safe. This study was the first phase of research, that was extended by Matthay et al. (85), and included much larger group of moderate to severe ARDS patients who received intravenously same dosage of human bone-marrow-derived MSCs. This study suggested no infusion-related haemodynamic or respiratory complications, even though higher numerically mortality and severity scores were observed in patients who received MSCs comparing to placebo group, but this difference was not statistically significant. Most important is the finding that showed direct impact of MSCs viability on angiopoetin 2 plasma concentrations, leading to drastic decrease of angiopoetin 2 concentrations, 6h after MSCs infusion which can be beneficial in ARDS. This study is planned to be continued, so more consistent and clear data could enlighten previous conclusions. In spite of insufficient and limited data in regards to clinical outcomes from patients that received MSCs therapy to fight Covid-19 respiratory disease, certain clinical trials emerged and propose MSCs as safe, beneficial and with no detrimental adverse effects (86, 87). Patients in China, on March in 2020, with severe COVID-19 pneumonia, were treated with MSCs, intravenously. In this study for the first time it is showed that MSCs are ACE2- and TMPRSS2- and that MSCs secrete anti-inflammatory factors to prevent the cytokine stormhence displaying that MSCs have natural immunity to the HCoV-19. This MSCs therapy improved vital condition of patients, reduced level of inflammatory cytokines and chemokines so less mononuclear/ macrophages were attracted to injured lung tissue. At the same time bigger number of regulatory DCs were directed to the inflammatory tissue niche. In addition, they noted enhanced levels of IL-10 and VEGF, decreased C-reactive protein and TNF-α levels (80). Among these data most important was the observation of lack of overactivated cytokine-secreting immune cells CXCR3+ CD4+ T cells, CXCR3+ CD8+ T cells and CXCR3+ NK cells (80), which in summary can explain lung regeneration and improvement in critical patients. Later on, in June, a detailed review by Rajarshi stated MSCs therapy in COVID-19 patients as justified and advantageous (88). Other study examined therapeutic potential of Wharton Jelly's MSCs (hWJCs) delivered intravenously in COVID-19 positive critically ill patient with pneumonia and diabetes. After his vital parameters stabilized, he received hWJCs intravenously. After hWJC adoptive transfer, there were no adverse effects whereas level of serum CRP and inflammatory factors (IL-6 and TNF-α) were drastically decreased, and vital parameters of the patient improved. Plus the level of CD3+, CD4+ and CD8+ T cell were significantly increased after intravenous injection of hWJCs (89). This is the first study of this kind, and though encouraging and promising, should be elaborated and further examined with much bigger group of patients. These preliminary clinical records lead to conclusion that MSCs alone or combined with other therapeutics could enhance the chances of survival and improve overall health condition in Covid-19 patients (80,90). One study examined exosomes (ExoFloTM) derived from allogeneic BM-MSCs as treatment for severe COVID-19 (91). 24 SARS-CoV-2 PCR positive patients received 15 mL dose of ExoFlo intravenously and were observed in regards to safety and effectiveness.

There were no any side effects of ExoFlo treatment 72 hours after treatment. 83% of the patients survived, 71% of patients cured; 13% stayed in critical though stable condition; 16% passed away of causes unconnected to the therapy. On the whole, after treatment, patients' clinical condition and oxygenation improved. Additionally, there were enhancements in absolute neutrophil number and lymphopenia. Also, there was significant diminishing of C-reactive protein (CRP), Ferritin and D-dimer, confirming therefore beneficial effect of ExoFlo on inflammatory response. Having in mind such data, ExoFlo could be a prommising tool of Covid-19 related pathology, due to it's safety, ability to halt inflammation, stabilize immune response and oxygenation. In spite of that, further research with bigger group of patients with similar results could guarantee ExoFlo as secure therapeutic approach.

Ongoing Clinical trials MSC-Based Therapies for COVID-19

In order to summarize ongoing MSC-based therapies in patients suffering from Covid-19 worldwide ClinicalTrials.gov database was analysed. There are 68 studies that include MSCs treatment in various Covid-19 related conditions-Pneumonia and ARDS. Most of these studies are randomised and open-label studies and in early phase (phase I, I/II, II). Specifically, 29 of the studies are currently recruiting, yet 26 are not recruiting yet. There are 8 completed studies, while there are 3 enrolling and 1 study is withdrawn. Most of the studies utilised BM-MSC, UC-MSC, WJ MSC, AT-MSCs. However, there are fewer studies that utilised allogeneic dental pulp MSCs, placenta-derived MSCs, stromal MSCs, MSC derived exosomes and secretomes. Most of the studies follow basic protocols of disease severity assessment such as inflammatory cytokine profile (TNF-α, IL-6 and IL-10), vital parameters and pulmonary function assessment. Studies groups include both, males and females varying in age. All of these data are summarized in Table 1.

