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Chapter

Mesenchymal Stem Cells and Extracellular Vesicles: An Emerging Alternative to Combat COVID-19

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Abstract

The global SARS-CoV-2 outbreak has been accompanied with severe socio-economic and health burdens that will ripple through history. It is now known that SARS-CoV-2 induces a cytokine storm that leads to acute respiratory distress syndrome and systemic organ damage. With no definitive nor safe therapy for COVID-19 as well as the rise of viral variants the need for an urgent treatment modality is paramount. Mesenchymal stem cells (MSCs) and their extracellular vesicles (EVs) have long been praised for their anti-viral, anti-inflammatory and tissue regenerative capabilities. MSCs and their EVs are now being studied for their possible use as a treatment modality for COVID-19. In this review we explore their capabilities and outline the evidence of their use in ALI, ARDS and COVID-19.

Keywords: COVID-19, Coronavirus, SARS-CoV-2, Mesenchymal stem cells, Extracellular vesicles, Exosomes, Regenerative medicine

1. Introduction

Over the past several months, the world has had to endure another global outbreak, the likes of which have not been seen since the Spanish flu pandemic of 1918 [1]. Coronavirus disease 2019 (COVID-19) caused from the virus now known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is understood to undergo human-to-human transmission by respiratory droplets and known to cause a broad range of symptoms contributing to its rapid spread [2]. As of February 14, 2021, there have been over 109 million reported cases and over 2.39 million deaths worldwide, with the United States having over 27.6 million reported cases along with over 484,000 deaths [3]. As cases continue to accumulate and cause significant strain on medical resources and society, the need for an urgent, effective and safe treatment is paramount. Current measures to curb the COVID-19 pandemic revolve around a broad range of pharmaceutical remedies and the distribution of a vaccine [4]. With vaccines being a prophylactic measure, current treatment options being unproven, non-definitive and suboptimal, and the emergence of new viral strains, attention needs to be placed on alternatives.

Investigations have identified that the majority of Intensive Care Unit (ICU) patients with COVID-19 have high plasma levels of granulocyte colony-stimulating factor (GCSF), tumor necrosis factor-alpha (TNF-α), interferon gamma inducible protein-10 (IP-10), monocyte chemoattractant protein-1 (MCP1) and macrophage inflammatory protein 1-alpha (MIP1A) [5]. These factors have been shown to be interconnected with the recruitment of proinflammatory cells and the production of a cytokine storm. A cytokine storm is a large and abrupt increase in proinflammatory cytokines that is suggested to be the main cause of acute respiratory distress syndrome (ARDS) and other severe pathophysiological effects seen in COVID-19 patients [6]. The cytokine storm induces a vast signaling cascade that recruits immune cells such as humoral B-cells, T-cells, and macrophages (MOs) as well as shifts most of these cells into a proinflammatory state [7]. Interestingly, clinicians have found that through the attenuation of the cytokine storm with mesenchymal stem cells (MSCs) patients have been able to recover even in severe cases [6].

MSCs have been successfully and safely used to treat pneumonia, acute lung injury (ALI), and ARDS in the past [8, 9]. Their effectiveness has been attributed to their ability to be directly antiviral, immunomodulate, induce tissue regeneration, inhibit apoptosis/fibrosis and clear alveolar fluid [10]. MSCs have also been shown to aggregate within the lung microvasculature when intravenously (IV) administered, affecting the local environment in an efficient manner [11]. MSCs are able to be so affective by inhibiting the function, recruitment and activation of MOs, dendritic cells (DCs), T-cells and B-cells, subsequently reducing proinflammatory cytokines such as interleukin-6 (IL-6) and TNF-α among others [12]. MSCs have also been shown to differentiate into a multitude of tissues, and secrete cytokine (CKs), growth factors (GFs) and extracellular vesicles (EVs), all of which play an integral part in their mechanism of action [13, 14]. MSCs can be derived from various types of tissues from both allogenic and autogenic sources. These tissues include: adipose, bone marrow, placenta, amniotic fluid, umbilical cord, and umbilical cord-derived Wharton jelly [15–18].

Extracellular vesicles (EVs) are composed of hypoimmunogenic properties that resemble amphipathic structures such as the lipid bilayer that allow the vesicles to migrate rapidly as well as harmlessly towards the target organs, without the occurrence of blood flow coagulations [19]. EVs can be obtained from any MSC source and act in a paracrine manner delivering enclosed biological molecules such as DNA, RNA, proteins, and lipids [20]. These EVs include microvesicles (MVs) and exosomes and provide microenvironment that further decreases inflammation, promotes tissue regeneration, and overall enhance the effects of MSCs [21].

In the face of the COVID-19 pandemic, scientists rush to generate and successfully distribute viable therapeutics and vaccines. Due to the urgent need and limitations with the current options, MSCs and their EVs may be a viable option. The cooperative mechanism of actions of MSCs and their EVs that include their ability to be directly antiviral, immunomodulate, induce tissue regeneration, inhibit apoptosis/fibrosis and clear alveolar fluid as well as sequester into the lung microvasculature make them an exciting alternative therapy.

2. Current treatments and therapeutic status

The scientific and medical community have been quick to adapt and have explored a plethora of therapeutic approaches. Treatments originally known for their efficacy against prior viral infections such as corticosteroids, and convalescent plasma (CP) have been repurposed for SARS-CoV-2 [22–24]. Recent novel treatments and vaccines have emerged such as the monoclonal antibodies casirivimab and imdevimab (REGN-COV2) and the Pfizer and Moderna mRNA vaccines [4]. Unfortunately, these current treatments have limitations and potentially dangerous adverse effects and although vaccinations are an effective preventive measure, they do not treat COVID-19 [4]. Considering these limitations and emergence of new viral strains there is an urgent need for a safe and effective therapeutic option [25].

Corticosteroids have long been used due to their immunomodulation and they have been a therapeutic option in many autoimmune diseases and in conditions such as ARDS [26]. Although they have a long history, their use in COVID-19 still remains controversial. Data from their prior use in viral infections indicated that they were associated with increased mortality, longer hospitalizations and increased tendency for mechanical ventilation [27–29]. In addition, observational studies in patients with SARS and MERS suggested that the use of corticosteroids delayed viral clearance, increased rates of secondary infections and had somewhat severe adverse effects of psychosis, hyperglycemia, and avascular necrosis [27, 30, 31]. Thus, similar adverse effects and outcomes can be expected in pateitns with COVID-19. Passive immunity with convalescent plasma has also been used and has been shown to improve the survival rate of patients with prior viral epidemics [32]. CP is a therapy that utilizes artificial passive immunity from pooled plasma of patients with resolved SARS-CoV-2 infections [32–33]. Although the science is sound, there are several limitations associated with CP [34]. The efficacy of CP is highly reliant on the time of its administration, as it seems to only be beneficial to patients a week after infection when viremia is at its highest [35]. Additionally, the effect of CP on SARS-CoV-2 is highly dependent on the neutralizing antibody titer which has to be >1:160, seen 12 weeks after onset of disease [34].

