



# Review of Trials Currently Testing Stem Cells for Treatment of Respiratory Diseases: Facts Known to Date and Possible Applications to COVID-19

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## Abstract

Therapeutic clinical and preclinical studies using cultured cells are on the rise, especially now that the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a “public health emergency of international concern”, in January, 2020. Thus, this study aims to review the outcomes of ongoing clinical studies on stem cells in Severe Acute Respiratory Syndrome (SARS), Acute Respiratory Distress Syndrome (ARDS), and Middle East Respiratory Syndrome (MERS). The results will be associated with possible applications to COVID-19. Only three clinical trials related to stem cells are considered complete, whereby two are in Phase 1 and one is in Phase 2. Basically, the ongoing studies on coronavirus are using mesenchymal stem cells (MSCs) derived from bone marrow or the umbilical cord to demonstrate their feasibility, safety, and tolerability. The studies not related to coronavirus are all in ARDS conditions; four of them are in Phase 1 and three in Phase 2. With the COVID-19 boom, many clinical trials are being carried out using different sources with an emphasis on MSC-based therapy used to inhibit inflammation. One of the biggest challenges in the current treatment of COVID-19 is the cytokine storm, however MSCs can prevent or mitigate this cytokine storm through their immunomodulatory capacity. We look forward to the results of the ongoing clinical trials to find a treatment for the disease. Researchers around the world are joining forces to help fight COVID-19. Stem cells used in the current clinical studies are a new therapeutic promise for COVID-19 where pharmacological treatments seem insufficient.

**Keywords** Acute Respiratory Distress Syndrome · Clinical Trials · Mesenchymal Stem Cells · Microvesicles · Middle East Respiratory Syndrome

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## Introduction

On January 31st, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a “public health emergency of international concern” [1]. The virus causing it is highly homologous to the coronavirus (CoV) that caused an outbreak of Severe Acute Respiratory Syndrome (SARS) in 2003 and is named SARS-CoV-2 [2]. Further, in 2011, the world also experienced outbreaks of a coronavirus infection that threatened to become a global pandemic called Middle East Respiratory Syndrome (MERS). In both cases, the causative agents (SARS-CoV and MERS-CoV, respectively) were newly identified coronaviruses from the genus *Betacoronavirus* having zoonotic origin [3]. Another lung disorder associated with CoV is the Acute Respiratory Distress Syndrome (ARDS) that developed in several patients causing pathological changes in the lungs such as diffuse alveolar damage leading to fibrotic lesions [4, 5].

Therapeutic clinical and preclinical studies using cultured cells are on the rise. Models for respiratory virus infections

and relevant clinical studies related to the administration of stem cells in patients are essential to define the patient population that can benefit from cell therapy [6]. Thus, this study aims to review the outcomes of ongoing clinical studies on stem cells in SARS, ARDS, and MERS. The results will be associated with possible applications to COVID-19.

## Stem Cells and Respiratory Diseases

Stem cells are specialized cells that differentiate into other cell types [7]. In certain organs, the stem cells produce descendants that maintain tissue homeostasis and also have the same function as the cells that are not generated from this differentiation [8]. This class of cells depicts a revolution in such studies enabling their application in patients with various disorders, including lung diseases, thus allowing to study cell-based therapies for their treatment. For the treatment of ARDS and sepsis, various cell types are used such as embryonic stem cells (ESCs), mesenchymal stem cells (MSCs), and epithelial progenitor cells (EpPCs). Currently, most of the pre-clinical studies are using MSCs, though induced pluripotent stem cells (iPSC) for the treatment of ARDS [9] are also being used.

The lungs were previously thought to be “post-mitotic” and unable to regenerate, while the stem cell populations, such as bone marrow, intestinal mucosa, and skin are considered regenerative. Yet it is known that different regions in the lungs are dependent on different cell populations, such as the endogenous stem cell complex for tissue repair demonstrating regenerative characteristics [10]. For example, idiopathic pulmonary fibrosis (IPF) is a fatal form of the disease characterized by scar tissue formation in the interstitial lungs with extracellular matrix deposited over time. The symptoms include cough, exertional dyspnea, functional and exercise limitation, acute respiratory failure, and death.

