Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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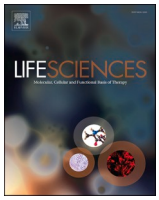

Mesenchymal stem cells in SARS-CoV-2 infection: A hype or hope

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ABSTRACT

COVID-19 is a serious viral infection that struck the world in December 2019 starting from Wuhan in China, spreading subsequently to all over the world. The disease has baffled scientists and doctors worldwide in terms of its presentation, behaviour, and treatment options till now. A low mortality rate is the only relief we get so far from COVID-19 in terms of numbers. Treatment options have gradually streamlined to steroids and very few FDA approved antiviral as well as plasma therapy and supportive treatment. Monoclonal antibodies are used to tide over any impending cytokine storm but are not equally effective in all patients. Ventilation support is invariably required for moderate to severe disease varying from a simple High Flow non-rebreathing mask to BiPAP (Bilevel Positive Airway Pressure) and HFNO (High-Flow Nasal Oxygen) extending to full-fledge ventilation *via* a Mechanical Ventilator. Because of the non-availability of satisfactory treatment so far, many researchers from different biomedical fields are looking for alternative therapeutic strategies to manage the pandemic. One such therapeutic approach showing a ray of hope to combat COVID-19 infection is Mesenchymal stem cell therapy. Mesenchymal cells have immunomodulatory, anti-inflammatory as well as regenerative properties and various preliminary studies have shown that MSCs can reverse the lung damage and overcome the cytokine storm incited by COVID-19 infection. Also, it has improved the recovery rate of critically ill patients on mechanical ventilation. In this review, we will discuss the possibility and relevance of MSCs in COVID-19 treatment and preview of various MSCs clinical trials.

1. Introduction

COVID-19 is a serious viral infection that has affected almost every country of the globe, leading to a huge number of deaths in a short period. To date, COVID-19 has infected 128 million people and is responsible for 2.8 million death worldwide. This infection was started a year ago in December 2019, in a seafood market in the city of Wuhan [1]. Infected patients showed symptoms of respiratory illness such as breathing difficulties along with dry cough, fever, and headache [1]. In January 2020, the novel coronavirus was confirmed as the causative agent of the disease. Later it was named SARS-CoV-2 and due to the occurrence of infection in 2019, it was named COVID-19, by WHO in February 2020 [2]. During COVID-19 infection there is release of pro-inflammatory cytokines interleukin-1β (IL-1β), IL-2, IL-6, IL-10, IL-12, IL-13, tumor necrosis factor-alpha (TNF-α), IFN-α/β, IFN-γ, monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1A (MIP-1A) granulocyte-macrophage colony-stimulating factor (GM-CSF) by the host cells [3]. This condition is collectively called cytokines storm syndrome and it results in pulmonary hyper inflammation, edema, dysfunction of air-exchange, acute respiratory distress syndrome, acute kidney injury, acute cardiac injury, and multiple organ failure which may lead to death [4]. Cytokines storm syndrome is central to the COVID-19 infection in severe cases.

In the current therapeutic regimen number of antivirals, antimalarial

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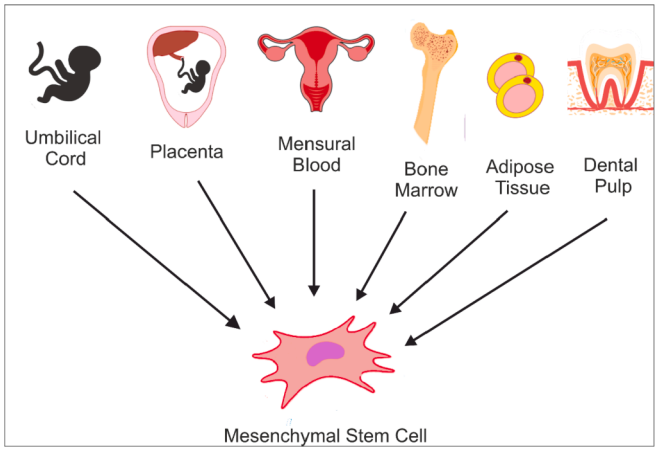

Fig. 1. Sources of mesenchymal stem cells.

and anti-inflammatory agents are being used as a line of treatment to combat COVID-19 infection [5]. But still, there is no specific cure for COVID-19 even after several months of pandemic. Vaccines have been developed targeting various components of virus structure and vary in efficacy depending on the same. Medical management of patients includes infection prevention or control and supportive care, including additional oxygen and support for respiratory equipment as and when required. However, these treatments have shown efficacy in some patient's survival and recovery but they failed to reverse the severe lung tissue damage caused by COVID-19 infection. Mesenchymal stem cells (MSCs) have attracted attention due to their immunomodulatory and regenerative properties [6]. It is evident from different studies, that on intravenous transplantation of MSCs majority population of cells accumulates in the capillary beds of lungs and while trapped in the lungs, MSCs secretes a wide variety of soluble mediators including antimicrobial peptides, anti-inflammatory cytokines, extracellular vesicle, and angiogenic growth factors that modulate inflammatory environment in the lungs and regenerate damaged tissues [7]. MSCs can activate immune-modulating pathways through toll-like receptors and the aryl-hydrocarbon receptor on its surface that gets activated by the surrounding environment [8]. MSCs secretes signaling mediators such as, indolamine 2,3-dioxygenase, galectins, prostaglandin E_2, nitric oxide, and damage- and pathogen-associated molecular patterns and stimulates critical signaling pathways such as nuclear factor NFkB, signal transducer and activator of transcription-1(STAT-1) and affects the proliferation of T cells, B-cells, natural killer cells (NK) and dendritic cells (DC), MSCs also upregulates nitric oxide synthase and cyclooxygenase-2 levels that stimulate the synthesis of T reg cells and anti-inflammatory macrophages contributing to its immune-suppressive properties [9,10].