CP infusions can also have severe adverse effects such as anaphylaxis, transfusion-related ALI and cardiac overload. Additionally, there are several limitations to the collection of CP such as age, weight, state of health, and informed consent all of which make CP a limited treatment option to the current pandemic [34].

Recently attention have been geared towards novel treatments such as REGN-COV-2, which is a cocktail of two human antibodies (casirivimab and imdevimab) using both transgenic mice and B cells from recovered COVID-19 patients [36]. REGN-COV-2, although approved by the FDA, has specific criteria that have to be met before a patient can receive it. REGN-COV-2 is authorized for use in mild to moderate COVID-19 in adults, pediatric patients (12 years or older) with a weight of 40 kg and who have had a positive SARS-CoV-2 test with a high risk of progressing to severe COVID-19. Patients are not indicated for treatment if they are hospitalized, require supplemental O2, and/or currently using chronic supplemental O2 due to another underlying condition [37].These criteria are limitations and important obstacles associated with REGN-COV-2.

Currently, the emergence of new vaccines against SARS-CoV-2 have drawn much excitement. There are several vaccine candidates that are subdivided into five general categories: protein subunit, virally vectored, nucleic acid (mRNA), inactivated and live attenuated [23]. The Pfizer and Moderna vaccines utilize nucleic acids (mRNA) and are composed of a lipid particle with nucleoside-modified RNA, encoding for the S protein [38]. These two vaccines have the most data and have been the most widely used [4]. Although the data suggest that these vaccines are 95% effective at preventing SARS-CoV-2 infections they fail to actively treat disease once patients develop symptoms leaving a substantial amount of the population without a safe and efficacious treatment [38, 39].

Considering the limitations and adverse effects associated with current treatments as well as vaccines being only a preventative measure the need to develop a safer and more efficacious therapy is vital. MSCs and their EVs lack severe adverse effects and studies suggest they have high efficacy making them a potential candidate for COVID-19 treatment. MSCs and their EVs immunomodulatory effects and regenerative capabilities make them an exciting new option combating COVID-19 [12].

3. Mesenchmal stem cells (MSCs)

3.1 Origins of MSCs

In 1968, Friedenstein et al. isolated stem cells from the bone marrow (BMSCs) of mice [40]. The study showed that BM contained clonogenic progenitor cells and adherent cells similar to fibroblasts, termed as a colony forming unit-fibroblast [40]. These cells were found to have the ability to differentiate into chondrocytes, osteocytes, osteoblasts and adipocytes *in vitro* [40]. In 1991, Arnold Caplan changed the terminology to "Mesenchymal Stem Cell", due to their similarities with stem cells from mesodermal origins in embryonic tissues [41]. Later in 2017 Caplan suggested that the name MSC be alerted to "medicinal signaling cells" to accurately reflect their *in vivo* abilities of acting as an in situ medication [42]. Currently, "Mesenchymal Stem Cell" is the most common nomenclature, however Caplan did manage to emphasize their function.

With the variations in nomenclature as well as controversy surrounding their characteristics, the need for an official and concise criterion was needed. In 2006, The International Society of Cellular Therapy (ISCT) established parameters with four minimum criteria should be used to define MSCs. The criteria were quickly accepted by the medical community and are the status quo currently [43, 44].

The ISCT criteria for MSCs: 1) Plastic adherence in standard culture condition, 2)Positive expression (≥95%) of CD105, CD90, CD73 cell surface antigens, 3) Low expression (≤ 2%) of CD45, CD34, CD14, CD11b, CD79, CD19 and HLA-DR cell surface antigens, 4)Potential to differentiate into osteoblasts, adipocytes and chondrocytes in vitro.

3.2 MSC sources

MSCs can be differentiated by either being totipotent, pluripotent, multipotent, or unipotent [45, 46]. Totipotent MSCs for example, can form both embryonic and extraembryonic structures and proliferate indefinitely into cell types from all three embryonic germ layers [45]. Multipotent MSCs or adult stem cell are the most widely used and can differentiate into cell types from their respective source tissue [46]. MSCs can then be further subdivided by their source tissue. Two of the most common sources of MSCs are BM and adipose tissue. These are autologous sources that have been studied substantially and have the most associated data. Both of these sources require the patient to undergo an invasive procedure and are considered the first and second most reputable sources respectively for MSCs [47, 48]. Allogenic birth derived tissues such as umbilical cord (UC), UC-derived Wharton's jelly, amniotic fluid and placenta are also viable sources for MSCs. These sources have advantages in relation to their availability, lack of invasiveness, and presence of more pluripotent cells [12, 49, 50]. However, these sources have less data and do not have such an extensive history of use in comparison with allogenic sources.

3.3 MSC's mechanisms of action

MSCs have a long history of use in the treatment of viral lung infections, pneumonia, ALI and ARDS [6, 12]. This prior literature has been used to support their current use in COVID-19. Studies have showed that when IV administered, MSCs have specific and optimal mechanisms of action for the treatment of COVID-19. MSCs are able to evade the body's immune system and accumulate within the lung microvasculature enabling them to act locally [51, 52]. They have direct anti-viral activity, as well as anti-inflammatory, anti-apoptotic, and anti-fibrotic properties [47]. MSCs have also been touted for their ability to induce tissue regeneration, transdifferentiate into cells and produce EVs [53].

IV infusion is the one of the most commonly used route for MSC delivery with hundreds of clinical trials showing evidence of its safety [54]. A systematic review and meta-analysis by Lalu et al. summarized the results of IV administered MSCs in over 1000 patients [55]. The review indicated that there were no associated adverse events within any of the studies and no patient developed any organ system complications, infusion related toxicity, infections nor death [55]. In a study by Hwa Lee et al. IV infused MSCs were shown to accumulate into emboli within the lungs with no negative physiological effects [51]. In fact, the cells were noted to secrete TSG-6, a potent anti-inflammatory, the effects of which were amplified due to the sequestration within the lung [51]. As immune privileged cells, MSCs can be used either allogenically or autologously, due to their low levels of class I major histocompatibility complex (MHC) and class II MHC [52]. MSCs have also been shown to lack the associated co-stimulatory molecules (B7–1, B7–2, CD40, CD80 and CD86) needed to activate antigen presenting cells and the inflammatory process [52]. With these factors in mind MSCs are primed to act locally within the lungs to effectively and efficiently carry out their functions.

3.4 MSCs and immunomodulation

3.4.1 Innate immune response

In addition to the therapeutic potential of MSCs in regenerative medicine, for which they been most known for, they have also shown promising results in the regulation of immune responses [47]. MSCs through their ability to secrete various soluble factors are able to suppress both the innate and adaptive immune responses [47].