With the emergence of stem cell therapy in treating diseases, the murine bleomycin model became the best-characterized one, in which the administration of allogeneic bone marrow-derived-MSCs (BM-MSCs) reduces inflammation and collagen deposition [11–13]. Also, it was observed that stem cells from the placenta and human umbilical cord demonstrated reduced lung tissue damage in the mouse bleomycin models [14–16].

Another example of stem cells applied to lung disease is chronic obstructive pulmonary disease (COPD), a major devastating disease worldwide. COPD is characterized by chronic small airway inflammation, commonly known as chronic bronchitis, causing progressive poor airflow leading to damage of lung tissues (emphysema). MSCs, as a therapy, are considered a strong candidate in clinical trials to repair damaged lung tissue in COPD or any other chronic lung disease [17–19].

Stem cells, particularly pluripotent cells such as ESCs or iPSCs, offer the potential to differentiate into lung cells reprogramming the immune response to reduce destructive inflammatory elements and directly replace damaged cells and tissues [20]. Thus, it can be a promising novel therapeutic strategy in ARDS to repair and resolve a lung injury restoring the whole epithelial and endothelial function [21]. They can also attenuate bacterial sepsis, directly associated with ARDS, via several mechanisms, such as improving the phagocytic ability, secreting anti-microbial peptides [22], and increasing bacterial clearance [23]. Furthermore, MSCs demonstrated a great potential when reducing the endotoxin-induced injury to explanted human lungs [24].

## Mesenchymal Stem Cells

Mesenchymal stem cells can be isolated from bone marrow and expanded extensively *in vitro*. They play an important role in the repair process or may engraft the injured lung [25, 26]. Engraftment may initiate simultaneously, where MSCs differentiate into lung epithelial cells and can directly replace the damaged cells in alveoli during the treatment of ARDS [27, 28]. Their applicability has been reported in treating cardiovascular and pulmonary diseases [26, 29] along with severe inflammation [30, 31]. These properties are also very attractive due to the immunosuppressive/immunomodulatory abilities [32, 33] influencing an increase in Keratinocyte growth factor (KGF) on epithelial cells, and in the study models of lung injury. Thus, they play a protective role in inducing type II cell proliferation and edema clearance [34]. Additionally, KGF could upregulate alveolar fluid clearance in *ex vivo* human lungs injured by an endotoxin [24]. MSCs play an anti-inflammatory role secreting several mediators that down-regulate the inflammatory process [35] and secrete growth factors, including KGF [36, 37].

In animal models with lung injury, intravenous MSCs led to favorable outcomes, such as reduction in inflammation, pro-inflammatory cytokines, and lung edema [38]. In mouse models, the treatment involving MSCs reduced pulmonary edema and extended survival in *Escherichia coli* endotoxin-induced lung injury [39]. The outcomes of involving MSCs in experimental models of ALI/ARDS have been promising as a cell-based therapy [40].

Previously, ARDS was defined within two simple concepts, namely [1] the pro-inflammatory (leading to host damage) and [2] fibrotic (repair and fibrosis) phase. These two phases make the disease progression more complex [41]. Moreover, the mechanism of action of MSCs is also unknown due to the diverse array of paracrine mediators which are directly associated with the therapeutic effects [42]. Several factors that influence these effects are [1] differences between the cell surface epitopes and genomic stability between mice and humans involved in the

studies [43]; [2] different inflammatory environment [44]; and [3] the heterogeneity of MSCs and their subtypes [45]. However, the complete success of MSCs as a cell therapy for patients with ARDS will probably depend on a better understanding of their mechanism of action and on defining the best strategies for their use in a clinical setting [46].