MSCs are already used in the treatment of Type 2 diabetes, Crohn's disease, graft *versus* host rejection, ulcerative colitis, multiple sclerosis blood disorders, autoimmune diseases and spinal cord injuries [11]. Although data is scarce but MSCs could prevent pulmonary fibrosis, protect alveolar epithelial cells, and improve lung dysfunction in a significant number of cases. According to the International Society for Stem cell Research (ISSCR) that there is no approved Stem cell-based therapy for the treatment of COVID-19 [12]. However, various studies are utilizing MSCs as a therapeutic approach in the treatment of COVID-19. Still, owing to the efficacy shown by MSC therapy in initial studies, several clinical trials have begun to confirm it as a curative therapy in the treatment of severe cases of COVID-19 infection.

In this review we will brief various studies that have utilized the MSC based approach for the treatment of COVID-19 patients. Further, we will also review current therapeutics in COVID-19 infection treatment their outcome, and their side effects. Also, advantages of MSCs therapy in COVID-19 infection. Additionally, we have tried to explore registered clinical tests to get useful information to the scientific community of stem cell-based therapy (Fig. 1).

2. SARS-CoV-2 and COVID-19

Coronaviruses are spherical in shape enclosed in a lipid envelope, which encapsulate large a single-stranded RNA, which is packed in the helical nucleoprotein capsid. These viruses contain the largest RNA genome typically ranging from 27 to 32 kb [1]. Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) are members of the Coronaviruses (CoV) family. SARS outbreaks were earlier reported in 2002 and 2003 in Guangdong Province, China

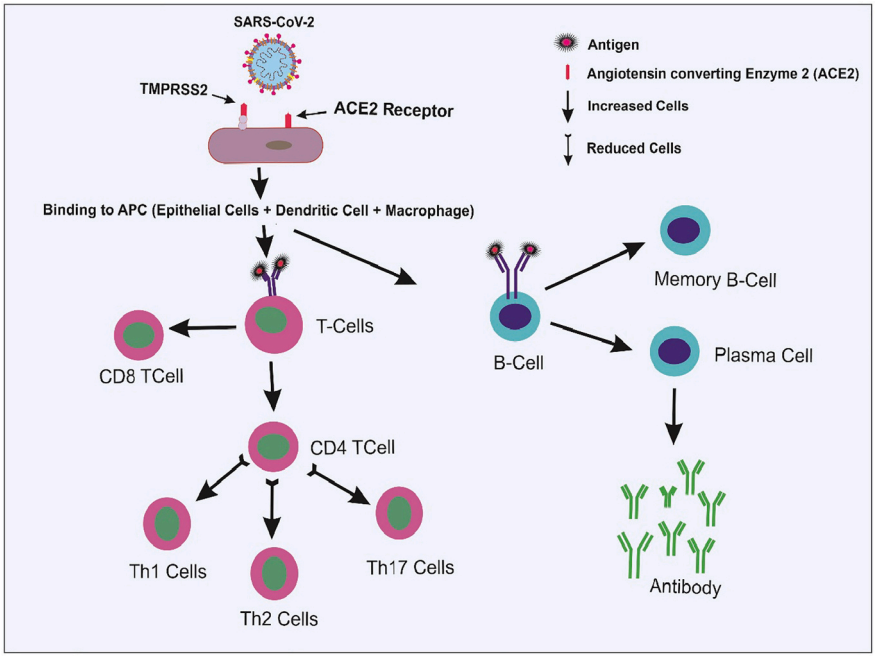

Fig. 2. Putative mechanism of SARS-CoV-2 infection and host immune response.

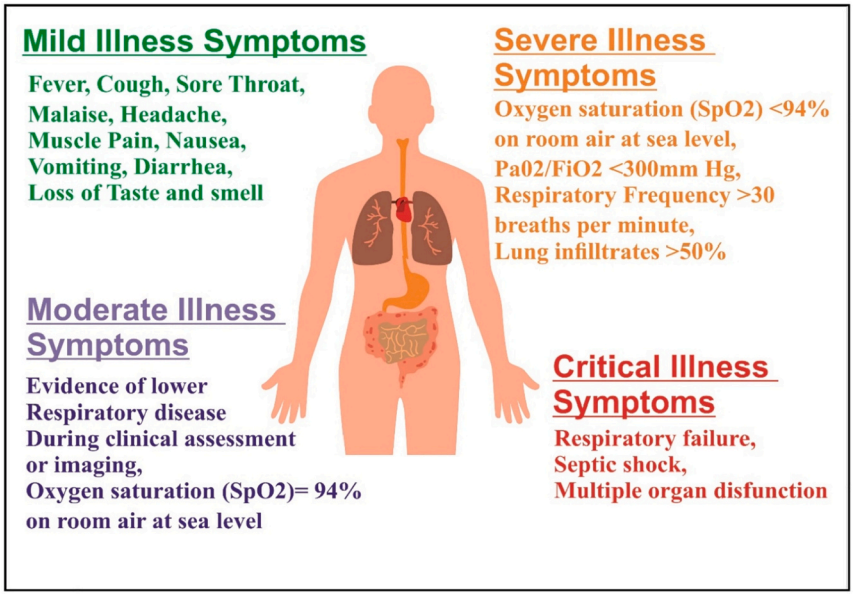

Fig. 3. Illustrations of various symptoms of COVID-19 patients.

[13] whereas the MERS-CoV outbreak occurred in the Middle East in 2012 [14]. SARS-CoV-2 is from Nidovirales order, a member of the genus Beta coronavirus [15]. SARS-CoV-2 is an enveloped non-segmented, single-stranded RNA virus [16]. 79.6% sequence of CoV is same to SARS-CoV [2] and it is known as the largest discovered RNA viruses SARS-CoV gain entry into the host cell through a spike protein which is present on the surface of viruses by binding to ACE2 (Angiotensin-converting enzyme) receptor and once binds to receptor, the virus can infect the healthy cell [17,18]. ACE2 receptor is expressed by a wide variety of cells that includes lung epithelial cells, endothelial cells, also cells of heart, kidney, liver, and some immune cells (Fig. 2).