NOs and MOs both play a vital role in the innate immune response with DCs being the gate keeper to the adaptive response [56]. MOs can be subdivided into M1 or M2 subtypes each with their own distinct functions [57]. The M1 subtype are well known to be classically activated and responsible for phagocytosis, antigen presentation to DCs and secretion of pro-inflammatory cytokines such as TNF-α, IL-1α, IL-β, IL-6, IL-12 ultimately promoting a Th1 response [57]. The M2 subtype are known for their high secretion of IL-10 promoting an anti-inflammatory Treg and Th2 response along with inducing tissue remodeling and wound repair [57]. MSCs have been shown to secrete prostaglandin E2 (PGE2) and induce a switch in the MO population into an M2 subtype as well as substantially decreasing levels of IL-1β and IL-6 [58]. Wahnon et al. further elucidated this anti- inflammatory switch by reporting that the transcription factor signal transducer activators of transcription-3 (STAT3) activated in MSCs through cell to cell interactions between MOs produced IL-10 and promoted an M2 phenotypic switch [59]. NO activation and function have also been shown to be inhibited by MSCs. NOs are known to be a key component of the innate immune response and in pathophysiology of ARDS. NOs when activated release harmful reactive oxygen species, superoxide anions, peroxidases and proteases that lead to diffuse alveolar damage, and accumulation of alveolar fluid that underlie ARDS [60]. MSCs have been shown to secrete a potent antioxidant enzyme, SOD3 that has been shown to decrease the release of peroxidases, proteases and the oxidative burst of NOs [61]. They have also able to directly engulf dead NOs through ICAM-1 thereby further inhibiting release of their toxic contents [61]. Secretion of tumor necrosis factor-inducible gene 6 protein (TSG-6) via MSCs has also been shown to bind to IL-8 and CXCL8, inhibiting further migration, extravasation and recruitment of NOs [62].

Immature DCs patrol peripheral tissues for foreign antigens and are activated by cytokines (TNF-α, IL-1β, and IL-6) from M1 MOs [63]. Once immature DCs are activated they mature into conventional DCs and present their cleaved epitopes on their HLA complexes, inducing a pro-inflammatory Th1 and Th17 response [63]. PGE2 from MSCs has been shown to decrease CD38, CD80, CD86, IL-6, and IL-12 thereby decreasing DC function and pro-inflammatory T cell responses [64]. Preventing the maturation of these conventional DCs is vital in order to prevent this T cell response and the associated pro inflammatory state. Furthermore, DC maturation was inhibited by the inactivation of MAPK and NF-κB signaling cascades via the secretion of the TSG-6 [65]. In a study by Chen et al. DC maturation was induced from a conventional (pro-inflammatory) DC into a plasmacytoid DC population by PGE2 from MSCs, shifting the T cell population into a Th2 (anti-inflammatory) subset [66]. In addition, specific miRNAs (miR-21-5p, miR-142-3p, miR-223-3p, miR-126-3p) within EVs of MSCs have shown to further attenuate the DC maturation process [67].

3.4.2 Adaptive immune response

MSCs role in modulating T and B cell responses begins with their attenuation of MO and DC functions and continues with PGE2 from MSCs. PGE2 has been proven to increase the production of cAMP in T cells down regulating IL-2, and the IL-2 receptor as well as inhibiting the release of intracellular Ca2+ resulting in the direct inhibition of T cell activation [68]. PGE2 has also been shown to inactivate T cells via the hydrolysis of phosphatidylinositol, diacylglycerol and inositol phosphate [68]. In addition, PGE2 promotes a Th2 and a T reg shift in the T cell population overall influencing immunosuppression and an anti-inflammatory response [13, 69]. MSCs through their secretion of IDO, PGE2, TGF-β1, and Hepatocyte growth factor (HGF) have also been shown to induce G0/G1 cell cycle arrest in T cells and B cells [70, 71]. Nitric oxide (NO) from MSCs has shown to play a role in this by suppressing the phosphorylation of signal transducer and activator of transcription 5, thereby inhibiting TCR activated T cell proliferation and production of cytokines [72]. Studies have also suggested that MSCs can induce T cell and B cell apoptosis through direct cell to cell contact. Utilizing their interactions with the Fas/Fas ligand, TNF-related apoptosis-inducing ligand/death receptor signaling and programed death ligand-1/programmed death-1 pathways have shown to promote T and B cell apoptosis [73, 74]. This process was especially seen in CD4+, CD8+ and Th17 cells with a synergistic increase in T reg cells [75]. The down regulation of CXCR4, and CXCR5 via MSCs has shown further evidence of inhibiting B cell migratory abilities towards chemoattractant agents such as CXCL12 and CXClL13 [74]. Lastly, GM-CSF from MSCs have been recognized as having inhibitory actions on the production of CXCR4, CXR5, IL-6, and IL-7 while having no negative effects on IL-4 and IL-10 from B cells with a net anti-inflammatory affect [74].

3.5 MSC's additional mechanisms of action

Studies have shown that MSCs have been effective in inhibiting the viral replication of influenza, hepatitis B, herpes simplex, cytomegalovirus and the measles virus [76–79]. In a study by Khatri et al. MSCs had the ability to inhibit viral replication, shedding and lung damage in a porcine model with influenza induced pneumonia [76]. MSC-derived EVs were shown to be the key players in this process via their transfer of RNAs to virus infected epithelial cells. Lung epithelial cell apoptosis, hemagglutination and viral shedding were all significantly reduced in the study [76]. MSC-derived EVs have also demonstrated to decrease pro-inflammatory cytokine while increasing IL-10 and increase T regs [76]. IDO via MSCs has also been shown to directly decrease viral replication in most of the viruses that have been studied [76–79].

The secretion of various CKs, GFs and EVs have been reported to promote tissue regeneration and inhibit apoptosis, tissue fibrosis and alveolar fluid accumulation. As previously elucidated, M2 MOs promote anti-inflammatory Treg and Th2 responses while inducing tissue remodeling and wound repair [57]. Direct tissue regeneration from MSCs has been attributed to keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF) all of which have also been known to contribute to the in decrease collagen build up and fibrosis [80, 81]. In an in vivo bleomycin-induced pulmonary fibrosis model, Aguilar et al. noted that KGF was the key factor in the inhibition of collagen accumulation, promoting endogenous type II pneumocyte proliferation and overall attenuation of lung damage [82]. Previous studies have also further characterized KGF as being a potent factor in lung epithelial cell proliferation, while simultaneously being capable to increase matrix metalloproteinase-9 (MMP-9), IL-1RA and promoting clearance of apoptotic cells and inhibiting fibrosis [82, 83]. Gazdhar et al. used an in vivo bleomycin induced lung injury model in which he found that MSC-derived HGF was able to inhibit lung fibrosis and induce alveolar epithelial repair by decreasing TGF-B and α-smooth muscle actin expression [84]. The positive effects of HGF was further studied by Wang et al. who showed that MSC-derived HGF was responsible for increasing endothelial cell proliferation, intercellular junction proteins (VE-cadherin and occludin), and IL-10 while decreasing IL-6 and overall apoptosis [85]. MSC-derived VEGF and HGF have also shown to be able to stabilize Bcl-2 and inhibit pro-apoptotic factors hypoxia-inducible factor-1α protein, Bnip3 and CHOP contributing to their anti-apoptotic and anti-fibrotic effects [86]. In addition to the intracellular stabilization via these aforementioned GFs, factors such as MSC derived aniopoietin-1, and EVs have shown to induce alveolar fluid clearance within the lungs adding in their therapeutic benefits in ARDS [87]. In a study by Zhu et al. using an E.coli endotoxin-induce ALI model, MSC-derived EVs showcased their ability to transfer mRNA encoding for KGF inhibiting NOs, pulmonary edema and lung permeability [88].

