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*Review Article*

# Clinical update on the use of mesenchymal stem cells in COVID-19

Fatima A Saleh, Joyce Ghazzawi

*Department of Medical Laboratory Sciences, Faculty of Health Sciences, Beirut Arab University, Beirut, Lebanon*

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**Abstract:** The COVID-19 pandemic has evoked the scientific community to combine all efforts needed to find a cure for the disease. With the limited therapeutic effects of pharmacological therapies, attention has been drawn to alternative ones such as stem-cell based therapy particularly with mesenchymal stem cells (MSCs). Recently, a large number of clinical trials are ongoing to evaluate the safety and efficacy of MSCs in patients with COVID-19; however, only very few data are released. Thereby, we anxiously await the results of FDA-approved trials to provide more definitive data on the use of MSCs in COVID-19 patients, especially the critically ill. Herein, we shed light on the therapeutic agents that have been tested and used for the treatment of COVID-19 and provide an insight into MSC-based approaches for COVID-19 at both preclinical and clinical levels.

**Keywords:** COVID-19, stem cell therapy, mesenchymal stem cells, clinical trials, preclinical

## Introduction

In December 2019, in the city of Wuhan in China, some pneumonia cases of unknown etiology were discovered and all linked to the seafood and wild animal market in the city [1]. Investigations found that what lies behind this is a newly discovered coronavirus called SARS-CoV-2. In January 2020, China confirmed the first known death from the virus and shared the sequence of the novel coronavirus followed by the World Health Organization (WHO) declaring on January 30$^{th}$, the novel coronavirus outbreak a Public Health Emergency of International Concern (PHEIC). On March 11, 2020, deeply alarmed by the escalating numbers of confirmed cases and severity worldwide, the WHO characterized the crisis as a global pandemic unlike any other we have ever seen in the United Nation's 75-year history [2, 3]. As of 26$^{th}$ of May 2021, after nearly 15 months into the declared pandemic, the crisis is nowhere near over with almost 168 million people infected with the virus worldwide as confirmed by molecular assays and more than 3.4 million people have lost their lives to the virus [4].

As the pandemic progresses, scientists around the globe have been working tirelessly and racing against time to find a safe and effective treatment to combat COVID-19. Therapies that are being investigated and recommended include already existing drugs for malaria and autoimmune diseases as well as antiviral drugs that have been successfully developed to treat other viruses. Despite the efforts, no medications to cure COVID-19 patients are available, especially for those who are severely ill. Therefore, the need for alternative treatments that are both safe and effective is urgent. Mesenchymal stem cell (MSC)-based therapies have attracted the attention as an alternative possible approach to treat COVID-19 and its complications, especially after Zhao and collaborators reported that intravenous administration of human MSCs into seven COVID-19 pneumonia patients was safe and effective [5]. After this pilot study has been published, several countries began conducting MSC-based clinical trials for the treatment of COVID-19. It is worth noting that, to date, no approval has been granted to MSC-based therapy for the prevention or treatment of COVID-19; besides, the U.S. National Institute of Health (NIH) rec-

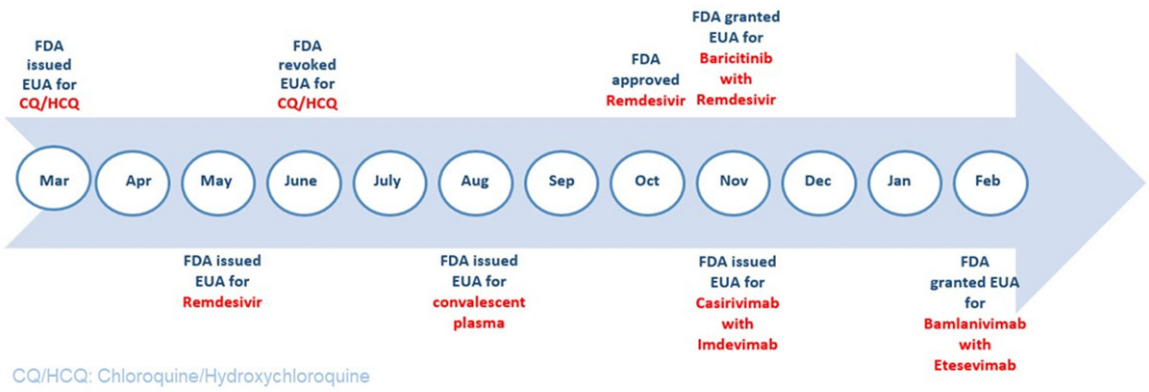


**Figure 1.** Timeline of therapeutic agents granted emergency use authorization (EUA) for patients with COVID-19 from March 2020 to February 2021.

ommended against its use for COVID-19 therapy, except in clinical trials [6]. In this review, we aim to provide a clinical update on the use of MSCs in COVID-19.