The benefit of MSCs utilization is directly related to paracrine soluble factors, transfer of mitochondria, and histologically active microvesicles [47]. siRNA knockdown was utilized to analyze the paracrine soluble factors in cultured human type 2 cells during *in vitro* MSCs treatment and it was found that angiopoietin-1 secretion was partially responsible for the beneficial effect of MSCs [48–50]. The presence of MSCs upregulates lipoxin A4, a pro-resolving lipid mediator which could play an important role in MSC-mediated healing of lung injury [49, 50]. Additionally, MSCs mediate the release of microvesicles during cell-to-cell communication [51].

The resistance of pulmonary epithelial cells during inflammation is an important tool to combat pulmonary edema. The interaction between epithelial cells and MSCs in an inflammatory process represents a critical information point in revealing the mechanism of MSC-mediated therapeutic effects, thus allowing to design a better practical protocol to manage these cells [52]. However, the genetic manipulation to improve the therapeutic efficacy of MSCs, so that they could work at the low level of trophic factors in the damaged host tissue, remains a permanent challenge [53].

### MSCs-derived Microvesicles

Among the MSC-derived extracellular vesicles (EVs) or microvesicles, the best-characterized ones are the exosomes. They have a conserved protein group known as tetraspanins which is important for cell targeting. These vesicles are rich in integrins, flotillins (lipid raft-associated), and cholesterol [54]. An important role of microvesicles is cell-cell-mediated communication and they are composed of small circular membrane fragments released from the endosomal cell membrane [33, 55]. MSC-derived EVs contain RNAs that are involved in transcription control, cell proliferation, and immune regulation [56], and interact using different mechanisms with the cell surface receptors [54, 57]. These exosomes activate molecules between the cells through the transfer of genetic material and specific organelles such as mitochondria [58]. Microvesicles derived from MSCs play an important role in the repair of lung injury in ARDS [59]. Zhu et al. [51] observed a decrease in lung edema and neutrophil counts by utilizing microvesicles from human bone marrow MSCs with an increased expression of KGF in this induced lung injury. Evidence from several studies supports the role of microvesicles in cell-based therapies associated with respiratory diseases [55, 60]. Furthermore, microvesicles from adult

MSCs protect against acute tubular injury ischemia–reperfusion-induced acute and chronic kidney injury [61, 62].

In relation to cell-free therapeutics in lung diseases, Monsel et al. [63] displayed various advantages of using MSC-derived extracellular vesicles compared to the MSCs. The advantages are as follows: they are non-self-replicating, have reduced risk of iatrogenic tumor formation, can be stored without DMSO at  $-80^{\circ}\text{C}$  to maintain a biologically active state, they do not express MHC I or II antigens, nor can be induced to express them, and they allow allogeneic transplantation.

## Stem Cells From Other Sources

### Induced Pluripotent Stem Cells

The headStartinduced pluripotent stem cellsheadEnd (iPSCs) produced by the method of Takahashi & Yamanaka [64] are based on the reprogramming of adult cells to a “stem cell state” through a gene transfection technique by manipulating them to undergo cellular differentiation, plasticity and behavioral transformation [64, 65].

There is a great potential of using iPSCs in ARDS and sepsis [9]. However, the associated problems arising from their use are unclear, and also their low efficiency during differentiation and the reprogramming process might be a concern. Thus, a possible genomic modification may be considered to address these drawbacks [66].

### Embryonic Stem Cells

The human headStartembryonic stem cellsheadEnd (ESCs) derived from the inner cell mass of blastocysts are pluripotent and able to differentiate into all three primary germ layers. Their capacity to self-renew makes them a viable treatment option for tissue regeneration [67]. These ESCs promote the MSCs through reprogramming and differentiation with demonstrated efficacy in murine endotoxin and bleomycin-induced lung injury [68]. To develop cell-based strategies for repairing lung injury, Banerjee et al. [69] differentiated human headStartembryonic stem cellsheadEnd (hES) into lung epithelial lineage-specific cells. According to the authors, the study indicated an increase in progenitor cell numbers in the airway and significantly reduced the collagen content in bleomycin-treated mice, after the transplantation of differentiated hES cells.