4. Extracellular vesicles

Extracellular vesicles (EVs) are currently being studied as potential therapeutic agents for immune related pathologies due to their immunomodulatory and regenerative properties [89]. Interest in EVs has grown due to their ability to have similar therapeutic effects as MSCs as a cell free therapy [89]. What was once viewed as cellular waste products, may now have the potential to treat one of the largest natural disasters in modern history that is the COVID-19 pandemic.

The field of EVs has grown significantly in the recent years leading to the formation of the International Society for Extracellular Vesicles (ISEV) [89]. ISEV defines EVs as particles naturally released from a cell that are delimited by a lipid bilayer and cannot replicate [90]. EVs are further subclassified as exosomes (40-120 nm), microvesicles (50-1000 nm), and apoptotic bodies (500-2000 nm). Both microvesicles and apoptotic bodies bud-off directly from the cellular membrane and participate in two distinct cellular pathways: apoptotic bodies are products of cell mediated death whereas microvesicles are involved in paracrine communication [89, 91]. Exosome biogenesis, however, differs greatly in that it involves cell membrane invagination and formation of an intraluminal vesicles that undergoes modification in what is called a multivesicular body (MVB) [92]. Once modifications are performed, the MVB fuses with the cell membrane and the ILV's are secreted into the extracellular space as exosomes [92].

Once secreted, EV's carry a variety of nucleic acids, proteins, and lipids that can regulate or alter a plethora of biological processes through effects on cell receptors, adhesion molecules, cytokines, and other cell signaling molecules [89, 93–96]. They have attracted significant attention for their ability to inhibit tumorigeneses, suppress immune responses, promote tissues repair, and have therapeutic effects on neurological disease [96]. A recent study by Schultz et al. performed bioinformatic analysis of mRNA and miRNA cargo of EV's using Gene Expression Omnibus (GEO) database and miRWalk 3.0 servers. The study found that 266 miRNA's within exosomes have the ability to attenuate cell death by inhibiting TNF-a, IFN-y, JAK2, and JAK1 among others. Similarly, 148 miRNA's were identified with 1 or 2 targets of molecules involved in the intrinsic and extrinsic coagulations cascade pathways [97]. Continually, EV's also have the capability of replenishing glycolytic enzymes such as glyceraldehyde 3-phosphate dehydrogenase (GAPDH), phosphoglycerate kinase (PGK), phosphoglucomutase (PGM), enolase (ENO), and pyruvate kinase m2 isoform (PKm2), and phosphorylated PFKFB3, all of which are involved in the production of glycolytic ATP. It was proposed that secretions of these enzymes can reduce levels of reactive oxygen species and consequently halt cellular death [96]. In addition, matrix metalloproteinase (MMP)-9, vascular endothelial growth factor (VEGF), extracellular and matrix metalloproteinase inducer (EMMPRIN) have also been found within exosomes further postulating their regenerative effects through angiogenesis stimulation and tissue repair [96].

In preclinical trials, EV's have already demonstrated their immunomodulatory capabilities. In a study by Monsel et al. [98] on pneumonia induced mice, EV's reduced neutrophils and macrophages by 73% and 49% respectively, while decreasing edema and permeability of the endothelial-epithelial barrier to protein [99]. In fact, a recent study demonstrated that EV's reduce levels of inflammatory interleukins: IL-8, IL-6, IL-17 and TNF-α, when transferring anti-apoptotic miR-21-5p to target cells which resulted in reduced edema and lung dysfunction [100]. Additionally, EV's have also demonstrated their efficacy against acute lung injury (ALI) through downregulation of TLR/NF-κB signaling in rat models [101]]. A recent study assessed the safety and efficacy of EVs on patients with severe COVID-19 infections. 24 patients were recruited under the specified trial criteria and followed for 14 days [102]. In addition to not having any notable adverse effects to the 15 mL IV dose of exosomes, the experimental group exhibited lower neutrophil count, c-reactive protein, ferritin, and D-dimer indicating an immunomodulatory effect [102]. Additionally, the overall survival rates were 83% with 17/24 patients fully recovered and 3/24 in stable conditions [102]. The study actively demonstrated EVs ability to safely attenuate the cytokine storm associated with severe COVID-19 infections. To fully appreciate the impact of EVs on COVID-19, further studies should be developed. As of February 18, 2021, applying the search word "exosomes" or "extracellular vesicles" and "COVID-19" on clinicaltrials.gov, results in 9 and 5 listed clinical trials, respectively. One of these trials, (NCT04491240) evaluated the safety and efficacy of exosome inhalation in SARS-CoV-1 pneumonia. Although results are published in c linicaltrails.gov, publication of the article is pending. The same experiment, however, has been approved for phase 2 and is currently enrolling participants (NCT04602442).

The field of EV's continues to show increasing promise as a therapeutic in the battle against COVID-19 based on their ability to carry a variety of cellular and nuclear components in a stable and hypoimmunogenic bilayer [6, 19].