## Available treatments for COVID-19

One of the early drugs to be studied for the potential use in the treatment of COVID-19 was chloroquine (CQ) phosphate or hydroxychloroquine (HCQ) sulfate, especially after the publication of Didier Raoult and his team showing the promising activity of HCQ treatment in COVID-19 patients [7]. It is worth mentioning that these drugs are FDA-approved to treat or prevent malaria with HCQ also approved to treat lupus and rheumatoid arthritis. Moreover, HCQ/CQ has demonstrated weak to moderate broad-spectrum antiviral activity. Studies have shown that these agents can exert their anti-SARS-CoV-2 effect by (1) interfering with angiotensin-converting enzyme 2 (ACE2) glycosylation and consequently obstructing virus-receptor attachment; (2) elevating the pH in the intracellular vesicles required for viral internalization into host cells thus preventing endocytosis; (3) contrasting the process of viral protein synthesis and virion assembly [8-10].

However, after limited evidence that both medications may benefit SARS-CoV-2-infected patients, the FDA issued on 28$^{th}$ of March 2020 a temporary authorization for use only in hospitalized patients under careful heart monitoring. This was followed by a safety communication on April 24, 2020, where the FDA cautioned against the use of both drugs for COVID-19 outside of hospital settings or clinical trials due to the risk of heart rhythm problems [11]. In June 2020, the FDA ended the emergency use authorization (EUA) for chloroquine and hydroxychloroquine in light of mounting evidence against their effectiveness in treating COVID-19 (**Figure 1**) [12].

As of 1$^{st}$ of May 2020, FDA granted the antiviral drug, Remdesivir, an EUA for the treatment of hospitalized COVID-19 patients on the basis of the very encouraging results from the Adaptive COVID-19 Treatment Trial (ACTT-1) conducted by the National Institute of Allergy and Infectious Diseases (NIAID) (NCT04280705) and from the Gilead-sponsored open-label trial (NCT04292899) [13, 14]. Almost six months later, on 22$^{nd}$ of October, the FDA approved Remdesivir (RDV) for the treatment of COVID-19 in hospitalized adults and pediatric patients aged ≥12 years and weighing ≥40 kg, to be the first drug for COVID-19 that receives full FDA approval [15].

Remdesivir, also known as GS-5734, is a broad spectrum antiviral monophosphoramidate nucleoside prodrug that was initially investigated to treat infections caused by Ebola virus [16]. Once Remdesivir enters the body, it is metabolized into the active metabolite, nucleoside triphosphate (NTP) of remdesivir or GS443902 which targets the viral RNA-dependent RNA polymerase (RdRp), responsible for integrating ribonucleotide units into nascent viral RNA chains [17, 18]. As a result, NTPs become misincorporated into replicating RNA by the viral RdRp resulting in premature termination of RNA synthesis [17, 18].

Based on another randomized-controlled clinical trial (ACTT-2), FDA authorized the emergency use of a Janus kinase (JAK) inhibitor Baricitinib, in combination with Remdesivir, for the treatment of certain hospitalized patients with suspected or confirmed COVID-19 [19]. It is worth to mention that Baricitinib is not authorized as a stand-alone drug to combat SARS-CoV-2 infection. The NIAID-sponsored ACTT-2 trial results published in *The New England Journal of Medicine* concluded that the combination of Baricitinib and Remdesivir was superior to Remdesivir alone in reducing the median time to recovery among hospitalized COVID-19 patients and improving their clinical status [20]. Baricitinib, a selective JAK1/JAK2 inhibitor, has been shown to limit the cytokine storm caused by COVID-19 by suppressing the JAK-STAT signaling pathway and interrupt the virus entry into cells by disrupting the AP2-associated protein kinase 1 (AAK1), one of the regulators of endocytosis [21-23].