### Clinical Trials

Only three headStartclinical trialsheadEnd related to stem cells are considered complete, whereby two are in Phase 1 and one is in Phase 2. All the completed studies were

associated with ARDS in the United States (USA) (Table 1). Wilson et al. [70] conducted a Phase 1 trial, where no adverse events were reported in the nine patients evaluated. However, in three patients, serious adverse events were observed weeks after the infusion, but none were MSC-related. The study was considered for an extension trial by Matthay et al. [71]. These researchers carried out a Phase 2 trial in a double-blind study with placebo-control and allogeneic bone marrow-derived-MSCs in a 2 (MSCs):1(Placebo) randomization. The MSC group had significantly higher mean scores than the placebo group for Acute Physiology and Chronic Health Evaluation III (APACHE III) (Table 1). No results were posted in NCT02804945 by the authors.

The ongoing headStartclinical trialsheadEnd related to stem cells for various respiratory disorders such as SARS, MERS, and ARDS are presented in Table 2. Six studies related to coronavirus are in Phase 1, and four studies are already in Phase 2. Basically, the ongoing studies on coronavirus are using MSCs derived from bone marrow or the umbilical cord to demonstrate their feasibility, safety, and tolerability.

The studies not related to coronavirus are all in ARDS conditions; four of them are in Phase 1 and three in Phase 2. Two particularly interesting situations are being developed in Phase 1, where firstly, menstrual blood stem cells are utilized to determine whether these cells are effective in the treatment of infection, and secondly, another study is testing the drug administration of HCR040 (drug based on allogeneic adipose-derived adult headStartmesenchymal stem cellsheadEnd, expanded and pulsed with H<sub>2</sub>O<sub>2</sub>) (Fig. 1).

Emukah et al. [72] conducted a systematic review on the effects of mesenchymal stromal cell conditioned media (CdM) on many lung diseases. The findings were enthusiastic because it was demonstrated that CdM improved inflammation and was as effective as MSCs. Further studies must be conducted to determine the ideal site of CdM delivery, dosage, and timing of the treatment according to the lung disease [72]. Zhao et al. [73] also conducted a systematic review and meta-analysis evaluating the safety of cell therapies and the clinical variables critical for these lung disorders. The authors concluded that the cell therapies do not cause complications in gas exchange, spirometry, quality of life, cardiopulmonary circulation, and immune system of those suffering from the lung disease. Phases 2 and 3 are very important to determine the efficacy of the cell therapies related to dosage and safety approaches. Moreover, death rate was lower in the MSCs-treated group than in the non-MSCs-treated patients [73]. Preclinical studies examined the efficacy of MSCs-treatment compared to the control group across different animals and acute lung injury induction models [74]. A reduced number of deaths was also shown in acute lung injury (ALI) studies of preclinical models [74].

## Possible Applications to COVID-19

### Cytokines Storm

Lymphopenia and higher levels of cytokines are features of COVID-19-patients, being potential biomarkers for disease progression. In severely ill patients, a “cytokine storm” is induced due to the high levels of cytokines, and consequently, numerous adverse reactions in the human body are observed [75]. Cytokine storms include the interleukins IL-1 $\beta$ , IL-2, IL-6, IL-7, IL-8, IL-10, Granulocyte colony stimulating factor (G-CSF), Granulocyte-macrophage colony-stimulating factor (GM-CSF), Interferon gamma inducible protein 10 kD (IP10), Monocyte chemoattractant protein-1 (MCP1), Macrophage inflammatory protein-1 alpha (MIP-1 $\alpha$ ), IFN- $\gamma$  and TNF- $\alpha$  [75–79]. For COVID-19, IL-6 serves as a key mediator cytokine in cytokine storm development [80]. After infection, CD4 + T cells can be quickly activated in pathogenic helper T cells (Th) 1 secreting GM-CSF, which further induces CD14+, CD16 + monocytes providing high levels of IL-6, accelerating the inflammation process [75, 81].

Successful treatment involves influencing the immune response to SARS-CoV-2, including increasing antiviral immunity and inhibiting systemic inflammation. Therefore, using specific immunological profiles of COVID-19, such as the increase of lymphocytes or the inhibition of inflammation, may be essential for treatment in severe cases [75].

