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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...
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 E2, 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 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.
 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 (TMPRSS2) 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
therefore it can inhibit tissue damage [25]. COVID-19 patients with adipose-derived MSCs (Median number of cells per dose: 0.98 × 10^6) to previous antiviral and anti-inflammatory drugs but when the usage of stem cells in the treatment of COVID-19 patients [40]. 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 [39]. MSCs can 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 transfused 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-reactive protein levels. Pulmonary function was improved in all the patients with an increase in oxygen saturation. Another clinical parameter lymphocyte count and CD14+CD11c+CD11b+ and 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 × 10^6 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 of allogenic clinical-grade human prenatal MSCs from placenta (PL-MSC) in critically ill COVID-19 induced ARDS patients improved 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 allogenic 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 allogenic clinical-grade human prenatal MSCs in 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 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. Transferring 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 re-infection 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
| Clinical trial no | Cell source | Sample size | Patient age (year) | Patient 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-MSCs | 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 |
| NCT04396600     | 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 |

(continued on next page)
| 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% | [Link](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% | [Link](https://clinicaltrials.gov) |
| NCT04348461     | Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells Wharton's jelly derived mesenchymal stem cells | 100 | ≥18 | Secondary to SARS-CoV-2 infection, blood gas compromise with a PaO2/FiO2 ratio < 200 mm-Hg | [Link](https://clinicaltrials.gov) |
| NCT04390152     | MSCs        | 40          | 18-80             | Moderate to severe ARDS, PaO2/FiO2 less than 200 mmHg, 36 h of orotracheal intubation | [Link](https://clinicaltrials.gov) |
| NCT04377334     | MSCs        | 40          | ≥18               | • COVID-19-positive subject, Horowitz index ≤ 200, Bilateral opacities on frontal chest radiograph | [Link](https://clinicaltrials.gov) |
| NCT04452097     | Human umbilical cord MSCs | 39 | 18-80 | cases of severe COVID-19 pneumonia with mild to moderate ARDS, | [Link](https://clinicaltrials.gov) |
| NCT04136401     | 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 | [Link](https://clinicaltrials.gov) |
| NCT04494386     | Umbilical Cord Lining Stem Cells (ULSC) | 60 | 18≥ | Patient with diagnosis of COVID-related ARDS | [Link](https://clinicaltrials.gov) |
| NCT04492501     | MSCs        | 600         | 18-90             | • Day of illness less than 14 days, PCR positive confirmed COVID-19 | [Link](https://clinicaltrials.gov) |
| NCT04392778     | MSCs        | 30          | 40-60             | • Confirmed 2019-nCoV infection with RT-PCR Laboratory test, Pneumonia with chest radiography and computer tomography | [Link](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 | [Link](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) | [Link](https://clinicaltrials.gov) |
| NCT04136401     | MSCs        | 24          | 18               | • ICU admission due to strongly suspected or proven COVID-19 | [Link](https://clinicaltrials.gov) |
| NCT0431942      | Mesenchymal stromal cells | 24 | ≥18 | SARS-CoV-2 infection confirmed by molecular testing, Respiratory distress, Basal oxygen saturation at rest ≤93% | [Link](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 | [Link](https://clinicaltrials.gov) |
| NCT04269525     | UC-MSCs     | 16          | 18-80             | Pneumonia caused by 2019-nCoV infection, Nucleotide or antibody of 2019-nCoV pneumonia was positive | [Link](https://clinicaltrials.gov) |
| NCT04437823     | Stem cells  | 20          | ≥18              | Moderate to severe COVID-19 symptoms, clinical diagnosis of COVID-19 | [Link](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 | [Link](https://clinicaltrials.gov) |
| NCT04371393     | MSCs        | 300         | ≥18              | Moderate to severe ARDS, CRP serum level > 4.0 mg/dL, Severe ARDS: PaO2/FiO2 ≤ 100 mmHg | [Link](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, | [Link](https://clinicaltrials.gov) |
| NCT04341610     | Stem cell product | 40 | 18-80 | • Confirmed HCoV-19 infection, Temperature above 38.0°C, Respiratory distress, RR ≥ 30/min, | [Link](https://clinicaltrials.gov) |
| NCT04400032     | Mesenchymal stromal cells | 9 | 18 | On invasive mechanical ventilation ≤48 h, ARDS as per the international consensus definition | [Link](https://clinicaltrials.gov) |
| NCT04302519     | Dental pulp mesenchymal stem cells | 24 | ≥18<-75 | Respiratory distress, RR > 30 times/minute, Oxygen saturation is less than 93% | [Link](https://clinicaltrials.gov) |
| NCT04362189     | HB-adMSCs   | 100         | ≥18              | • Patient is hospitalized due to suspected COVID-19 infection | [Link](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 | [Link](https://clinicaltrials.gov) |
| 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                                                     | 90          | 18                | Characterized as high-risk or very high-risk participant, body temperature > 100 F and pulse rate > 100 BPM, No signs or symptoms of infection, Oxygen saturation (SpO2) ≥ 94% at room air | 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 CT image is characteristic of 2019 novel coronavirus pneumonia | https://clinicaltrials.gov   |
| NCT04293692     | UC-MSCs                                                  | 48          | 18- ≤75           | Laboratory confirmation of 2019-nCoV Pneumonia                                                                                                                                                                                  | 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® M cells                                       | 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                                                                                                                                                           | https://clinicaltrials.gov   |