Another drug that has recently received increasing attention as a potential treatment for COVID-19 is the antiparasitic agent, Ivermectin. It has been proven that Ivermectin exerts a broad spectrum antiviral activity against a wide range of viruses, both RNA and DNA viruses. Regarding its activity against SARS-CoV-2, it suppresses the replication cycle of the virus and inhibits the importin alpha/beta1-mediated nuclear import of viral proteins, therefore leading to efficient anti-SARS-CoV-2 response [24, 25]. Despite evidence from in vitro studies demonstrating the inhibitory effect of Ivermectin on SARS-CoV-2 replication, no conclusive evidence on whether this drug has any clinical use in COVID-19 patients [24]. Therefore, Ivermectin has been neither approved nor authorized for treating COVID-19 patients. However, WHO issued an advice for Ivermectin to be only used to treat COVID-19 within clinical trials [26].

While researchers worldwide are still evaluating the use of the above drugs for the treatment of COVID-19 patients, others are exploring the use of monoclonal antibodies collected from previously SARS-CoV-2-infected individuals, as a potential therapy for COVID-19. Bamlanivimab and Etesevimab are both investigational antispike neutralizing monoclonal antibodies that were derived from the blood of two COVID-19 recovered patients from the United States and China, respectively [27, 28]. The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies (BLAZE-1) randomized trial carried out on 577 outpatients with mild to moderate COVID-19 in 49 US study sites revealed that treatment with Bamlanivimab and Etesevimab, but not Bamlanivimab alone, was sufficient to significantly reduce SARS-CoV-2 viral load at day 11 as compared to placebo [29]. In February 2021, the combination of Bamlanivimab and Etesevimab was granted EUA by the FDA to treat patients suffering from mild to moderate COVID-19 infection and who are at risk of progressing into severe condition [30].

Despite the wide spectrum of therapeutic agents that have been tested and used for the treatment of COVID-19, there is still no cure available. Owing to the lack of successful cure and the need to combat the pandemic, alternative therapeutic options, such as cell-based therapy, are being investigated.

### Alternative stem cell therapies for COVID-19

Cell-based therapies especially those using stem cells have shown great promise for the treatment of various diseases such as cardiovascular diseases, neurodegenerative diseases, muscular degenerative diseases, immune system and metabolic disorders as well as graft-versus-host diseases due to their immunomodulatory and paracrine effects [31-35]. In particular, MSCs have gained the spotlight and are becoming increasingly attractive for a wide range of therapeutic applications due to their spectacular properties. (1) MSCs have the ability to differentiate into mesodermal lineages including osteocytes, adipocytes, chondrocytes and myocytes, or even transdifferentiate into cells of the ectodermal and endodermal lineages such as neuronal, hepatic and pancreatic cells [36]. (2) Besides, MSCs are easily accessible and can be obtained from various sources such as the bone marrow, cord blood, placenta, dental pulp and adipose tissue [37]. (3) They can be easily expanded for clinical use in a suitable period of time and can be stored for repetitive usage [38]. (4) MSCs display potent immunomodulatory and anti-inflammatory properties [39]. (5) Moreover, they have the ability to migrate and home to the site of injury to induce tissue repair [40]. All these characteristics have made MSCs a potential

candidate for the treatment of COVID-19. In COVID-19 patients, there is production of a large number of inflammatory cytokines referred to as a cytokine storm that contributes to tissue injury [41]. Owing to their immunomodulatory, anti-inflammatory and regenerative properties, it is hypothesized that MSC therapy can prevent the cytokine storm production and encourage tissue repair [42, 43]. Moreover, MSCs were shown to lack the expression of ACE2 receptor, which has been discovered to mediate the entry of SARS-CoV-2 into the host cell [5, 44]. As ACE2-negative cells, MSCs cannot be targeted by the virus and therefore can be proven to be a very promising therapy for COVID-19. A study by Leng et al. has demonstrated that transplantation of ACE2-negative MSCs was effective in treating patients with COVID-19 pneumonia and that the cells used remained resistant to infection with SARS-CoV-2 [5]. In this review, we aim to provide an insight into MSC-based therapies on COVID-19 at both preclinical and clinical levels.