Given the potential of modular MSCs in sepsis and evolution of chronic conditions, strategies such as MSC-based therapy can be used to inhibit inflammation. One of the biggest challenges in the current treatment of COVID-19 is the cytokine storm, where some of them with a most important role, evolve to irreversible chronicity, and in this sense, MSCs can prevent or mitigate this cytokine storm through their immunomodulatory capacity [82]. Promising and unprecedented results for COVID-19 were obtained 14 days after the injection of MSCs in 7 patients with pneumonia at Youan Hospital of Beijing, China. Both, regulatory T cells and CD increased significantly after cell therapy. Before transplantation of MSCs, the patients in a severe condition had a significant increase in cells T CXCR3<sup>+</sup> CD4<sup>+</sup>, T CXCR3<sup>+</sup> CD8<sup>+</sup> and CXCR3 + NK compared to the healthy control (without pathological manifestation), thus being reported as the cytokine storm. Nevertheless, once the transplantation of MSCs was performed in the patient, it could be observed on the 6th day that previously overactivated T and NK cells were drastically reduced, almost disappearing, and many other cells were restored to their normal dosages in the patient, especially the regulatory dendritic cells CD14<sup>+</sup> CD11c<sup>+</sup> CD11b. When transplanting MSCs, anti-inflammatory and trophic factors like TGF- $\beta$ , HGF, LIF, GAL, NOA1, FGF, VEGF, EGF, BDNF e NGF were highly expressed in these cells confirming the immunomodulatory action of MSCs [82] (Fig. 2).

**Table 1** Summary of completed headStartclinical trialsheadEnd related to stem cells in ClinicalTrials.gov

&nbsp;ClinicalTrials.gov Identifier	Conditions	Study Design	Objective	Study Start / End	Country	Participants / Ages Eligible for Study	Interventions
Not related to coronavirus Phase 1 NCT01775774	ARDS	Multi-center	To assess the safety of hMSCs in patients with ARDS.	July, 2013 / February, 2015	United States	9 / 18	Allogeneic BM-MSCs
NCT02804945	ARDS	Pilot study - interventional (clinical trial)	To learn about the safety of giving mesenchymal stem cellsheadEnd (MSCs) to patients who have ARDS. Researchers also want to learn if these cells can help control ARDS when given with drugs that are routinely used to treat ARDS. This trial is the extension of the Phase 1 pilot trial (NCT01775774).	February, 2017 / June, 2019	United States	20 / 18	Blood and marrow transplantation MSCs
Phase 2 NCT02097641	ARDS	Prospective, randomized, multi-center - interventional		March, 2014 / February, 2018	United States	60 – 18	Allogeneic BM-MSCs Plasma-Lyte A

## Angiotensin-converting Enzyme 2 (ACE2) Receptor

Both, the angiotensin-converting enzyme 2 (ACE2), widely distributed on cell's surfaces in humans, especially type II alveolar cells (AT2) and the capillary endothelium, as well as the presence of Transmembrane Protease Serine 2 (TMPRSS2), highly expressed by AT2 cells, are fundamental to the pathogenesis of HCoV-19, activating the Spike protein (S). Since many cells of the immune system are negative for ACE2, immune therapy may be an alternative in the treatment of infected patients [83].

According to the results of the above-mentioned study, MSCs have a natural immunity to HCoV-19, being ACE2- or TMPRSS2-negative according to transplant analyses. Thus, especially for patients critically ill with COVID-19 pneumonia, transplantation of MSCs was a safe and effective treatment regulating the inflammatory response and promoting tissue repair and regeneration [82].