Due to the expression of ACE 2 receptor in different cells virus can target many vital parts of the human body and leads to different clinical outcomes [19]. This is the reason behind different clinical presentations of disease by infected patients, not all patients develop acute respiratory distress syndrome (ARDS) but some patients have other complications such as myocardial, kidney injury, and death from multiple organ dysfunction. A study has depicted that the cellular protease transmembrane serine protease 2 (TMRRSS2) is also essential to allow the entry of coronavirus into host cells [19]. ACE2 receptor is widely distributed on capillary epithelium, alveolar type 2(AT2) and also AT2 cells largely express TMPRSS2 [19]. Bone marrow, spleen, thymus, lymph nodes and immune cells such as macrophages B and T lymphocytes are negative for ACE2 [1]. COVID-19 diagnosis is made based on RT-PCR assay, Oxygen saturation level, respiratory distress, arterial partial pressure of oxygen [20]. Different therapeutic regimens are being given to the patients depending upon their symptoms ranging from mild to critical illness that may be subject to various factors including immune response from the patient. (Fig. 3).

3. Therapeutic regimen in COVID-19

3.1. Antivirals

These drugs inhibit viral entry *via* ACE2 receptor and TMPRSS2, viral membrane fusion and endocytosis, or the activity of the SARS-CoV 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase [21]. They prevent viral replication in an early phase of the disease reducing the severity and duration of overall illness once the body can mount a response against the virus.

Lopinavir/Ritonavir–Failed to prove a reduction in overall mortality and was discarded eventually [22].

Remdesivir-Broad-spectrum antiviral which inhibits viral RNA polymerase. It inhibits viral replication through premature termination of viral replication. Gained FDA approval for treatment in hospitalized adult and pediatric patients (>12 yrs of age and >40 kg wt) [23].

3.2. Antimalarial drugs

Hydroxychloroquine emerged as a cost effective promising treatment option during the initial days of pandemic [24] but subsequently multiple studies showed no survival benefit and enthusiasm for its use has declined significantly [25].

3.3. Monoclonal antibodies

Tocilizumab-Targets IL-6 receptors plays a key role in the inflammatory process of COVID-19 infection. It profoundly helps to tide over cytokine storm during illness. The accurate time and infection stage to start this drug is still not very much clear [26].

3.4. Nonspecific anti-inflammatory

Steroids have played a vital role in COVID-19 treatment owing to their anti-inflammatory and immunosuppressive role. They have proven to reduce mortality at 28 days. Indicated for severe and critical disease by WHO [27].

3.5. Anti-parasitic

Ivermectin is still under investigation for treatment in COVID-19 but it has shown efficacy against the SARS-COV-2 virus in *in-vitro* [28].

3.6. Convalescent plasma

Passive immunization with plasma (carrying antibodies) donated from a recovered patient to a patient who has still not recovered. Besides being cost-effective compared to other treatment regimens, convalescent plasma is becoming more readily available with more and more people recovering from the disease plus it prevents any post-treatment immunosuppression side effects as associated with monoclonal antibodies. Potential for transfusion reactions as well as varying levels of

Table 1
Advantages of mesenchymal cells for COVID-19 treatment.

Advantage of MSCs therapy in COVID-19 infections are:
1. MSCs can modulate the hyperactive immune system.
2. MSCs can easily scale up according to the requirement as they have a high multiplication rate.
3. MSCs can be isolated from various sources such as umbilical cord, menstrual blood, bone marrow, dental and Warton Jelly, Amniotic fluid. These MSCs are under investigation for effective treatment in COVID-19 patients [32,33]
4. Transfusion of MSCs is a non-invasive procedure [34]
5. Isolated MSCs can be stored for the long term for future usage [35]

antibodies per donor remain as few of the concerns associated with this treatment [29].

3.7. Vaccines

Vaccines generate acquired immunity in the recipient against infectious diseases. Recombinant adenovirus based vaccine was world's first registered vaccine against SARS-COV-2. Now mRNA based and inactivated virus based vaccines are also available [30]. Immunization programme has already been started all over the world. Despite the best efforts in finding a vaccine in the least possible time still reinfection after vaccination remains possibility. Also, emerging mutations in SARS-COV-2 virus is posing a greater challenge to efficacy of vaccines [31]. To curb this pandemic situation, vaccine as effective prophylactic measures and development of additional therapies for the better clinical management of the severe COVID-19 are essentially required.