## Preclinical studies for COVID-19

Preclinical testing is a crucial part in determining the safety and potential efficacy of any new therapeutic intervention. However, in the era of COVID-19 pandemic and the unprecedented speed of which SARA-CoV-2 has spread, the investigative effort was primarily centered on clinical rather than preclinical studies. Therefore, preclinical testing utilizing MSCs on animal and cell-based models for COVID-19 was not highly pursued during the pandemic, as the process is time-consuming and involves extensive laboratory safety techniques. However, several preclinical studies have demonstrated potential effectiveness of MSC intervention in models of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) [45, 46].

A study by Hong and colleagues has reported that human adipose-derived MSCs were effective in the short (2 days) and long term (7 days) in a lipopolysaccharide (LPS)-induced ARDS mouse model as shown by reduction in LPS-induced lung injury and neutrophil infiltration [47]. In a similar study, MSCs ameliorated hydrochloric acid-induced ALI in a rat model via suppression of inflammation, oxidative stress and apoptosis [48]. In a mouse model of influenza A (H5N1) virus-associated ALI, MSCs attenuated ALI with slight improvement in the survival of infected mice [49]. As such, MSCs administration was shown to improve LPS-induced ALI in a rat model. Moreover, inflammatory cells and inflammatory cytokines such as IL-1β, IL-6 and TNF-α were reduced in the injured alveoli after treatment with MSCs [50]. Notably, in this study, MSCs were found to migrate to and retain in the site of injury of LPS group. The entrapment of injected MSCs in the injured site is ideal in the context of COVID-19-associated lung injury [50, 51].

## MSC-based clinical trials for COVID-19

As of April 2021, 69 clinical trials evaluating the safety and efficacy of MSCs in patients with COVID-19 have been registered on Clinicaltrials.gov (as shown in **Table 1**), most of which have been undertaken in North America (https://clinicalTrials.gov). It is worth noting that almost 90% of these trials are in the early phases (phase I, I/II, or II) and still in the recruitment process. MSCs used in the clinical studies were mostly obtained from the umbilical cord (33%), followed by the bone marrow (16%), adipose tissue (16%) and wharton's jelly (7.2%) as shown in **Figure 2**. Other sources were also used such as dental pulp. Despite the relatively high number of registered trials at ClinicalTrials.gov testing the use of MSCs for COVID-19 patients, the majority of these trials are still ongoing with just little data available to date.

During the early stages of the pandemic, a research team led by Dr. Fu-Sheng Wang performed a phase I clinical trial to determine the safety of UC-MSC infusions in 18 hospitalized patients with moderate and severe COVID-19 (NCT04252118) [52]. Preliminary results were promising showing that MSC therapy was safe and tolerable with no serious adverse events reported. Based on encouraging phase I data, the same team embarked on a randomized, double-blinded, placebo-controlled phase II trial (NCT04288102) to evaluate the safety and efficacy of intravenous UC-MSCs in 100 COVID-19 patients with lung damage during a 28-day follow up period [53]. Interestingly, MSC treatment was proven safe and effective as it improved the resolution of the lung solid component lesions compared with placebo when detected by computed tomography (CT)