Table 1. MSC-based ongoing clinical trials for Covid-19 infection diseases

Study Name:	Mesenchymal Stem Cell Infusion for COVID-19 Infection (NCT04444271)
Status:	Recruiting (Phase II)
Treatment:	MSC

Study Name:	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (NCT04416139)
Status:	Recruiting (Phase II)
Treatment:	MSC

Study Name:	Mesenchymal Stem Cells Therapy in Patients With COVID-19 Pneumonia (NCT04713878)
Status:	Completed
Treatment:	MSC

Study Name:	Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia (NCT04429763)
Status:	Not yet recruiting (Phase II)
Treatment:	UC-MSC

Study Name:	Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome (NCT04565665)
Status:	Recruiting (Phase I)
Treatment:	MSC

Study Name:	NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 (NCT04315987)
Status:	Not yet recruiting (Phase II)
Treatment:	MSCs (NestaCell®)

Study Name:	Mesenchymal Stem Cells in Patients Diagnosed With COVID-19 (NCT04611256)
Status:	Recruiting(Phase I)
Treatment:	MSC

Study Name:	Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19 (NCT04456361)
Status:	Early Phase I
Treatment:	WJ-MSC

Study Name:	Efficacy of Infusions of MSC From Wharton Jelly in the SARS-Cov-2 (COVID-19) Related Acute Respiratory Distress Syndrome (NCT04625738)
Status:	Not yet recruiting (Phase II)
Treatment:	WJ-MSC

Study Name:	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19 (NCT04252118)
Status:	Recruiting(Phase I)
Treatment:	MSCs

Study Name:	Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19 (NCT04366271)
Status:	Recruiting (Phase II)
Treatment:	WJ-MSC

Study Name:	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells (NCT04313322)
Status:	Recruiting(Phase I)
Treatment:	Use of Stem Cells for COVID-19 Treatment WJ-MSCs

Study Name:	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 (NCT04366323)
Status:	Active, not recruiting (Phase II)
Treatment:	AT-MSC

Study Name:	Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia (NCT04753476)
Status:	Recruiting (Phase II)
Treatment:	Injection of Secretome-MSCs

Study Name:	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients (NCT04336254)
Status:	Recruiting (Phase I, II)
Treatment:	Allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC)|

Study Name:	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19) (NCT04346368)
Status:	Not yet recruiting (Phase I, II)
Treatment:	BM-MSCs

Study Name:	Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19) (NCT04288102)
Status:	Completed (Phase II)
Treatment:	UC-MSCs

Study Name:	Study to Evaluate the Efficacy and Safety of AstroStem-V in Treatment of COVID-19 Pneumonia (NCT04527224)
Status:	Not yet recruiting (Phase I, II)
Treatment:	Adipose tissue-derived mesenchymal stem cells (AstroStem-V)

Study Name:	Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (NCT04629105)
Status:	Recruiting (Phase I)
Treatment:	Longeveron Mesenchymal Stem Cells (LMSCs)

Study Name:	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19 (NCT04273646)
Status:	Not yet recruiting
Treatment:	UC-MSCs

Study Name:	Study of Intravenous Administration of Allogeneic Adipose-Derived Mesenchymal Stem Cells for COVID-19-Induced Acute Respiratory Distress (NCT04728698)
Status:	Not yet recruiting (Phase II)
Treatment:	COVI-MSC

Study Name:	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 (NCT04348435)
Status:	Enrolling by invitation (Phase II)
Treatment:	HB-adMSCs

Study Name:	Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells (NCT04382547)
Status:	Enrolling by invitation (Phase I,II)
Treatment:	Allogenic pooled olfactory mucosa-derived MSC

Study Name:	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia (NCT04339660)
Status:	Recruiting(Phase I,II)
Treatment:	UC-MSCs

Study Name:	Expanded Access Protocol on Bone Marrow Mesenchymal Stem Cell Derived Extracellular Vesicle Infusion Treatment for Patients With COVID-19 Associated ARDS (NCT04657458)
Status:	Phase I
Treatment:	BM-MSC Derived Extracellular Vesicles Infusion Treatment

Study Name:	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome (NCT04366063)
Status:	Recruiting(Phase II,III)
Treatment:	Cell therapy protocol

Study Name:	Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19 (NCT04428801)
Status:	Not yet recruiting(Phase II)
Treatment:	Autologous adipose-derived stem cells

Study Name:	Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients (NCT04457609)
Status:	Recruiting (Phase I)
Treatment:	Oseltamivir| UC-MSC

Study Name:	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 (NCT04349631)
Status:	Active, not recruiting (Phase II)
Treatment:	HB-adMSCs

Study Name:	Adipose Mesenchymal Cells for Abatement of SARS-CoV-2 Respiratory Compromise in COVID-19 Disease (NCT04352803)
Status:	Not yet recruiting(Phase I)
Treatment:	Autologous Adipose MSC's