Interferon-stimulated genes (ISGs) present in MSCs may explain why these cells are resistant to viral infections. MSCs, for example, express several ISGs, some of which are known to show typical antiviral responses. The member proteins of the Interferon Induced Transmembrane Family (IFITM) are peculiar because they prevent infection before the virus can cross the lipid bilayer on cells [84]. Cells cultivated by viruses such as SARS coronavirus, Ebola virus, influenza A and dengue were not infected because of the assigned activity to IFITM proteins [85]. Therefore, in this scenario of the COVID-19 respiratory viral infection, as suggested by Rajarshi et al. [84], the unique antiviral mechanisms of MSCs include constitutive elevation of MSC-specific ISG levels acting as regulators of antiviral protection and secondary response to IFN, which induces ISG, offering broad viral resistance [84].

In the case of hematopoietic stem / progenitor cells (HSPCs), evidence suggests that the SARS-CoV-2 virus input receptor (ACE2) and the angiotensin II receptor (AT1) are expressed and functional on the surface of these cells [86, 87]. Therefore, it is possible for SARS-CoV-2 upon binding to ACE2 via the Spike protein to directly activate the Nlrp3 inflammasome, contributing to the cytokine storm, affecting the mitochondrial function, leading to cell death by pyroptosis [87–93]. The Nlrp3 inflammasome, which can affect various tissues and organs as well as potentially hematopoiesis [93], may be responsible for certain complications during a SARS-CoV-2 infection.

In 2014, Min et al. [94] evaluated the therapeutic effects of human umbilical cord MSCs in the presence of angiotensin converting enzyme 2 gene (ACE2; ACE2uMSCs) using bleomycin (BLM)induced lung injury and pulmonary fibrosis in mice. The injection of ACE2-uMSC demonstrated significantly more effective results in the treatment of bleomycin-induced pulmonary fibrosis

**Table 2** Summary of ongoing headStartclinical trialsheadEnd related to stem cells and SARS, MERS and ARDS in ClinicalTrials.gov