3.8. Mesenchymal stem cell therapy

Coronavirus infection in the lungs causes severe pneumonia-like symptoms which are associated with increased proinflammatory cytokines/chemokines such as C reactive proteins, fibrinogen, LDH and D-dimer, and immune reactive cells invasion [36]. Cytokines storm can cause ARDS, macrophage activation syndrome (MAS), alveolar and endothelial damage in adverse conditions that may lead to death [37]. The most important objective in the treatment of COVID-19 is to avoid cytokine storm. Mesenchymal stem cell therapy has an added advantage to override this condition (Table 1). When given intravenously 90% of MSCs get trapped in the lungs [38]. After accumulation in the lungs, MSCs secrete various anti-inflammatory cytokines, extracellular vesicles, and angiogenic growth factors in abundance that promotes tissue repair, develop lung environment, and improves pulmonary functions [39]. MSCs can regulate the immune response as it can convert Th1 to Th2, or directly interact with immune cells such as T cells, B cells. MSCs can modulate dendritic cell maturation, activate M2 macrophages therefore it can inhibit tissue damage [25]. COVID-19 patients with severe comorbidities show poor response to pre-approved antiviral, anti-inflammatory therapies, and often needs intensive care. In the present scenario, the availability of medical beds and mechanical ventilation are far less than are required in this pandemic situation. Therefore, to minimize the burden on ICUs, the Italian College of Anesthesia, Analgesia, Resuscitation, and Intensive Care has released the guidelines for the usage of stem cells in the treatment of COVID-19 patients [40]. MSCs have been reported to reduce mechanical ventilation requirement and improved recovery rate in critically ill COVID-19 infected patients. A proof of concept study has shown that 13 critically ill patients with severe SARS-COV-2 pneumonia on mechanical ventilators did not respond well to previous antiviral and anti-inflammatory drugs but when adipose-derived MSCs (Median number of cells per dose: 0.98×10^6 AT-MSC/kg of recipient's body weight) were given intravenously, nine patients showed clinical improvement out of which seven patients were extubated at a median follow up of 16 days. The distinctive feature of COVID-19 infection which is different from other viral infection is an endothelial thrombo-inflammatory syndrome (with elevated D-dimer) which is related to poor prognosis There was a significant improvement in the biochemical parameters of patients with a significant decrease in D dimer, c-reactive protein, LDH and ferritin levels [41]. A study by Leng et al [38] investigated MSC's potential in improving the condition of COVID-19 infected patients. In the study, seven patients with confirmed COVID-19 infection were transplanted with 1×10^6 per kg body weight MSCs in normal saline. Inflammation levels were alleviated in a short period with a decrease in C-reaction protein levels. Pulmonary function was improved in all the patients with an increase in oxygen saturation. Another clinical parameter lymphocyte count and CD14+CD11c+CD11bmid regulatory DC cell population were increased. Due to the immunomodulatory effect of MSCs pro-inflammatory cytokines secreting cells CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK were decreased. This study suggests that immunoregulatory and tissue repair properties of MSCs improved the outcome of COVID-19 patients. Another, case report was published in which a COVID-19 patient with a severe COVID-19 pneumonia and history of diabetes were treated with human umbilical cord Wharton's jelly-derived MSCs (hWJCs, 1×10^6 cells per kg of weight.) from a healthy donor. After treatment patient's pulmonary function and symptoms were significantly improved. Also, there was a decrease in levels of inflammatory markers such as IL-6, TNF-α, and C-reactive protein with a concomitant increase in lymphocytes count ($CD3^+$, $CD4^+$, and $CD8^+$ T cell) [42].

In another case report from china suggested that MSCs therapy can delay the worsening of a patient's conditions. In this case, a 72-year-old COVID-19 patient with reported life-threatening conditions such as diabetic nephropathy, high blood pressure, lymphopenia, elevated c-reactive protein, and renal insufficiency was given UC-MSCs (1.5×10^6 cells per kg of patient's body weight) intravenously for five times [43]. The patient was responding poorly to antiviral therapy consisting of recombinant human interferon and lopinavir/ritonavir and due to deterioration of condition patient was put on mechanical ventilation. After MSCs infusion, levels of lymphocytes were increased and renal function was improved and later on patient received lung transplantation. This case report suggests that MSCs transfusion can delay serious deterioration of patient condition and provide valuable time to further decide the effective treatment therapy to rescue the patient. Similarly, a 65-year-old woman in China with severe multi-organ injury caused by an inflammatory response, acute respiratory distress, multi-organ injury (liver, respiratory system, and blood), hypertension, type 2 diabetes, electrolyte disturbance, immunosuppression, acute gastrointestinal bleeding, and allergy to corticosteroid therapy was transfused with allogenic hUCMSCs (5×10^7 cells each time). Following receipt of the second dose, the patient's neutrophil and lymphocyte counts were improved with improvement in lung condition as detected in chest CT scans and invasive ventilation was removed. This case report suggested a good clinical outcome of hUCMSCs therapy with severe lung inflammation [44]. Similarly, another study has shown that administration allogeneic clinical-grade human prenatal MSCs from placenta (PL-MSC) in critically ill COVID-19 induced ARDS patients improved improve respiratory distress and reduce inflammation. Five patients received 3 doses of 200×10^6 PL-MSCs cells every alternate day per infusion. A total dose of 600×10^6 allogeneic MSCs was given to each patient by intravenously infusions. Although the patient number was lower in the study but it suggest the efficacy and safety of allogeneic clinical-grade human prenatal MSCs in the critically ill COVID-19 patients with lung damage and also it disproves the usage of MSCs therapy in the patients with sepsis and organ failure [45]. H7N9-infection has few overlapping clinical manifestations like COVID-19 infection. H7N9 influenza severe cases infection cause ARDS, pneumonia, and lung failure. During the 2013 H7N9 outbreak, 17 patients with H7N9 induced ARDS were given MSCs isolated from menstrual blood. Whereas, in the control group, 44 patients with H7N9 ARDS were given standard antiviral treatments. In an experimental group, there was 54% mortality rate whereas in the test

Table 2
Reported clinical trials for preventing COVID-19 [47,48].