**Table 1.** Ongoing clinical trials on the use of mesenchymal stem cells in the treatment of COVID-19

| NCT Number | Title | Status | Phase | Country |
|---|---|---|---|---|
| NCT04444271 | Mesenchymal Stem Cell Infusion for COVID-19 Infection | Recruiting | Phase 2 | Pakistan |
| NCT04416139 | Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 | Recruiting | Phase 2 | Mexico |
| NCT04713878 | Mesenchymal Stem Cells Therapy in Patients With COVID-19 Pneumonia | Completed | NA | Turkey |
| NCT04429763 | Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia | Not yet recruiting | Phase 2 | |
| NCT04565665 | Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome | Recruiting | Phase 1 | United States |
| NCT04315987 | NestaCellÂ® Mesenchymal Stem Cell to Treat Patients with Severe COVID-19 Pneumonia | Not yet recruiting | Phase 2 | Brazil |
| NCT04456361 | Use of Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Caused by COVID-19 | Active, not recruiting | Early Phase 1 | Mexico |
| NCT04611256 | Mesenchymal Stem Cells in Patients Diagnosed With COVID-19 | Recruiting | Phase 1 | Mexico |
| NCT04366323 | Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded Adipose Tissue in Patients with Severe Pneumonia Due to COVID-19 | Active, not recruiting | Phase 1\|Phase 2 | Spain |
| NCT04625738 | Efficacy of Infusions of MSC From Wharton Jelly in the SARS-Cov-2 (COVID-19) Related Acute Respiratory Distress Syndrome | Not yet recruiting | Phase 2 | |
| NCT04366271 | Clinical Trial of Allogeneic Mesenchymal Cells from Umbilical Cord Tissue in Patients With COVID-19 | Recruiting | Phase 2 | Spain |
| NCT04252118 | Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19 | Recruiting | Phase 1 | China |
| NCT04313322 | Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells | Recruiting | Phase 1 | Jordan |
| NCT04336254 | Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients | Recruiting | Phase 1\|Phase 2 | China |
| NCT04346368 | Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients with Coronavirus Disease 2019 (COVID-19) | Not yet recruiting | Phase 1\|Phase 2 | China |
| NCT04288102 | Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19) | Completed | Phase 2 | China |
| NCT04629105 | Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (RECOVER) | Recruiting | Phase 1 | United States |
| NCT04753476 | Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia | Recruiting | Phase 2 | Indonesia |
| NCT04273646 | Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19 | Not yet recruiting | NA | China |
| NCT04527224 | Study to Evaluate the Efficacy and Safety of AstroStem-V in Treatment of COVID-19 Pneumonia | Not yet recruiting | Phase 1\|Phase 2 | |
| NCT04728698 | Study of Intravenous Administration of Allogeneic Adipose-Derived Mesenchymal Stem Cells for COVID-19-Induced Acute Respiratory Distress | Not yet recruiting | Phase 2 | United States |
| NCT04348435 | A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19 | Active, not recruiting | Phase 2 | United States |
| NCT04339660 | Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia | Recruiting | Phase 1\|Phase 2 | China |
| NCT04428801 | Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19 | Not yet recruiting | Phase 2 | |
| NCT04457609 | Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients | Recruiting | Phase 1 | Indonesia |
| NCT04352803 | Adipose Mesenchymal Cells for Abatement of SARS-CoV-2 Respiratory Compromise in COVID-19 Disease | Not yet recruiting | Phase 1 | |
| NCT04573270 | Mesenchymal Stem Cells for the Treatment of COVID-19 | Completed | Phase 1 | United States |
| NCT04382547 | Treatment of Covid-19 Associated Pneumonia with Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells | Enrolling by invitation | Phase 1\|Phase 2 | Belarus |
| NCT04349631 | A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19 | Active, not recruiting | Phase 2 | United States |
| NCT04366063 | Mesenchymal Stem Cell Therapy for SARS-CoV-2-related acute respiratory distress syndrome | Recruiting | Phase 2\|Phase 3 | Iran |