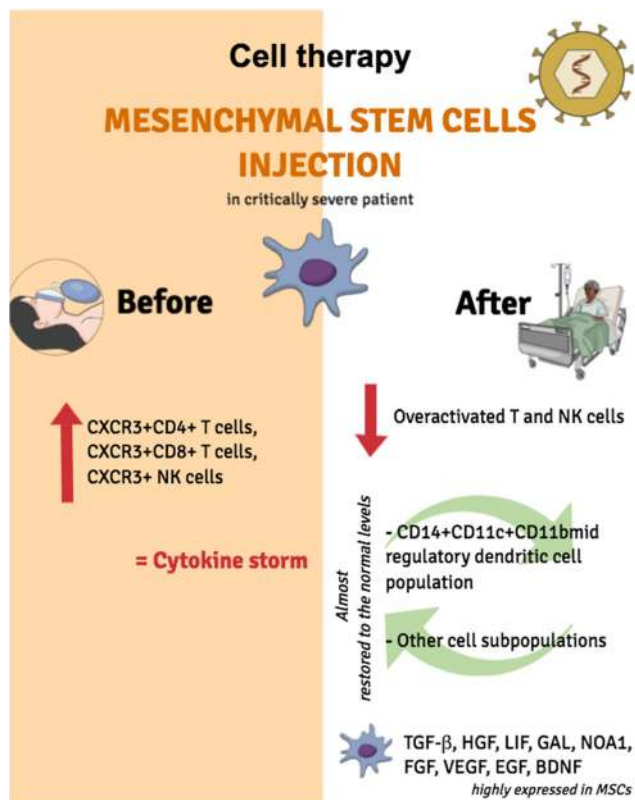
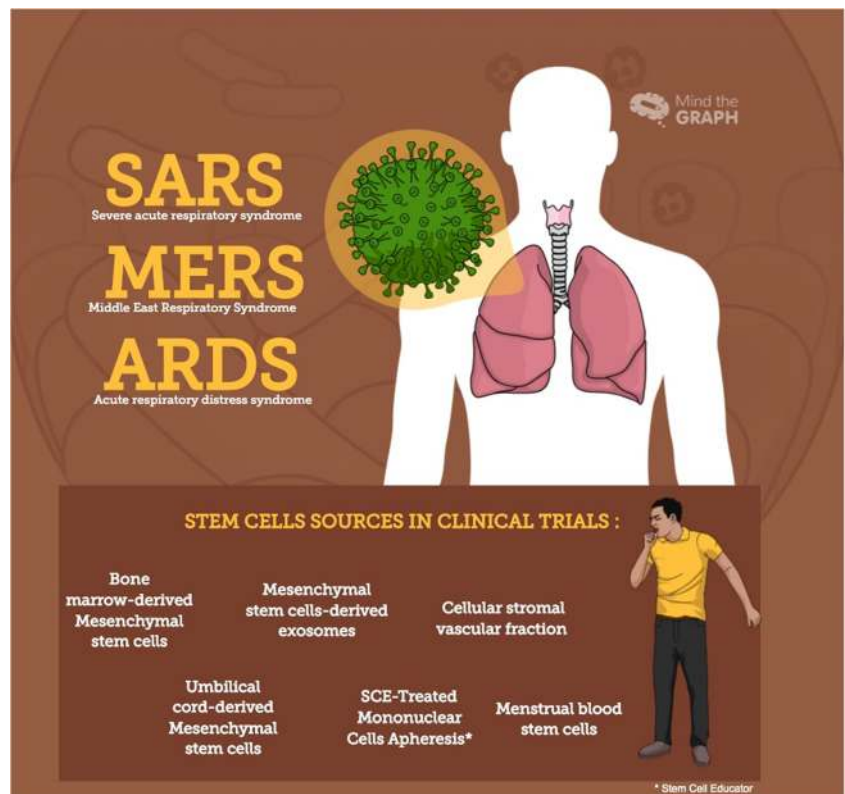
&nbsp;	ClinicalTrials.gov Identifier	Conditions	Study design	Objective	Study Start	Locations	Participants / Ages Eligible for Study	Interventions	Status
Coronavirus Phase 1	NCT02215811	ARDS on extracorporeal membrane oxygenation (ECMO)	Multi-center, open-label, non-randomized controlled trial.	Patients will be enrolled and receive allogeneic BM-MSCs.	March 2014	Sweden	10 / 18	Allogeneic BM-MSCs	Unknown status
	NCT04276987	SARS	Single-arm design, open label, combined interventional clinical trial.	To explore the safety and efficiency of aerosol inhalation of the exosomes derived from allogeneic adipose MSCs in the treatment of severe patients hospitalized with novel coronavirus pneumonia.	February 15, 2020	China	30 / 18–75	MSCs-derived exosomes	Not yet recruiting
	NCT04326036 (Early Phase I)	Pulmonary alveolar proteinosis COPD Idiopathic pulmonary fibrosis	Interventional, non-randomized	To use of autologous, cellular stromal vascular fraction (cSVF) deployed intravenously to examine the anti-inflammatory and structural potential to improve the residual, permanently damaged alveolar tissues of the lungs.	March 25, 2020	United States	10 / 18–90	Cellular stromal vascular fraction (cSVF)	Enrolling by invitation
Phase 1 Phase 2	NCT04333368	ARDS	Interventional, randomized	To treat intubated-ventilated patients with a SARS-CoV-2-related ARDS of less than 96&nbsp;h by three intravenous infusions of umbilical cord Wharton’s jelly-derived mesenchymal stromal cells (UC-MSC).	April 6, 2020	France	60 / 18	UC-MSCs	Not yet recruiting
	NCT04355728 (Phase 1 Phase 2)	ARDS	Interventional, randomized	The trial has two groups, each with 12 subjects (n = 24). All eligible subjects will be randomized to either the treatment group or standard of care, and randomization will be stratified by ARDS severity.	April 25, 2020	United States	24 / 18	UC-MSCs	Recruiting
	NCT04346368	SARS	Interventional, randomized	To investigate the safety and efficacy of intravenous infusion of MSCs in severe patients with COVID-19.	April 2020	China	20 / 18–75	BM-MSCs	Not yet recruiting
Phase 2	NCT04288102	SARS	Prospective, double-blind, multi-center, randomized trial	To assess treatment with three intravenous doses of MSCs compared with placebo.	March 5, 2020	China	90 / 18–75	MSCs	Recruiting
	NCT04299152	SARS	Prospective, two-arm, partially masked, single center clinical study	To assess the safety, feasibility, and efficacy of Stem Cell Educator (SCE) therapy for the treatment of patients with SARS-CoV-2.	May 10, 2020	Not mentioned	20 / 18–60	SCE-Treated Mononuclear cells apheresis	Not yet recruiting
- Applicable	NCT04273646	Pneumonia	Interventional, randomized	To investigate efficiency and safety of UC-MSCs in treating severe	April 20, 2020	China	48 / 18–65	UC-MSCs	Not yet recruiting