5. MSCs and COVID-19

Due to the mechanisms of action of MSCs as well as their success as a therapy in ALI and ARDS, MSCs have attracted the attention now for their possible use in COVID-19. Leng et al. conducted one of the first studies exploring the case for MSCs in COVID-19 [103]. Ten adult patients with a positive real-time reverse transcription polymerase chain reaction assay and that meet the clinical classification for COVID-19 by the National Health Commission of China were enrolled in the study. Of the ten patients seven patients were in the treatment group, of those seven one was categorized as critically severe type, four were severe, and two were common types. MSCs were administered via IV infusion with 1 x 106 cells per kilogram and patients were assessed for a 14 day period. Two-four days after infusion all patients with symptoms of a high fever, weakness, shortness of breath and low oxygen saturation resolved. None of the patients experienced any infusion-related nor allergic reactions with no delayed hypersensitivity reactions or infections. Three of the patients that subsequently recovered were discharged 10 days after treatment with one of them being characterized as a severe subtype. In regard to the patient having a critically severe type of COVID-19, their C-reactive protein (CRP) decreased from 19.0 g/L to 10.1 g/L, and their oxygen saturation (SaO2) increased from 89–98% without supplemental O2. The critically severe patient also had significant improvements in lymphopenia, as well as in indicators of liver, myocardial and kidney damage/disease (aspartic aminotransferase, creatine kinase and myoglobin). Chest CT imaging with the characteristic ground-glass opacity and pneumonia infiltration were also reduced by the 9th day after MSC infusion. Overall levels of pro-inflammatory CD4+/CD8+ T cells, TNF-α and conventional DCs all decreased while IL-10, VEGF, HGF and TGFβ increased, promoting a tissue regeneration state. It was also concluded that MSCs were ACE2R and TMPRSS2 negative, theoretically making them immune from possible SARS-COV-2 infection [103]. Additionally, evidence by Sanches-Guijo et al. indicated similar results [104]. Adipose-derived MSCs were used as a treatment for 13 COVID-19 patients. There were no adverse events in the MSC treatment group with no worsening of respiratory or hemodynamic parameters. Clinical improvement was seen in 70% of the patients, seven of them extubated and discharged, and two showing signs of improvement in their ventilatory and radiological parameters, two resulting in fatalities and the rest of the patients in stable condition. Overall levels of CRP, IL-6, ferritin, and D-dimer were decreased [104].These positive effects of MSCs in COVID-19 were further elucidated by Tang et al., the study included two patients with COVID-19 which received three separate IV infusions of menstrual blood derived MSCs [105]. The first patient (Patient 1) was a 37 year old woman with a past medical history of hypertension. Patient 1's levels of CRP, TNF-α, and IL-6 decreased while their SaO2 dramatically increased from 98%

on 100% fraction of inspired O2 (FiO2) to 97% SaO2 on 55% FiO2. Initial CXR findings revealed large, patches of high density lesions in bilateral lungs that resolved with treatment along with viral RNA testing. Patient 2 was a 71 year old male that similar improvements in inflammatory markers, SaO2 and CXR findings [105].

Recently, a study conducted by Shi et al. used UC-derived MSCs as a therapeutic in 101 patients diagnosed with severe COVID-19 [106]. The study was a double-blind, placebo-controlled phase 2 trial with 101 patients randomized in a 2:1 ratio with sixty six patients, with one patient withdrawing, in the treatment group and 35 in the placebo group. Overall chest CTs, age, sex, BMI, and onset of symptoms matched between the groups. The occurrence of adverse events during the study was similar between the treatment (55.38%) and the placebo group (60%) with none directly related to the MSCs. Three IV infusions of UC-derived MSCs with 4 x 107 cells per infusion were administered. High resolution chest CT images were assessed using both radiologist and artificial intelligence software to estimate the total lesion proportion (TLP) via the Hodges-Lehmann estimator of the entire lung. The median change in the TLP was −19.40% in the treatment group −7.30% in the placebo group with the overall difference of −13.31%. Solid lesions were found to decrease by −57.70% in the treatment group with an overall decrease in the ground-glass lesions. A 6-minute walk test (6-MWT) was used to assess the restoration of lung function and reserve capability in both groups. The median 6-MWT was 420 meters in the MSC treatment group in comparison with 403 meters in the placebo group [106]. In a similar study using UC-MSCs for COVID-19, Lanzoni et al. conducted a double-blind, phase 1/2a, randomized controlled trial [107]. Twenty-four patients hospitalized for COVID-19 were randomized 1:1 into either the treatment or control group. Two infusions of UC-derived MSCs with 100 ± 20 x 106 MSCs in each were administered. There were two serious adverse events (SAEs) observed in the treatment group while the control group had 16 SAEs, the intervention was deemed safe as it did not lead to an increase in specified infusion related AEs. Overall, the survival rate in the treatment group was far greater than in the control group with 91% of subjects in the treatment group surviving 31 days post first infusion in comparison with 42% in the control group. The time of recovery was also shorter for the MSC group, with a hazard ratio for recovery in the control group vs. the MSC group of 0.29 indicating a lower rate of recovery in the control group. Concentrations of GM-CSF, IFN- γ, IL-5, IL-6, IL-7, TNF-α, TNF-β, were also statistically decreased in the MSC treatment group in comparison with control [107].

With the current supporting data surrounding the use of MSCs in COVID-19 as well as their historical efficacy in lung injury models the case for their use on a compassionate basis can be made. In the future more randomized, controlled, multi-centered clinical trials are needed in order to increase the knowledge of the use of MSCs in COVID-19.

6. Ongoing clinical trials

Clinical trials that utilize MSCs and EVs and that are registered on ClinicalTrials.gov can be seen in **Table 1**. and **Table 2** respectively. The data from current studies are promising and promotes the use of MSCs and EVs as a possible treatment for COVID-19. However, more multi-center, controlled, randomized clinical trias are needed to further solidify the use of MSCs and EVs in COVID-19.

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Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04313322	Wharton's Jelly Mesenchymal stem cells	Phase I; N = 5	Clinical outcome (Time Frame: 3 weeks); CT Scan (Time Frame: 3 weeks); RT-PCR results (Time Frame: 3 weeks)	Recruiting	Jordan
NCT04473170	Autologous Non-Hematopoietic Peripheral Blood Stem Cells	Phase I/II; N = 146	Adverse reactions incidence (Time Frame: Day 0–28); Rate of mortality within 28-days (Time Frame: Day 0–28); Time to clinical improvement on a seven-category ordinal scale (Time Frame: Day 0–28)	Completed	United Arab Emirates
NCT04428801	Autologous adipose-derived stem cells	Phase II; N = 200	Tolerability and acute safety of AdMSC infusion by assessment of the total number of AEs/SAEs related and non-related with the medication (Time Frame: 6 months); The overall proportion of subjects who develop any AEs/SAEs related and non-related with the AdMSC infusions as compared to the control group (Time Frame: 6 months); COVID-19 incidence rates in both the study and control groups (Time Frame: 6 months)	Not yet recruiting	USA
NCT04444271	Bone marrow derived Mesenchymal stem cells		Overall survival (Time Frame: 30 days post intervention)	Recruiting	Pakistan
NCT04416139	Umbilical Cord Mesenchymal stem cells	Phase II; N = 10	Functional Respiratory changes: PaO2/FiO2 ratio (Time Frame: 3 weeks); Clinical cardiac changes: Heart rate per minute (Time Frame: 3 weeks); Clinical Respiratory Changes: Respiratory rate per minute (Time Frame: 3 weeks); Changes in body temperature (Time Frame: 3 weeks)	Recruiting	Mexico
NCT04486001	Adipose-derived allogeneic Mesenchymal stem cells	Phase I; N = 20	Frequency of all adverse events (Time Frame: Through study completion, an average of three months); Frequency of infusion related serious adverse events (Time Frame: 6 hours post infusion); Frequency of serious adverse events (Time Frame: Through study completion, an average of three months)	Recruiting	USA
NCT04336254	Allogeneic human dental pulp mesenchymal stem cells	Phase I/II; N = 20	Time to Clinical Improvement (Time Frame: 1–28 days)	Recruiting	China

Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04565665	Cord Blood-Derived Mesenchymal stem cells	Phase I; N = 70	Incidence of composite serious adverse events (Pilot) (Time Frame: Within 30 days of the first mesenchymal stem cell (MSC) infusion); Patients alive without grade 3, 4 infusional toxicity (Phase II) (Time Frame: At day 30 post MSC infusion); Patients alive with grade 3 or 4 infusional toxicity (Phase II) (Time Frame: At day 30 post MSC infusion); Patients not alive (Phase II) (Time Frame: At day 30 post MSC infusion)	Recruiting	USA
NCT04429763	Umbilical cord derived Mesenchymal stem cells	Phase II; N = 30	Clinical deterioration or death (Time Frame: 4 weeks)	Not yet recruiting	Colombia
NCT04315987	Mesenchymal stem cells (source not defined)	Phase II; N = 90	Change in Clinical Condition (Time Frame: 10 days)	Not yet recruiting	Brazil
NCT04456361	Mesenchymal stem cells derived from Wharton Jelly of Umbilical cords	Early Phase I; N = 9	Oxygen saturation (Time Frame: Baseline, and at days 2, 4 and 14 post-treatment)	Active, not recruiting	Mexico
NCT04366323	Allogenic and Expanded Adipose Tissue-Derived Mesenchymal stem cells	Phase I/II; N = 26	Safety of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Adverse Event Rate (Time Frame: 12 months); Efficacy of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Survival Rate (Time Frame: 28 days)	Active, not recruiting	Spain
NCT04348435	Allogeneic Adipose-derived Mesenchymal stem cells	Phase II; N = 100	Incidence of hospitalization for COVID-19 (Time Frame: week 0 through week 26); Incidence of symptoms associated with COVID-19 (Time Frame: week 0 through week 26)	Enrolling by invitation	USA
NCT04611256	Adipose tissue derived-Mesenchymal stem cells	Phase I; N = 20	Change form baseline in Arterial oxygen saturation (Time Frame: up to 25 days); Change form baseline in Arterial oxygen saturation (Time Frame: up to 25 days); Days to clinical improvement (Time Frame: up to 25 days)	Recruiting	Mexico

Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04625738	Wharton's Jelly Mesenchymal stem cells	Phase II; N = 30	PaO2/FiO2 ratio (Time Frame: day 10)	Not yet recruiting	France
NCT04252118	Umbilical cord derived Mesenchymal stem cells	Phase I; N = 20	Size of lesion area by chest radiograph or CT (Time Frame: At Baseline, Day 3, Day 6, Day 10, Day 14, Day 21, Day 28); Side effects in the MSCs treatment group (Time Frame: At Baseline, Day 3, Day 6, Day 10, Day 14, Day 21, Day 28, Day 90 and Day 180)	Recruiting	China
NCT04273646	Human Umbilical Cord Mesenchymal stem cells	Not Applicable; N = 48	Pneumonia severity index (Time Frame: From Baseline (0 W) to 12 week after treatment); Oxygenation index (PaO2/FiO2) (Time Frame: From Baseline (0 W) to 12 week after treatment)	Not yet recruiting	China
NCT04349631	Autologous Adipose-derived Mesenchymal stem cells	Phase II; N = 56	Incidence of hospitalization for COVID-19 (Time Frame: Week 0 through week 26); Incidence of symptoms for COVID-19 (Time Frame: week 0 through week 26)	Active, not recruiting	USA
NCT04346368	Bone Marrow-derived Mesenchymal stem cells	Phase I/II; N = 20	Changes of oxygenation index (PaO2/FiO2) (Time Frame: At baseline, 6 hour, Day 1, Day 3, Week 1, Week 2, Week 4, Month 6); Side effects in the BM-MSCs treatment group (Time Frame: Baseline through 6 months)	Not yet recruiting	China
NCT04382547	Allogenic-pooled olfactory mucosa-derived Mesenchymal stem cells	Phase I/II; N = 40	Number of cured patients (Time Frame: 3 weeks)	Enrolling by invitation	Belarus
NCT04288102	Umbilical cord derived Mesenchymal stem cells	Phase II; N = 100	Change in lesion proportion (%) of full lung volume from baseline to day 28. (Time Frame: Day 28)	Completed	China
NCT04629105	Mesenchymal stem cells (source not defined)	Phase I; N = 70	Incidence of Treatment-Emergent Serious Adverse Events (Time Frame: Within 4 weeks after treatment); Number of Participants with Abnormal Clinical Significant Laboratory Values in Hematology (Time Frame: Baseline to 6 Months); Number of Participants with Changes in Echocardiography Overall Assessment (Time Frame: Baseline to 6 Months);	Recruiting	USA

Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
			Number of Participants with Changes to overall assessment of Electrocardiogram (Time Frame: Baseline to 6 Months); Time to recovery of Sp02 (Time Frame: Baseline to 6 Months); Number of Participants with Abnormal Clinical Significant Lab Values in the Blood Chemistry testing (Time Frame: Baseline to 6 months); Number of Participants with Abnormal Clinical Significant Lab Values in the Coagulation (Time Frame: Baseline to 6 months); Number of Participants with Abnormal Clinical Significant Lab Values in the Urinalysis (Time Frame: Baseline to 6 months)		
NCT04527224	Allogenic adipose tissue derived Mesenchymal stem cells	Phase I/II; N = 10	Treatment related adverse events (Time Frame: From baseline to Week 12); Number of subjects with treatment related abnormal variation of vital signs, physical examination and laboratory test values (Time Frame: From baseline to Week 12)	Not yet recruiting	South Korea
NCT04366063	Mesenchymal stem cells (source not defined)	Phase II/III; N = 60	Adverse events assessment (Time Frame: From baseline to day 28); Blood oxygen saturation (Time Frame: From baseline to day 14)	Recruiting	Iran
NCT04573270	Mesenchymal stem cells derived from human umbilical cords	Phase I; N = 40	Survival Rates (Time Frame: 30 Days); Contraction Rates (Time Frame: 30 Days)	Completed	USA
NCT04302519	Dental pulp mesenchymal stem cells	Early Phase I; N = 24	Disappear time of ground-glass shadow in the lungs (Time Frame: 14 days)	Not yet recruiting	China
NCT04437823	Umbilical cord derived Mesenchymal stem cells	Phase II; N = 20	Safety and efficacy assessment of infusion associated adverse events (Time Frame: Day 01 to Day 30); Chest Radiograph or Chest CT Scan (Time Frame: Day 01 to Day 30)	Recruiting	Pakistan
NCT04494386	Umbilical Cord Lining Stem Cells	Phase I/II; N = 60	Incidence of Dose Limiting Toxicity (DLT) (Time Frame: 24 hours); Incidence of Dose Limiting Toxicity (DLT),	Recruiting	USA