Clinical trial no	Cell source	Sample size	Patient age (year)	Patients inclusion criteria	References
NCT04444271	MSCs	20	≥10	Respiratory failure, septic shock, multifunction organ dysfunction shock	https://clinicaltrials.gov
NCT04429763	Umbilical cord derived stem cells	30	≥18	Severe COVID-19 Infection confirmed by PCR test. Hospitalized in general room (respiratory isolation area).	https://clinicaltrials.gov
NCT04565665	Cord blood-derived MSCs	70	≥18	Moderate to Severe ARD (Acute respiratory distress syndrome), Negative pregnancy test in a woman	https://clinicaltrials.gov
NCT04416139	MSCs	10	≥18	CT compatible with bilateral pneumonia, Severe ARDS with PaO2/FiO2 less than 150.	https://clinicaltrials.gov
NCT04252118	MSCs	40	18-70	Confirmed COVID-19 by RT PCR, Pneumonia judged by chest radiography	https://clinicaltrials.gov
NCT04611256	MSCs	20	18-65	Moderate to severe acute respiratory insufficiency, RT –PCR for SARS-COV-2	https://clinicaltrials.gov
NCT04288102	UC-MSCs	100	18-75	Hospitalized, Pneumonia judged by CT, ILD judged by CT	https://clinicaltrials.gov
NCT04456361	Wharton's Jelly derived-MSC	9	≥18	• Diagnosis of ARDS, Diagnostic test positive for SARS-CoV-2	https://clinicaltrials.gov
NCT04625738	*Ex vivo* expanded Wharton's Jelly MSCs	30	≥18	RT-PCR positive, Patients admitted in ICU, childbearing age with a negative Beta HCG test	https://clinicaltrials.gov
NCT04366271	MSCs	106	40-80	RT-PCR positive, Body weight between 50 kg and 100 kg, Respiratory distress with ≥30 breaths	https://clinicaltrials.gov
NCT04366323	Allogenic and expanded adipose tissue-derived mesenchymal stem cells	26	18–80	Clinical diagnosis of Pneumonia, severe or critical, Life expectancy >48 h	https://clinicaltrials.gov
NCT04339660	UC-MSCs	30	18-75	CT image is characteristic of 2019, RT-PCR positive report,	https://clinicaltrials.gov
NCT04428801	Autologous adipose-derived stem cells	200	≥18	• Highly susceptible to SARS-Cov-2 infections, SARS-CoV-2 RT-PCR or equivalent tests negative in respiratory tract specimen	https://clinicaltrials.gov
NCT04629105	Longeveron mesenchymal stem cells	70	18	Mild to severe ARDS, pulmonary edema on frontal chest radiograph, left atrial hypertension for bilateral pulmonary infiltrates,	https://clinicaltrials.gov
NCT04527224	AstroStem-V	10	19-80	Pneumonia by radiologic examination, pneumonia caused by COVID-19 infection at screening, signs indicative of severe COVID-19 disease severity	https://clinicaltrials.gov
NCT04382547	Allogenic pooled olfactory mucosa-derived MSCs	40	18–70	• Respiratory failure, PCR-confirmed COVID-19 pneumonia	https://clinicaltrials.gov
NCT04371601	MSCs	60	18-70	Patients with severe COVID-19 pneumonia,	https://clinicaltrials.gov
NCT04657458	Bone marrow MSCs	Intermediate-size Population	≥18	PCR-confirmed COVID-19	https://clinicaltrials.gov
NCT04366063	MSCs	60	18-65	• Confirmation of 2019-nCoV infection by RT-PCR, Pneumonia that is judged by chest radiograph or CT,	https://clinicaltrials.gov
NCT04457609	UC-MSCs	40	18-95	RT-PCR from nasopharyngeal swab, Chest radiography shows pneumonia appearance, results showed leukopenia and lymphopenic	https://clinicaltrials.gov
NCT04490486	UC-MSCs	21	≥18	• Moderate symptoms of fever, Willingness to use FDA-recommended birth control until 6 months post treatment, fever, cough, headache, myalgia, sore throat, nasal congestion, nausea, vomiting, diarrhea, fatigue,	https://clinicaltrials.gov
NCT04573270	MSCs	40	≥18	• Ability to provide informed consent	https://clinicaltrials.gov
NCT04461925	Placenta-derived MMSCs	30	18–75	• Laboratory confirmation of SARS-CoV-2, dyspnea (RR ≥ 30 times/min); Pneumonia that is judged by X-ray imaging	https://clinicaltrials.gov
NCT04355728	UC-MSCs	24	≥18	PaO2/FiO2 ratio < 300 mmHg, oxygen saturation (SpO2) ≤ 94% at room air, bilateral ground glass opacities on a chest CT scan	https://clinicaltrials.gov

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Table 2 (*continued*)