Study Name:	Mesenchymal Stem Cells for the Treatment of COVID-19 (NCT04573270)
Status:	Completed(Phase I)
Treatment:	UC-MSC (PrimePro)

Study Name:	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells (NCT04302519)
Status:	Not yet recruiting(Phase I)
Treatment:	Dental pulp MSC

Study Name:	Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19 (NCT04490486)
Status:	Not yet recruiting(Phase I)
Treatment:	UCMSCs

Study Name:	Use of UC-MSCs for COVID-19 Patients (NCT04355728)
Status:	Completed (Phase I,II)
Treatment:	Umbilical Cord Mesenchymal Stem Cells + Heparin along with best supportive care.

Study Name:	An Exploratory Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection (NCT04522986)
Status:	Not yet recruiting (Phase I)
Treatment:	MSC

Study Name:	Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs (NCT04461925)
Status:	Recruiting (Phase I,II)
Treatment:	Placenta-Derived MMSCs; Cryopreserved Placenta-Derived Multipotent Mesenchymal Stromal Cells

Study Name:	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019 (NCT04371601)
Status:	Active, not recruiting (Phase I)
Treatment:	Oseltamivir mesenchymal stem cells

Study Name:	BAttLe Against COVID-19 Using MesenchYmal Stromal Cells (NCT04348461)
Status:	Not yet recruiting (Phase II)
Treatment:	Allogeneic and expanded adipose tissue-derived Mesenchymal stromal cells

Study Name:	Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19 (NCT04362189)
Status:	Active, not recruiting (Phase II)
Treatment:	HB-adMSC

Study Name:	Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients (NCT04535856)
Status:	Completed(Phase I)
Treatment:	Allogeneic mesenchymal stem cell

Study Name:	Therapy for Pneumonia Patients iInfected by 2019 Novel Coronavirus (NCT04293692)
Status:	Withdrawn
Treatment:	UC-MSCs

Study Name:	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19 (NCT04390152)
Status:	Recruiting (Phase I,II)
Treatment:	WJ-MSC

Study Name:	Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation (NCT04397796)
Status:	Recruiting(Phase I)
Treatment:	BM-Allo.MSC

Study Name:	A Phase II Study in Patients With Moderate to Severe ARDS Due to COVID-19 (NCT04780685)
Status:	Recruiting (Phase II)
Treatment:	hMSC

Study Name:	Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS (NCT04494386)
Status:	Recruiting (Phase I,II)
Treatment:	Umbilical Cord Lining Stem Cells (ULSC)

Study Name:	Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS) (NCT04377334)
Status:	Not yet recruiting (Phase II)
Treatment:	MSC

Study Name:	Use of hUC-MSC Product (BX-U001) for the Treatment of COVID-19 With ARDS (NCT04452097)
Status:	Not yet recruiting(Phase I,II)
Treatment:	Human umbilical cord mesenchymal stem cells

Study Name:	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease) (NCT04345601)
Status:	Recruiting (Phase I,II)
Treatment:	Mesenchymal Stromal Cells

Study Name:	Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 (NCT04390139)
Status:	Recruiting (Phase I,II)
Treatment:	Expanded MSC from Wharton Jelly (XCEL-UMC-BETA)

Study Name:	Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan (NCT04492501)
Status:	Completed
Treatment:	Convalescent Plasma|Drug: Tocilizumab|Drug: Remdesivir|MSC

Study Name:	Clinical Use of Stem Cells for the Treatment of Covid-19 (NCT04392778)
Status:	Recruiting(Phase I,II)
Treatment:	MSC Treatment

Study Name:	Safety and Feasibility of Allogenic MSC in the Treatment of COVID-19 (NCT04467047)
Status:	Not yet recruiting (Phase I)
Treatment:	Mesenchymal Stromal Cells infusion

Study Name:	The MEseNchymal coviD-19 Trial: a Pilot Study to Investigate Early Efficacy of MSCs in Adults With COVID-19 (NCT04537351)
Status:	Recruiting(Phase I,II)
Treatment:	Allogeneic mesenchymoangioblast-derived mesenchymal stem cells (MCA-derived MSCs)- (CYP-001)

Study Name:	ACT-20 in Patients With Severe COVID-19 Pneumonia (NCT04398303)
Status:	Not yet recruiting(Phase I,II)
Treatment:	Allogenic human umbilical derived mesenchymal stem cells (ACT-20-MSC), Allogenic human umbilical derived mesenchymal stem cells in conditioned media (ACT-20-CM)

Study Name:	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV) (NCT04361942)
Status:	Recruiting (Phase II)
Treatment:	Mesenchymal Stromal Cells|