(continued on next page)
Table 2 (continued)

| Clinical trial no | Cell source            | Sample size | Patient age (year) | Patients inclusion criteria                                                                 | References |
|-------------------|------------------------|-------------|--------------------|-----------------------------------------------------------------------------------------------|------------|
| NCT04299152      | MSCs                   | 20          | 18                 | clinical diagnosis of SARS-CoV-2, fever $\geq 38$ °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 $\leq 93\%$       | 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 $\leq 93\%$ | 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) $\leq 300$ 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 $\leq 93\%$ (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   | 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   | 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 |
| 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, Aggregate onset or epidemiological association with new coronavirus infection | http://www.chictr.org.cn |
| ChiCTR2000029812  | Umbilical cord blood   | 60          | 18                 | Extremely ill patients with shock, acute respiratory distress syndrome                         | http://www.chictr.org.cn |
| ChiCTR2000029816  | hUCB-MSCs              | 60          | 18                 | Patients with confirmed novel 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 |
| ChiCTR2000030122  | MSCs                   | 32          | 18-100             | SARS-CoV-2 nucleic acid test positive, Lung CT examination showed evaluable lesions            | http://www.chictr.org.cn |
| ChiCTR2000030200  | Human umbilical cord MSCs (hue-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 $\geq 30$ times/unit; S. Under resting state, blood oxygen saturation $<93\%$ | http://www.chictr.org.cn |
| ChiCTR2000031139  | Human embryonic stem cell-derived M cells (CASOB) | 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 $\geq 21$ 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 bMNC-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 experienced 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 exosome-based study, investigators isolated exosomes (Ex) or microvesicles (MV) from murine hypohalamic neural stem/progenitor cells (hNSC) or subtype hNSC-PGDM 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 or 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 DPSCs in COVID-19 patients, DPSCs 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 (IFN-γ, TNFa, 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 DPSCs. These in vitro findings confirm the potential of DPSCs 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 MSC 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.