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Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
			suspected adverse reaction (SAR), or serious adverse event (SAE) (Time Frame: 1 week); Treatment-emergent adverse events (AE) and serious adverse events (SAE) (Time Frame: 1 month); Treatment-emergent adverse events (AE) and serious adverse events (SAE) (Time Frame: 12 months)		
NCT04457609	Umbilical Cord Mesenchymal stem cells	Phase I; N = 40	Clinical improvement: Presence of dyspnea (Time Frame: 15 days); Clinical improvement: presence of sputum (Time Frame: 15 days); Clinical improvement: fever (Time Frame: 15 days); Clinical improvement: ventilation status (Time Frame: 15 days); Clinical improvement: blood pressure (Time Frame: 15 days); Clinical improvement: heart rate (Time Frame: 15 days); Clinical improvement: respiratory rate (Time Frame: 15 days); Clinical improvement: oxygen saturation (Time Frame: 15 days)	Recruiting	Indonesia
NCT04339660	Human umbilical cord-derived Mesenchymal stem cells	Phase I/II; N = 30	The immune function (TNF-α IL-1β IL-6 TGF-β IL-8 PCT CRP) (Time Frame: Observe the immune function of the participants within 4 weeks); Blood oxygen saturation (Time Frame: Monitor blood oxygen saturation of the participants within 4 weeks)	Recruiting	China
NCT04392778	Umbilical Cord-derived Mesenchymal stem cells	Phase I/II; N = 30	Clinical improvement (Time Frame: 3 months)	Recruiting	Turkey
NCT04490486	Umbilical Cord Tissue Derived Mesenchymal stem cells	Phase I; N = 21	Percent of participants with treatment related Serious Adverse Events (SAE) (Time Frame: 12 months)	Not yet recruiting	USA
NCT04355728	Human umbilical cord derived Mesenchymal stem cells	Phase I/II; N = 24	Incidence of pre-specified infusion associated adverse events (Time Frame: Day 5); Incidence of Severe Adverse Events (Time Frame: 90 days)	Completed	USA
NCT04522986	Adipose-derived Mesenchymal stem cells	Phase I; N = 6	Safety: Adverse Event (Time Frame: 12 weeks)	Not yet recruiting	Japan

Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04371601	Umbilical Cord-derived Mensechynmal stem cells	Early Phase I; N = 60	Changes of oxygenation index (PaO2/FiO2), blood gas test (Time Frame: 12 months)	Active, not recruiting	China
NCT04362189	Allogeneic Adipose-derived Mesenchymal stem cells	Phase II; N = 100	Interleukin-6 (Time Frame: screening, day 0, 7, 10); C Reactive protein (Time Frame: screening, day 0, 7, 10); Oxygenation (Time Frame: screening, day 0, 7, 10); TNF alpha (Time Frame: screening, day 0, 7, 10); IL-10 (Time Frame: screening, day 0, 7. 10); Return to room air (RTRA) (Time Frame: Day 0, 3, 7, 10, 28)	Active, not recruiting	USA
NCT04390152	Wharton's Jelly derived Mesenchymal stem cells	Phase I/II; N = 40	Intergroup mortality difference with treatment (Time Frame: 28 days)	Not yet recruiting	Colombia
NCT04461925	Placenta-Derived MMSCs; Cryopreserved Placenta-Derived Multipotent Mesenchymal Stromal Cells	Phase I/II; N = 30	Changes of oxygenation index PaO2/FiO2, most conveniently the P/F ratio. (Time Frame: up to 28 days); Changes in length of hospital stay (Time Frame: up to 28 days); Changes in mortality rate (Time Frame: up to 28 days)	Recruiting	Ukraine
NCT04299152	Human cord blood stem cells	Phase II; N = 20	Determine the number of Covid-19 patients who were unable to complete SCE Therapy (Time Frame: 4 weeks)	Not yet recruiting	USA
NCT04348461	Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells	Phase II; N = 100	Efficacy of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Survival Rate) (Time Frame: 28 days); Safety of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Adverse Event Rate (Time Frame: 6 months)	Not yet recruiting	Spain
NCT04535856	Allogeneic Mesenchymal stem cells (source not defined)	Phase I; N = 9	Incidence of TEAE* in Treatment group (Time Frame: 28 days)	Active, not recruiting	Indonesia
NCT04393415	Cord blood stem cells	Not Applicable; N = 100	The number of patients with positive covid 19 who will improve after receiving stem cells (Time Frame: 2 weeks)	Recruiting	Egypt

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Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04447833	Allogenic bone marrow derived Mesenchymal Stromal Stem Cells	Phase I; N = 9	The incidence of pre-specified treatment related adverse events of interest (TRAEIs). (Time Frame: From drug administration to day 10 post-infusion)	Recruiting	Sweden
NCT04397796	Allogenic Bone Marrow derived Mesenchymal stem cells	Phase I; N = 45	Incidence of AEs (Time Frame: 30 days); Mortality (Time Frame: 30 days); Death (Time Frame: 30 days); Number of ventilator-free days (Time Frame: 60 days)	Recruiting	USA
NCT04452097	Human umbilical cord Mesenchymal stem cells	Phase I/II; N = 39	Incidence of infusion-related adverse events (Time Frame: Day 3); Incidence of any treatment-emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) (Time Frame: Day 28)	Not yet recruiting	USA
NCT04377334	Allogeneic bone marrow-derived human mesenchymal stem (stromal) cells	Phase II; N = 40	Lung injury score (Time Frame: day 10)	Not yet recruiting	Germany
NCT04331613	Differentiated cells obtained from human embryonic stem cells	Phase I/II; N = 9	Adverse reaction (AE) and severe adverse reaction (SAE) (Time Frame: Within 28 days after treatment); Changes of lung imaging examinations (Time Frame: Within 28 days after treatment)	Recruiting	China
NCT04345601	Bone Marrow Mesenchymal Stromal Cells	Early Phase I; N = 30	Treatment-related serious adverse events (tSAEs) (Time Frame: 28 days post cell infusion); Change in clinical status at day 14 (Time Frame: 14 days post cell infusion)	Not yet recruiting	USA
NCT04390139	Wharton-Jelly mesenchymal stromal cells	Phase I/II; N = 30	All-cause mortality at day 28 (Time Frame: Day 28)	Recruiting	Spain
NCT04398303	Allogenic human umbilical derived Mesenchymal stem cells	Phase I/II; N = 70	Mortality at day 30 (Time Frame: 30 days post treatment)	Not yet recruiting	USA
NCT04400032	Bone Marrow derived Mesenchymal Stromal Cells	Phase I; N = 9	Number of Participants With Treatment-Related Adverse Events as Assessed by CTCAE v4.0 (Time Frame: At time of infusion until one year post-infusion)	Recruiting	Canada

Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04537351	Induced Pluripotent stem cells derived mesenchymoangioblasts	Phase I/II; N = 24	Trend in trajectory of PaO2/FiO2 ratio (P/F ratio) between groups (Time Frame: 7 days)	Recruiting	Australia
NCT04467047	Allogenic Bone Marrow Mesenchymal Stromal Cells	Phase I; N = 10	Overall survival (Time Frame: 60 days)	Not yet recruiting	Brazil
NCT04365101	Natural Killer (NK) cells derived from human placental hematopoietic stem (CD34+) cells	Phase I/II; N = 86	Phase 1: Frequency and Severity of Adverse Events (AE) (Time Frame: Up to 12 months); Phase 1: Rate of clearance of SARS-CoV-2 (Time Frame: Up to 12 months); Phase 1: Rate of clinical improvement (Time Frame: Up to 12 months); Phase 2: Time to Clearance of SARS-CoV-2 (Time Frame: Up to 28 days); Phase 2: Time to Clinical Improvement by NEWS2 Score (Time Frame: Up to 28 days)	Recruiting	USA
NCT03042143	Human umbilical cord derived CD362 enriched Mesenchymal stem cells	Phase I/II; N = 75	Oxygenation index (OI) (Time Frame: Day 7); Incidence of Serious Adverse Events (SAEs) (Time Frame: 28 days)	Recruiting	United Kingdom
NCT04269525	Umbilical cord derived Mesenchymal stem cells	Phase II; N = 16	Oxygenation index (Time Frame: on the day 14 after enrollment)	Recruiting	China
NCT04361942	Allogenic Mesenchymal stem cells (source not defined)	Phase II; N = 24	Proportion of patients who have achieved withdrawal of invasive mechanical ventilation (Time Frame: 0–7 days); Rate of mortality (Time Frame: 28 days)	Recruiting	Spain
NCT04333368	Umbilical cord Wharton's jelly-derived mesenchymal stromal cells	Phase I/II; N = 47	Respiratory efficacy evaluated by the increase in PaO2/FiO2 ratio from baseline to day 7 in the experimental group compared with the placebo group (Time Frame: From baseline to day 7)	Active, not recruiting	France
NCT04371393	Allogenic Bone Marrow derived mesenchymal stem cells	Phase III; N = 223	Number of all-cause mortality (Time Frame: 30 days)	Active, not recruiting	USA
NCT04367077	Multipotent adult progenitor cells (source not defined)	Phase II/III; N = 400	Ventilator-Free Days (Time Frame: Day 0 through Day 28); Safety and Tolerability as measured by the incidence of	Recruiting	USA

Study Identifier	Stem Cell Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
			treatment-emergent adverse events as assessed by CTCAE v5.0. (Time Frame: Day 28)		
NCT04524962	Allogenic mesenchymal stem cells (source not defined)	Phase I/II; N = 30	To assess the safety of Descartes-30 in patients with moderate-to-severe ARDS (Time Frame: 2 years)	Recruiting	USA
NCT04445220	Allogenic Bone Marrow derived Mesenchymal stromal cells	Phase I/II; N = 22	Safety and tolerability as measured by incidence of IP-related serious adverse events (Time Frame: Outcomes and Serious Adverse Events through Day 180)	Recruiting	USA
NCT04466098	Mesenchymal stromal cells (source not defined)	Phase II; N = 30	Incidence of grade 3–5 infusional toxicities and predefined hemodynamic or respiratory adverse events related to the infusion of mesenchymal stem cells (Time Frame: Within 6 hours of the start of the infusion)	Recruiting	USA

Table 1.
Clinical trials registered on ClinicalTrials.gov till January 5, 2021 utilizing sem cells for the treatment of COVID-19.

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Study Identifier	Exosome Source	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04602442	Mesenchymal stem cells	Phase II; N = 90	Number of participants with non-serious and serious adverse events during trial (Time Frame: through study, an average of 2 months); Number of participants with non-serious and serious adverse during inhalation procedure (Time Frame: 10 days during inhalation procedures)	Enrolling by invitation	Russia
NCT04491240	Mesenchymal stem cells	Phase I/II; N = 30	Number of participants with non-serious and serious adverse events during trial (Time Frame: 30 days after clinic discharge); Number of participants with non-serious and serious adverse during inhalation procedure (Time Frame: after each inhalation during 10 days)	Completed	Russia
NCT04389385	T cell derived exosomes	Phase I; N = 60	Adverse reaction (AE) and severe AE (SAE) (Time Frame: 28 days); Efficacy Assessment – Time to Clinical Recovery (Time Frame: 28 days); The rate of recovery without Mechanical Ventilator (Time Frame: 28 days)	Active, not recruiting	Turkey
NCT04384445	Human Amniotic Fluid	Phase I/II; N = 20	Incidence of any infusion associated adverse events (Time Frame: 60 days); Incidence of Severe Adverse Events (Time Frame: 60 days)	Recruiting	USA
NCT04493242	Bone Marrow	Phase II; N = 60	All-cause mortality (Time Frame: 28 days); Median days to recovery (Time Frame: 28 days)	Not yet recruiting	USA
NCT04276987	Allogenic adipose Mesenchymal stem cells	Phase I; N = 24	Adverse reaction and severe adverse reaction (Time frame: up to 28 days); time to clinical improvement (Time frame: up to 28 days)	Completed	China
NCT04657458	Bone marrow Mesenchymal stem cells	Expanded Access	N/A	Expanded Access Available	USA

Table 2.
Clinical trials registered on ClinicalTrials.gov till January 5, 2021 utilizing extracellular vesicles and/or exosomes for the treatment of COVID-19.

7. Conclusion

The current pandemic we are encountering has placed an unprecedented burden upon the world and is likely to leave an everlasting impact for generations to come. With the lack of definitive and safe treatment along with the congruent rise in unknown viral variants the demand for a safe source of mitigation is urgently needed. Clincial studies have specified tht patients who suffer from SARS-CoV-2 related ARDS have an indued cytokine storm composed of a large and rapid surge in pro-inflammatory cytokines and inflammatory cells. MSCs and their EVs have a long been touted for their safty and effectiveness in the treatment of immune related diseases, ALI and ARDS. MSCs and EVs have are now being repourposed for COVID-19 due to their antiviral, anti-inflammatory and tissue regenerative capabilities. Data from clinical trials using MSCs and EVs have shown promising results that warrant their use on a compassionate basis for COVID-19. Eventually more pre-clinical and clinical trials are needed to further establish the safety and efficacy of MSCs and their EVs as a potential treatment for COVID-19.

Conflict of interest

The authors declare no conflict of interest.

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