Study Name:	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) (NCT03042143)
Status:	Recruiting(Phase I,II)
Treatment:	Human umbilical cord derived CD362 enriched MSCs

Study Name:	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(nCOV) Pneumonia (NCT04269525)
Status:	Recruiting(Phase II)
Treatment:	UC-MSCs

Study Name:	Mesenchymal Stromal Cell Therapy For The Treatment Of Acute Respiratory Distress Syndrome (NCT04447833)
Status:	Active, not recruiting(Phase I)
Treatment:	Mesenchymal Stromal Stem Cells - KI-MSC-PL-205

Study Name:	Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients (NCT04437823)
Status:	Recruiting(Phase II)
Treatment:	Intravenous Infusions of Stem Cells

Study Name:	Safety and Efficiency of Method of Exosome Inhalation in COVID-19 Associated Pneumonia (NCT04602442)
Status:	Enrolling by invitation(Phase II)
Treatment:	Exosome inhalation (EXO 1 inhalation)| (EXO 2 inhalation)

Study Name:	Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia. (NCT04491240)
Status:	Completed(Phase I,II)
Treatment:	Exosome inhalation (EXO 1 inhalation)| (EXO 2 inhalation)

Study Name:	Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS (NCT04333368)
Status:	Active, not recruiting(Phase I,II)
Treatment:	Umbilical cord Wharton's jelly-derived human Mesenchymal Stromal Cells|

Study Name:	MSCs in COVID-19 ARDS (NCT04371393)
Status:	Active, not recruiting (Phase III)
Treatment:	Expanded mesenchymal stromal cells derived from the bone marrow (Remestemcel-L)

Study Name:	Study of Descartes-30 in Acute Respiratory Distress Syndrome (NCT04524962)
Status:	Recruiting(Phase I,II)
Treatment:	RNA-engineered off-the-shelf allogeneic mesenchymal stem cell MSC (Descartes 30)

Study Name:	Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19) (NCT04466098)
Status:	Recruiting(Phase II)
Treatment:	Mesenchymal stromal cells

Study Name:	Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome - Vanguard (NCT04400032)
Status:	Recruiting(Phase I)
Treatment:	Mesenchymal Stromal Cells

Study Name:	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia (NCT04276987)
Status:	Completed(Phase I)
Treatment:	MSCs-derived exosomes

Study Name:	Mesenchymal Stem Cells for the Treatment of Various Chronic and Acute Conditions (NCT04684602)
Status:	Recruiting(Phase I,II)
Treatment:	Human umbilical chord tissue-derived MSC (PrimePro™/ PrimeMSK™)

*data from ClinicalTrials.gov searched on March 6th 2021.

Future directions

Other clinical trials also accentuate the significance and safety of MSCs usage in the treatment of COVID-19 patients with no reporting of any serious adverse events related to MSCs (92-100), although there is a necessity for large randomized multicenter clinical trials in order to determine precise therapeutic potentials of MSC in COVID-19-induced disease (92,93,97). It is also very important to emphasize that MSCs should not be administered in the early period of viral infection because inflammation is very pertinent and advantageous to combat viral infection. “Physiological inflammation” which is very important for control of virus infection and replication, can be abrogated by too much immunosuppression that is induced by inadequate use of MSCs in terms of the time of MSCs administration and their dose (101-104). However, there is the urge to investigate the safety of using human MSCs in long period follow- up. It is well- known that MSCs exhibit potential risks of adverse events during MSC transplantation (105) in CVDs (cardiovascular disease), neurological disease, GVHD (graft- versus host disease), and orthopedics, such as pro-tumorigenic effect, perturbed differentiation capacity, short surviving after implantation, not so amazing improvements, immune response and infection-related mortality (106). Some animal studies reported that MSCs therapy for CVDs can exhibit some adverse events such as proarrhythmic (107) and tumorigenic ability in heart tissue (108) as well as the ability to differentiate into unwanted tissue type (109). Although many studies suggest the usage of MSCs as a treatment in orthopedics, it is important to note that MSCs are able to take part in ectopically forming bone tissue in non-bone tissues, which is better known as heterotopic ossification (HO) (110). Although MSCs are cells with doubtful- advantage in numerous animal studies that

showed MSCs promoted tumor growth and metastasis (111,112), or even suppressed their growth (112), MSCs should be used with caution in clinical studies.

CONCLUSION

All of the effects from MSCs in regards to immune system, regeneration, neoangiogenesis, antiviral capacity, ubiquitous presence in almost all postnatal tissues and ease of transplantation make MSCs potentially excellent choice against Covid-19. However, MSCs therapy is a double edged sword, and if not applied correctly and responsibly can worsen clinical condition of patients and lead to adverse effect. So, in spite the data from small number of completed clinical trials that displayed MSCs therapy as safe and beneficial and on the other hand, dozens of ongoing clinical trials, final conclusion is yet to be brought.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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