References

[1] P. Zhou, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[2] N. Zhu, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.
[3] A. Faru, et al., Cytokine storm and COVID-19: a chronic of pro-inflammatory cytokines, Open Biol. 10 (9) (2020), 200160.
[4] S.M. Metcalfe, Mesenchymal stem cells and management of COVID-19 pneumonia, Med. Drug. Discov. 5 (2020), 100019.
[5] C. Gharibo, et al., Triaging interventional pain procedures during COVID-19 or related elective surgery represents evidence-informed guidance from the American Society of Interventional Pain Physicians (ASIPP), Pain Physician 23 (4S) (2020) S183–S204.
[6] X. Chen, et al., Mesenchymal stem cell therapy in severe COVID-19: a retrospective study of short-term treatment efficacy and side effects, J. Infect. 81 (4) (2020) 647–679.
[7] M.A. Ganham, J.D.M. Campbell, J.C. Mountford, The use of mesenchymal stromal cells in the treatment of coronavirus disease 2019, J. Transl. Med. 18 (1) (2020) 359.
[8] O. Delarosa, W. Dalemans, E. Lombardo, Toll-like receptors as modulators of mesenchymal stem cells, Front. Immunol. 3 (2012) 182.
[9] L.I. de Castro, et al., Current understanding of the immunosuppressive properties of mesenchymal stem cells, J. Mol. Med. (Berl) 97 (5) (2019) 605–618.
[10] A.R.R. Weiss, M.H. Dahlke, Immunomodulation by mesenchymal stem cells (MSCs): mechanisms of action of living, apoptotic, and dead MSCs, Front. Immunol. 10 (2019) 1191.
[11] A. Himada, et al., Therapeutic potential of mesenchymal stem cells for cancer therapy, Front. Bioeng. Biotechnol. 8 (2020) 43.
[12] A. Golchini, E. Seyedjafari, A. Arshadshirizami, Mesenchymal stem cell therapy for COVID-19: present or future, Stem Cell Rev. Rep. 16 (3) (2020) 427–433.
[13] N.S. Zhong, et al., Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People’s Republic of China, in February, 2003, Lancet 362 (9353) (2003) 1355–1358.
[14] A.M. Zaki, et al., Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med. 367 (19) (2012) 1814–1820.
[15] A.C.P. Wong, et al., Global epidemiology of bat coronaviruses, Viruses 11 (2019) 2.
[16] C. Huang, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.
[17] R. Lu, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (10224) (2020) 565–574.
[18] F. Li, et al., Structure of SARS coronavirus spike receptor-binding domain complexed with receptor, Science 309 (5742) (2005) 1864–1868.
[19] M. Hoffmann, et al., SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280, e9.
[20] M.M. Berek, Insights into the COVID-19 pandemic: origin, pathogenesis, diagnosis, and therapeutic interventions, Front. Biosci. (Elite Ed) 13 (2021) 117–139.
[21] N. Huang, et al., The effect of antivirals on COVID-19: a systematic review, Expert Rev. Anti-Infect. Ther. 2020) 1–14.
[22] B. Cao, et al., A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19, N. Engl. J. Med. 382 (19) (2020) 1787–1799.
[23] J.A. Bolarin, et al., Therapeutic drugs for SARS-CoV-2 treatment: current state and perspective, Int. Immunopharmacol. 90 (2020), 107228.
[24] X. Yao, et al., In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), Clin. Infect. Dis. 71 (15) (2020) 732–739.
[25] C.P. Skipper, et al., Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial, Ann. Intern. Med. 173 (8) (2020) 623–631.
[26] Y. Zhang, et al., Treat 2019 novel coronavirus (COVID-19) with IL-6 inhibitor: are we already that far? Drug. Discov. Ther. 14 (2) (2020) 100–102.
[27] M. Saiz-Rodriguez, et al., Outpatient treatment of COVID-19 with steroids in the phase of mild pneumonia without the need for admission as an opportunity to modify the course of the disease: a structured summary of a randomised controlled trial, Trials 21 (1) (2020) 632.
[28] Y. Caly, et al., The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro, Antivir. Res. 178 (2020), 104787.
[29] H. Harvala, et al., Convalescent plasma therapy for the treatment of patients with COVID-19: assessment of methods available for antibody detection and their correlation with neutralising antibody levels, Transfus. Med. 31 (3) (2020) 167–175, https://doi.org/10.1111/tme.12746.
[30] Q. He, et al., Heterologous prime-boost: breaking the protective immune response bottleneck of COVID-19 vaccine candidates, Emerg. Microbes Infect. 10 (1) (2021) 629–637.
[31] S. Su, Y. Shao, S. Jiang, Human challenge trials to assess the efficacy of currently approved COVID-19 vaccines against SARS-CoV-2 variants, Emerg. Microbes Infect. 10 (1) (2021) 439–441.
[32] S. Liu, et al., Mesenchymal stem cells as a potential therapy for COVID-19, Stem Cell Res. Ther. 11 (1) (2020) 169.
[33] Q. Xie, et al., What is the impact of human umbilical cord mesenchymal stem cell transplantation on clinical treatment? Stem Cell Res. Ther. 11 (1) (2020) 519.