Clinical trial no	Cell source	Sample size	Patient age (year)	Patients inclusion criteria	References
NCT04293692	UC-MSCs	48	≤18-≤75	Reverse-transcription polymerase chain reaction (RT-PCR), in resting state, means oxygen saturation ≤ 93%	https://clinicaltrials.gov
NCT04522986	MSCs	6	≥20	PaO2/FiO2 ratio < 300 mmHg, Peripheral capillary oxygen saturation (SpO2) ≤ 94%, Hypoxemia requiring an increase in the fraction of inspired oxygen (FiO2) of ≥20%	https://clinicaltrials.gov
NCT04348461	Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells	100	≥18	Secondary to SARS-CoV-2 infection, blood gas compromise with a PaO2/FiO2 ratio < 200 mm-Hg	https://clinicaltrials.gov
NCT04390152	Wharton's jelly derived mesenchymal stem cells	40	18–80	Moderate to severe ASRD, PaO2/FiO2 less than 200 mmHg, 36 h of orotrachea l intubation	https://clinicaltrials.gov
NCT04377334	MSCs	40	≥18	• COVID-19-positive subject, Horowitz index ≤200, Bilateral opacities on frontal chest radiograph	https://clinicaltrials.gov
NCT04452097	Human umbilical cord MSCs	39	18–80	cases of severe COVID-19 pneumonia with mild to moderate ARDS,	https://clinicaltrials.gov
NCT04345601	Mesenchymal stromal cells	30	18≥	Moderate to severe acute respiratory distress (ARDS), PaO2/FiO2 100–200 mmHg, Severe ARDS: PaO2/FiO2 ≤ 100 mmHg on ventilator settings that include PEEP ≥5 cm H2O	https://clinicaltrials.gov
NCT04494386	Umbilical Cord Lining Stem Cells (ULSC)	60	18≥	Patient with diagnosis of COVID-related ARDS	https://clinicaltrials.gov
NCT04492501	MSCs	600	18-90	• Day of illness less than 14 days, PCR positive confirmed COVID-19	https://clinicaltrials.gov
NCT04392778	MSCs	30	40-60	• Confirmed 2019-nCoV infection with RT-PCR Laboratory test, Pneumonia with chest radiography and computer tomography	https://clinicaltrials.gov
NCT04467047	Mesenchymal stromal cells	10	Child, Adult, Older Adult	• Confirmation of COVID-19 infection, Patients with orange or red criteria according to the score proposed by Liao 2020	https://clinicaltrials.gov
NCT04398303	ACT-20-MSC	70	18-85	Confirmed positive test for COVID-19, On mechanical ventilation (n = 35), or high-flow O2 support (*n* = 35)	https://clinicaltrials.gov
NCT04537351	MSCs	24	18	• ICU admission due to strongly suspected or proven COVID-19	https://clinicaltrials.gov
NCT04361942	Mesenchymal stromal cells	24	≥18	SARS-CoV-2 infection confirmed by molecular testing, Respiratory distress, Basal oxygen saturation at rest ≤93%	https://clinicaltrials.gov
NCT03042143	Human umbilical cord derived CD362 enriched MSCs	75	<16	ARDS as defined by the Berlin definition, Patient is receiving invasive mechanical ventilation	https://clinicaltrials.gov
NCT04269525	UC-MSCs	16	18-80	Pneumonia caused by 2019-nCoV infection, Nucleotide or antibody of 2019-nCoV pneumonia was positive	https://clinicaltrials.gov
NCT04437823	Stem cells	20	>18	Moderate to severe COVID-19 symptoms, clinical diagnosis of COVID-19	https://clinicaltrials.gov
NCT04333368	Umbilical cord Wharton's jelly-derived human	60	>18	• Onset of ARDS <96 h, high-flow nasal oxygen therapy (PEEP ≥5 cmH2O), Onset of ARDS <96 h, Diagnosis of ARDS	https://clinicaltrials.gov
NCT04371393	MSCs	300	>18	Moderate to severe ARDS, CRP serum level > 4.0 mg/dL, Severe ARDS: PaO2/FiO2 ≤ 100 mmHg	https://clinicaltrials.gov
NCT04466098	Mesenchymal stromal cells	9	18–80	• Moderate to severe ARDS for a minimum of 4 h, Less than 48 h on a ventilator, PaO2/FiO2 < 250,	https://clinicaltrials.gov
NCT04341610	Stem cell product	40	18–80	• Confirmed HCoV-19 infection, Temperature above 38.0o C, Respiratory distress, RR ≥ 30/min,	https://clinicaltrials.gov
NCT04400032	Mesenchymal stromal cells	9	18	• On invasive mechanical ventilation ≤48 h, ARDS as per the international consensus definition	https://clinicaltrials.gov
NCT04302519	Dental pulp mesenchymal stem cells	24	≥18-≤75	Respiratory distress, RR > 30 times/minute, Oxygen saturation is less than 93%	https://clinicaltrials.gov
NCT04362189	HB-adMSCs	100	18≥	• Patient is hospitalized due to suspected COVID-19 infection	https://clinicaltrials.gov
NCT04447833	Mesenchymal stromal stem cells	7	18–65	Coronavirus (SARS-CoV-2) infection confirmed, Patient is on respirator support within 3 weeks to 48 h prior to enrolment	https://clinicaltrials.gov

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Table 2 (*continued*)

Clinical trial no	Cell source	Sample size	Patient age (year)	Patients inclusion criteria	References
NCT04445454	Mesenchymal stromal cells	20	18–70	Extensive interstitial pneumonia on CT scan, Radiologically confirmed COVID-19 pneumonia	https://clinicaltrials.gov
NCT04399889	hCT-MSCs	30	18≥	Positive RT-PCR testing for COVID-19, Patient meets ARDS criteria	https://clinicaltrials.gov
NCT04397796	BM-Allo MSC	45	≥18	Severity of the hypoxemia defines the severity of the ARDS, laboratory confirmed positive novel coronavirus	https://clinicaltrials.gov
NCT04390139	MSCs	30	18-70	Intensive Care Unit admission for less than 3 days, Moderate acute respiratory distress	https://clinicaltrials.gov
NCT04367077	Multistem (stem cell product)	400	18–89	Diagnosis of new acute-onset moderate to severe ARDS	https://clinicaltrials.gov
NCT04366323	MSCs	26	≥ 18	Caused by COVID-19 infection, Life expectancy >48 h.	https://clinicaltrials.gov
NCT04361942	Mesenchymal stromal cells	24	≥18	Intensive Care Unit with pneumonia by COVID-19 infection in the last 48 h	https://clinicaltrials.gov
NCT04355728	UC-MSCs	24	≥18	Oxygen saturation (SpO2) ≤ 94% at room air, PaO2/FiO2 ratio < 300 mmHg	https://clinicaltrials.gov
NCT04352803	Adipose Mesenchymal cells	20	≥18	COVID-19 diagnosis confirmed, Hospitalized	https://clinicaltrials.gov
NCT04349631	Human embryonic stem cell-derived M cells	56	65≥	No signs or symptoms of infection, body temperature > 100 F and pulse rate > 100 BPM, Participant works in healthcare facility	https://clinicaltrials.gov
NCT04348435	MSCs	100	18	Characterized as high-risk or very high-risk participant works, body temperature > 100 F and pulse rate > 100 BPM, No signs or symptoms of infection	https://clinicaltrials.gov
NCT04346368	Bone marrow derived MSCs	20	≥18-≤75	A confirmed case of COVID-19, Clinical classification is severe case,	https://clinicaltrials.gov
NCT04345601	Mesenchymal stromal cells	30	18≥	Confirmed SARS-CoV2 infection real-time reverse, Moderate to severe acute respiratory distress syndrome (ARDS)	https://clinicaltrials.gov
NCT04336254	Allogenic human dental pulp MSCs	20	18–65	Diagnosed with severe pneumonia of COVID-19, Respiratory distress, RR >30 times/min, Confirm COVID-19 featured lesions in lung.	https://clinicaltrials.gov
NCT04331613	Human embryonic stem cell-derived M cells (CA-Stem)	9	18–70	Diagnosis of COVID-19, and confirm by chest CT scan, Respiratory distress, RR ≥ 30 times/min, Respiratory failure, the mechanical ventilation required	https://clinicaltrials.gov
NCT04293692	UC-MSCs	48	18-≤75	CT image is characteristic of 2019 novel coronavirus pneumonia, Laboratory confirmation of 2019-nCoV	https://clinicaltrials.gov
NCT04288102	UC-MSCs	100	18-75	Hospitalized, Laboratory confirmation of SARS-CoV-2, Pneumonia that is judged by computed tomography	https://clinicaltrials.gov
NCT04280224	NK cells	30	18–65	Pneumonia that is judged by chest radiograph or computed tomography, Laboratory confirmation of NCP infection by reverse-transcription polymerase chain reaction	https://clinicaltrials.gov
NCT04269525	UC-MSCs	16	18-80	• According to Diagnosis and Clinical Management of Pneumonia caused by 2019-nCoV infection, Previous detection of Nucleotide or antibody of 2019-nCoV pneumonia was positive	https://clinicaltrials.gov
NCT04252118	MSCs	40	18-70	Pneumonia that is judged by chest radiograph or computed tomography, Confirmed COVID-19	https://clinicaltrials.gov
NCT04390152	Wharton's Jelly derived-MSC	40	18–80	Moderate to severe ASRD, PaO2/FiO2 less than 200 mmHg, SARS-CoV-2 positive	https://clinicaltrials.gov
NCT04313322	Wharton's Jelly derived-MSC	5	18>	COVID-19 positive,	https://clinicaltrials.gov
NCT04315987	NestaCell® MSCs	90	>18	SARS-CoV-2 infection, pulmonary impairment greater than or equal to 50%	https://clinicaltrials.gov
NCT04302519	Dental Pulp-MSCs	24	≥18-≤75	novel coronavirus diagnosed severe pneumonia and confirmed no effective treatment plan	https://clinicaltrials.gov
NCT04273646	UC-MSCs	48	18-65	CT image is characteristic of viral pneumonia, 2019-ncov infection	