| | | | | |
|---|---|---|---|---|
| NCT04490486 | Umbilical Cord Tissue (UC) Derived Mesenchymal Stem Cells (MSCs) Versus Placebo to Treat Acute Pulmonary Inflammation Due to COVID-19 | Not yet recruiting | Phase 1 | United States |
| NCT04355728 | Use of UC-MSCs for COVID-19 Patients | Completed | Phase 1\|Phase 2 | United States |
| NCT04302519 | Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells | Not yet recruiting | Early Phase 1 | |
| NCT04461925 | Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs | Recruiting | Phase 1\|Phase 2 | Ukraine |
| NCT04522986 | An Exploratory Study of ADR-001 in Patients with Severe Pneumonia Caused by SARS-CoV-2 Infection | Completed | Phase 1 | Japan |
| NCT04535856 | Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients | Completed | Phase 1 | Indonesia |
| NCT04362189 | Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19 | Active, not recruiting | Phase 2 | United States |
| NCT04371601 | Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019 | Active, not recruiting | Early Phase 1 | China |
| NCT04390152 | Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19 | Recruiting | Phase 1\|Phase 2 | Colombia |
| NCT04494386 | Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS | Recruiting | Phase 1\|Phase 2 | United States |
| NCT04397796 | Study of the Safety of Therapeutic Tx with Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation | Recruiting | Phase 1 | United States |
| NCT04452097 | Use of hUC-MSC Product (BX-U001) for the Treatment of COVID-19 With ARDS | Not yet recruiting | Phase 1\|Phase 2 | |
| NCT04780685 | A Phase II Study in Patients with Moderate to Severe ARDS Due to COVID-19 | Recruiting | Phase 2 | United States |
| NCT04345601 | Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease) | Recruiting | Phase 1\|Phase 2 | United States |
| NCT04377334 | Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS) | Not yet recruiting | Phase 2 | Germany |
| NCT04492501 | Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan | Completed | NA | Pakistan |
| NCT04390139 | Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients with Respiratory Distress Due to COVID-19 | Recruiting | Phase 1\|Phase 2 | Spain |
| NCT04798716 | The Use of Exosomes for the Treatment of Acute Respiratory Distress Syndrome or Novel Coronavirus Pneumonia Caused by COVID-19 | Not yet recruiting | Phase 1\|Phase 2 | United States |
| NCT04392778 | Clinical Use of Stem Cells for the Treatment of Covid-19 | Recruiting | Phase 1\|Phase 2 | Turkey |
| NCT04467047 | Safety and Feasibility of Allogenic MSC in the Treatment of COVID-19 | Not yet recruiting | Phase 1 | |
| NCT04537351 | The MESeNchymal coviD-19 Trial: a Pilot Study to Investigate Early Efficacy of MSCs in Adults With COVID-19 | Recruiting | Phase 1\|Phase 2 | Australia |
| NCT04398303 | ACT-20 in Patients with Severe COVID-19 Pneumonia | Not yet recruiting | Phase 1\|Phase 2 | |
| NCT03042143 | Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) | Recruiting | Phase 1\|Phase 2 | United Kingdom |
| NCT04361942 | Treatment of Severe COVID-19 Pneumonia with Allogeneic Mesenchymal Stromal Cells (COVID_MSV) | Recruiting | Phase 2 | Spain |
| NCT04437823 | Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients | Recruiting | Phase 2 | Pakistan |
| NCT04269525 | Umbilical Cord (UC)-Derived Mesenchymal Stem Cells (MSCs) Treatment for the 2019-novel Coronavirus(nCOV) Pneumonia | Recruiting | Phase 2 | China |
| NCT04602442 | Safety and Efficiency of Method of Exosome Inhalation in COVID-19 Associated Pneumonia | Enrolling by invitation | Phase 2 | Russia |
| NCT04447833 | Mesenchymal Stromal Cell Therapy for The Treatment of Acute Respiratory Distress Syndrome | Active, not recruiting | Phase 1 | Sweden |
| NCT04371393 | MSCs in COVID-19 ARDS | Active, not recruiting | Phase 3 | United States |
| NCT04491240 | Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia. | Completed | Phase 1\|Phase 2 | Russia |
| NCT04333368 | Cell Therapy Using Umbilical Cord-derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS | Active, not recruiting | Phase 1\|Phase 2 | France |

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|---|---|---|---|---|
| NCT04299152 | Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19 | Not yet recruiting | Phase 2 | |
| NCT04524962 | Study of Descartes-30 in Acute Respiratory Distress Syndrome | Recruiting | Phase 1\|Phase 2 | United States |
| NCT04541680 | Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis | Recruiting | Phase 3 | France |
| NCT04466098 | Multiple Dosing of Mesenchymal Stromal Cells in Patients with ARDS (COVID-19) | Active, not recruiting | Phase 2 | United States |
| NCT04445220 | A Study of Cell Therapy in COVID-19 Subjects with Acute Kidney Injury Who Are Receiving Renal Replacement Therapy | Recruiting | Phase 1\|Phase 2 | United States |
| NCT04400032 | Cellular Immuno-Therapy for COVID-19 acute respiratory distress syndrome | Recruiting | Phase 1\|Phase 2 | Canada |
| NCT04276987 | A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia | Completed | Phase 1 | China |
| NCT04684602 | Mesenchymal Stem Cells for the Treatment of Various Chronic and Acute Conditions | Recruiting | Phase 1\|Phase 2 | United States |