[34] K. Rajanbhi, A. Chatterjee, S. Ray, Combating COVID-19 with mesenchymal stem cell therapy, Biotechnol. Rep. (Amst.) 26 (2020), e00467.

[35] X. Wei, et al., Mesenchymal stem cells: a new trend for cell therapy, Acta Pharmacol. Sin. 34 (6) (2013) 747-754.

[36] F. Ciceri, et al., Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis, Crit. Care Resusc. 22 (2) (2020) 95–97.

[37] D. McGonagle, et al., The role of cytokines including Interleukin-6 in COVID-19 and macrophage activation syndrome-like disease, Autoimmun. Rev. 19 (6) (2020), 102537.

[38] Z. Leng, et al., Transplantation of ACE2(-) mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia, Aging Dis. 11 (2) (2020) 216–226.

[39] S.S. Iyer, C. Co, M. Rojas, Mesenchymal stem cells and inflammatory lung diseases, Panminerva Med. 51 (1) (2009) 5–16.

[40] S. Aduri, L. Manchikanti, J.A. Hirsch, Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically ill COVID-19 patients: the case for compassionate use, Pain Physician 23 (2) (2020) E71–E83.

[41] F. Sanchez-Guijo, et al., Adipose-derived mesenchymal stromal cells for the treatment of patients with severe SARS-CoV-2 pneumonia requiring mechanical ventilation. A proof of concept study, EClinicalMedicine 25 (2020), 100454.

[42] Y. Zhang, et al., Intravenous infusion of human umbilical cord Wharton’s jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia, Stem Cell Res. Ther. 11 (1) (2020) 207.

[43] J. Tao, et al., Umbilical cord blood-derived mesenchymal stem cells in treating a critically ill COVID-19 patient, J. Infect. Dev. Ctries. 14 (10) (2020) 1138–1145.

[44] B. Liang, et al., Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: a case report, Medicine (Baltimore) 99 (31) (2020), e21429.

[45] S.R. Hashemian, et al., Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: a case series, Stem Cell Res. Ther 12 (1) (2021) 91.

[46] J. Chen, et al., Clinical study of mesenchymal stem cell treatment for acute respiratory distress syndrome induced by epidemic influenza a (H7N9) infection: a hint for COVID-19 treatment, Engineering (Beijing) 6 (10) (2020) 1153–1161.

[47] V. Sengupta, et al., Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19, Stem Cells Dev. 29 (12) (2020) 747-754.

[48] B. Yu, et al., Innate and adaptive immunity of murine neural stem cell-derived piRNA exosomes/microvesicles against pseudotyped SARS-CoV-2 and HIV-based lentivirus, iScience 23 (12) (2020), 101806.

[49] S. Croci, et al., Human dental pulp stem cells modulate cytokine production in vitro by peripheral blood mononuclear cells from coronavirus disease 2019 patients, Front. Cell Dev. Biol. 8 (2020), 609204.

[50] S. Al-Khawaga, E.M. Abdelalim, Potential application of mesenchymal stem cells and their exosomes in lung injury: an emerging therapeutic option for COVID-19 patients, Stem Cell Res. Ther. 11 (1) (2020) 437.

[51] L. Coppin, E. Sokal, X. Stephenne, Thrombogenic risk induced by intravascular mesenchymal stem cell therapy, Curr. Status Future Perspectives. Cells 8 (10) (2019).