(*continued on next page*)

Table 2 (*continued*)

Clinical trial no	Cell source	Sample size	Patient age (year)	Patients inclusion criteria	References
					https://clinicaltrials.gov
NCT04299152	MSCs	20	18	clinical diagnosis of SARS-CoV-2, fever ≥38 °C, fatigue, cough	https://clinicaltrials.gov
NCT04276987	MSCs-derived exosomes	24	18–75	Confirmation of SARS-CoV-2 infection, Pulse oxygen saturation (SpO2) at rest ≤93%	https://clinicaltrials.gov
ChiCTR2000030138	hUC-MSCs	30	16-75	COVID-19 infection, Image findings are consistent with pneumonia	http://www.chictr.org.cn
ChiCTR2000030835	hUC-MSCs	10	16-75	Novel coronavirus pneumonia novel coronavirus infection, Severe pneumonia, At rest, the oxygen saturation ≤93%	http://www.chictr.org.cn
ChiCTR2000030866	hUC-MSCs	30	18-85	Patients diagnosed as severe or critical COVID-19, arterial blood oxygen partial pressure (PaO2), oxygen concentration (FiO2) ≤300 mmHg (1 mmHg = 0.133 kPa)	http://www.chictr.org.cn
ChiCTR2000030484	HU-MSCs and exosomes	30	18–70	RT-PCR confirmed, Lung imaging showed significant progress in 24–48 h, respiratory rate > 30 times/min, SpO2 ≤ 93% (quiet, resting state)	http://www.chictr.org.cn
ChiCTR2000030116	hUC-MSCs	16	18-75	The patient meets the ARDS diagnostic standard, Imaging data suggest bilateral lung lesions	http://www.chictr.org.cn
ChiCTR2000029569	Umbilical cord blood mononuclear cells	15	18	patients with severe 2019-ncov, Respiratory distress, RR ≥30 times/min, In resting state, oxygen saturation is less than 93%	http://www.chictr.org.cn
ChiCTR2000029572	Umbilical cord blood mononuclear cells	15	18	Patients with severe 2019-ncov, Respiratory distress, RR ≥30 times/min; (2) In resting state, oxygen saturation is less than 93%	http://www.chictr.org.cn
ChiCTR2000029580	Ruxolitinib in combination with MSCs	35	18–75	Patients clinically diagnosed as novel coronavirus infection; or with positive serum antibodies (IgM or IgG)	http://www.chictr.org.cn
ChiCTR2000029606	human menstrual blood-derived stem cells	63	1–99	Diagnosed as novel coronavirus pneumonia, Epidemiological history, Aggregative onset or epidemiological association with new coronavirus infection	http://www.chictr.org.cn
ChiCTR2000029812	Umbilical cord blood mononuclear cells	60	18	Extremely ill patients with shock, acute respiratory distress syndrome	http://www.chictr.org.cn
ChiCTR2000029816	hUCB-MSCs	60	18	Patients with confirmed new coronavirus-infected pneumonia	http://www.chictr.org.cn
ChiCTR2000030020	MSCs	20	1-100	Clinically diagnosed as infected with the new coronavirus	http://www.chictr.org.cn
ChiCTR2000030088	Umbilical cord Wharton's Jelly derived-MSC	40	18–80	The diagnosis criteria of severe nCoV pneumonia, Combined with other organ failure, intensive care unit is required	http://www.chictr.org.cn
ChiCTR2000031319	Human MSCs	20	18–65	Diagnosed with severe pneumonia of COVID-19: respiratory distress, RR >30 times/min	http://www.chictr.org.cn
ChiCTR2000030173	hUC-MSCs	60	18-70	Patients with clinical symptoms, signs, auxiliary detection combined with 1 or more nucleic acid test to confirm the diagnosis of new coronavirus pneumonia	http://www.chictr.org.cn
ChiCTR2000030224	MSCs	32	18-100	SARS-CoV-2 nucleic acid test positive, Lung CT examination showed evaluable lesions	http://www.chictr.org.cn
ChiCTR2000030300	Human umbilical cord MSCs (huc-MSCs)	9	18–75	SARS-CoV-2 nucleic acid test positive	http://www.chictr.org.cn
ChiCTR2000030329	Umbilical cord blood CIK and NK cells	90	18–65	New-type coronavirus infection is diagnosed as mild or common,	http://www.chictr.org.cn
ChiCTR2000030509	NK cells	40	18–80	Patients with confirmed novel coronavirus-infected pneumonia; Diagnosed as moderate cases of COVID-19 with fever	http://www.chictr.org.cn
ChiCTR2000030944	Human NK cells and MSC transplantation	20	4–80	The patients met the diagnostic criteria of 2019-nCoV pneumonia, Respiratory distress, RP ≥30 times/unit; 5. Under resting state, blood oxygen saturation ≤93%	http://www.chictr.org.cn
ChiCTR2000031139	Human embryonic stem cell-derived M cells (CAStem)	20	18–80	The diagnosis of pulmonary fibrosis is based on the chest CT, Pulmonary function examination, showing restricted ventilation dysfunction	http://www.chictr.org.cn
ChiCTR2000031139	Allogeneic human dental pulp-MSC	20	18–80	Patients diagnosed with novel coronavirus pneumonia (COVID-19); 3) Patients ≥21 days from the first symptom	http://www.chictr.org.cn