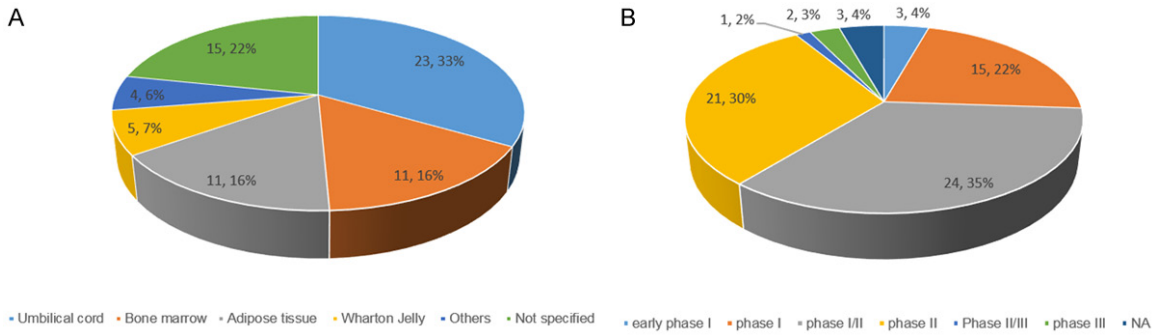


**Figure 2.** MSC clinical trials for COVID-19 collected from clinicaltrials.gov with the term "mesenchymal" and "COVID-19" listed 69 trials. A. MSCs used were obtained from umbilical cord (33%), bone marrow (16%), adipose tissue (16%), and wharton's jelly (7%). B. The majority of these trials are in Phase I, I/II and II (63 trials).

scanning [53]. Accordingly, stem cell treatment for serious COVID-19 patients has been granted "expanded access compassionate use" by the US-FDA.

A similar double-blind, phase I/II, randomized controlled trial (NCT04355728) conducted in 24 subjects with COVID-19 and ARDS demonstrated safety of UC-MSC infusion after a 1-month follow-up. Moreover, UC-MSC administration significantly improved patient survival and time to recovery with decrease in inflammatory markers involved in the COVID-19 "cytokine storm" such as IFNg, IL-6, and TNFa rather than reduction in viral load [54].

Several studies are using MSC-exosomes as an alternative cell-free approach to parent MSCs. At present, two registered trials (NCT04276987, NCT04491240) examining the safety and efficiency of aerosol inhalation of MSC-exosomes in severely ill COVID-19 pneumonia patients have been completed. The utilization of MSC-exosomes will offer considerable advantages over their cellular counterparts such as their reachability to the site of injury, thanks to their nanoscale and extremely stable properties [55-57].

## Challenges of MSC therapy in COVID-19

In spite of thousands of published papers and hundreds of registered clinical trials, stem cell therapy is not FDA approved for most disorders and remains debatable. Recently, the International Society for Stem Cell Research (ISSCR) has issued a statement to clarify that no stem cell-based therapy has been approved to prevent or treat COVID-19 despite the promising results they have shown in various diseases and disorders [58]. As shown above, encouraging results of MSC therapy in treating COVID-19 were obtained in recent clinical trials; however, no firm conclusions can be drawn since most trials were conducted on a small number of patients, for a short-term follow up and in the absence of proper control groups. To better assess the efficacy and safe-

ty of MSC therapy for COVID-19, larger sample size, randomization and proper controls with long-term follow up are required.

Another challenge that has to be addressed in MSC therapy is the limited cell number. In urgent situations like COVID-19, it is not achievable to produce in vitro the relevant and optimal number of stem cells in a short period of time from autologous sources that are known to be best approach in terms of function and safety. Hence, long term in vitro expansion may reduce the regenerative potential and genomic stability of the cells. In addition, the target group to be treated will be in critical conditions so precautions must be taken when treating with stem cells.

The thrombogenic risk after cell infusion is a serious concern especially in COVID-19 patients who suffer from a hyper-coagulopathy [59]. The pro-thrombotic profile of MSCs is promoted by higher passage quantity and higher cell doses; therefore, a limited quantity of MSCs harvested in low passage is considered a worthy candidate to prevent thrombotic risk.

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None.

**Address correspondence to:** Fatima A Saleh, Department of Medical Laboratory Technology, Faculty of Health Sciences, Beirut Arab University, P.O. Box: 11-5020, Beirut, Lebanon. Tel: +961-1-300110 Ext. 2747; E-mail: f.saleh@bau.edu.lb

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