group mortality rate was 17%. In the test group, no adverse effect was reported, including the four patients who were part of 5 year follow up study. This study provides the base for testing, the efficacy of menstrual blood-derived MSCs in COVID-19 treatment [46]. MSCs derived exosomes have an added advantage over direct transfusion of MSCs in terms of safety, scalability, and regulatory issues. In animal models of inflammation, ARDS, and acute lung injury, intravenous transfer of bone marrow-derived exosomes showed reduction in cytokine release, alveolar inflammation, and restoration of damaged epithelial lining. In a study by Sengupta et al. [47], ExoFlo, a bmMSC-derived exosome agent was tested for efficacy in 24 COVID-19 patients with moderate to severe ARDS. Each patient received a single dose of 15 milliliter ExoFlo in 100 milliliter saline intravenously for 60 mins. None of the patients experience adverse events till 72 h of transfusion. Safety and efficacy were monitored for two weeks. The patient overall clinical condition and oxygen saturation improved after a single dose of treatment. The survival rate was observed to be 83%. There was a significant mean reduction in acute phase reactants CRP (77%), ferritin (42%), and D-dimer (43%). Also, there was significant increase in CD3+ (46%), CD4+ (45%), and CD8+ T (46%) lymphocytes count and reduction in neutrophil counts (32%). This study suggested the convenience and benefit of, bone marrow-derived exosomes over MSCs to suppress the

cytokine storm and enhance the body's antiviral defenses in COVID-19 infection. Further, improvement in neutrophilia and lymphopenia conditions confirmed the immunomodulatory role of exosome vesicles. In another exosomes-based study, investigators isolated exosomes (Ex) or microvesicles (MV) from murine hypothalamic neural stem/progenitor cells (htNSC) or subtype htNSC^{PGHM} as well as hippocampal NSC. In the study, authors have observed that exosomes can act as cell-free innate antiviral immunity against pseudotype SARS-CoV-2 viruses. MSCs can also show adaptive immunity-like antiviral function when induced with viral exposure. It is found that induced Ex/Mv were stronger than basal Ex/Mv in lowering viral infections. The antiviral activity NSC Ex/Mv is attributed to the production of P element-induced wimpy testis (PIWI)-interacting RNAs (piRNAs) against viral genomes [48]. A recent *in vitro* based study provides an insight of Dental pulp stem cells (DPMSCs) potential in modulating the cytokine production by peripheral blood mononuclear cells (PBMCs) isolated from COVID-19 patients. In order, to determine the immunomodulatory role of DPMSCs in COVID-19 patients. DPMSCs isolated from healthy donors were co cultured with CD3/CD28-stimulated PBMCs from COVID-19 patients with pneumonia and hyper inflammation symptoms. It was observed that pro-inflammatory cytokines levels (IFNγ, TNFα, IL-2, IL-5, IL-9, IL-10, IL-12 (p70), IL-17A, IL-18, IL-21, IL-23, and IL-27) were low in supernatants of activated PBMCs, co-cultured with DPMSCs. These *in vitro* findings confirm the potential of DPMSCs administration in COVID-19 patients with hyper inflammation [49].

3.9. Drawbacks of mesenchymal stem cell therapy

Administration of MSCs has some drawbacks also, owing to its immunosuppressive abilities; infusion of MSCs at earlier stage of disease can terminate the normal physiological process of inflammation required for controlling viral infection [50]. Also, in worst case scenarios poorly characterize MSCs can cause thromboembolism [51]. As currently is a pandemic situation and SARS-CoV-2 virus induces life threatening inflammatory response in some patients therefore, usage of MSCs therapy in the COVID-19 is purely on compassionate grounds. Drug regulatory agencies across the world emphasize on minimizing inappropriate usage of cell based therapies.

3.10. Mesenchymal stem cells clinical trials for COVID-1909

Several clinical trials have been reported and details have been provided in Table 2.

4. Conclusion

Taken together all the studies discussed in the article shows that mesenchymal stem cell therapy can alleviate lung injury and improve the condition of more specifically critically ill COVID-19 patients. But still, the results are not conclusive due to a small sample size. All the discussed studies emphasized on consideration of MSC-based therapy for severe or critically ill COVID-19 patients with ARDS. At present, there is no approved MSCs therapy in COVID-19 treatment and it is given to COVID-19 patients on a compassionate basis due to pandemic crisis. Therefore, long-term studies with a large number of patients and with detailed analysis of clinical outcome and side effects are required to further confirm the therapeutic efficacy of MSCs in COVID-19 treatment.

CRediT authorship contribution statement

Deeksha Pal, Jyoti Goyal, Umesh Kumar: Data curation, Writing - Original draft preparation: Umesh Kumar: Visualization, Investigation. Umesh Kumar: Supervision.: Aman Sharma, Saurabh Prashar, Bunty Sharma: Image Preparation, Validation.: Garima Rathi, Umesh Kumar, Ujjawal Sharma: Writing.

Declaration of competing interest

The authors declare no competing interests.

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