Table 2 (continued)

&nbsp;ClinicalTrials.gov Identifier	Conditions	Study design	Objective	Study Start	Locations	Participants / Ages Eligible for Study	Interventions	Status
Not related to coronavirus Phase 1 Phase 1 Phase 1 Phase 2	ARDS	Multi-center, open-label, non-randomized controlled trial. Interventional, randomized	pneumonia patients infected with 2019-nCoV. To treat ARDS with allogeneic bone marrow-derived MSCs.	March 2014	Sweden	10 / 18	Allogeneic BM-MSCs	Unknown
NCT01902082	ARDS	Interventional, randomized	To assess the safety of allogeneic adipose-derived mesenchymal stem cells in patients with ARDS.	November 2012	China	20 / 18–90	MSCs	Unknown
NCT02095444	ARDS Multiple organ failure	Interventional, single group assignment	To determine whether human menstrual blood-derived stem cells are effective in the treatment of infection of H7N9 virus-caused acute lung injury.	March 2014	China	20 / 18	Menstrual blood stem cells	Unknown
NCT04289194 (Phase 1 Phase 2)	ARDS	Interventional, randomized	To assess the feasibility, safety, and tolerability of the administration of HCR040 in patients with ARDS.	December 10, 2019	Spain	26 / 18	HCR040, a drug whose active substance is HCO16, allogeneic adipose-derived adult MSCs expanded and pulsed with H2O2 BM-MSCs Cell reconstitution media	Active, not recruiting
Phase 2 Phase 2	ARDS	Randomized, double-blind, placebo-controlled, multi-center	An assignment will be made by computer-generated randomization to administer either hMSCs therapy or placebo with a 1:1 allocation to the hMSCs:placebo arms.	November, 2019	United States	120 / 18	BM-MSCs Cell reconstitution media	Recruiting
NCT02112500	ARDS	Pilot study, interventional, single group assignment	To evaluate the efficacy and safety of MSCs treatment in patients with respiratory failure.	February 2014	Korea	10 / 20–80	MSCs	Unknown
-	ARDS	Interventional, single group assignment	A package of 100&nbsp;ml normal saline with 10% kg UC-MSCs suspension will be infused from central venous catheter.	June 1, 2018	China	26 / 18	UC-MSCs	Recruiting

BM-MSCs, Bone Marrow-Derived Mesenchymal Stem Cell; UC-MSCs, Umbilical cord derived MSCs

**Fig. 1** Stem cells sources in headStartclinical trialsheadEnd



**Fig. 2** Effects of MSCs-therapy before and after of transplantation on cytokine storm. Source: Leng, et al., (2020). Transplantation of ACE2-headStartMesenchymal Stem CellsheadEnd Improves the Outcome of Patients with COVID-19 Pneumonia. Aging and Disease, 11(2), 216–228

*in vivo* compared to those of the ACE2 and uMSC treatments alone. Thus, according to the authors suggestions, the synergistic effect of ACE2 and uMSCs may be used as a promising novel treatment for lung injury [94].

As suggested by Ulrich & Pillat [95], it is possible that CD147, the second incoming receptor for SARS-CoV-2, is expressed by untransformed lung stem and progenitor cells, but there is still no experimental evidence. This bone marrow receptor can be expressed by tissue-specific stem cells [96]. Soon, it is realized that the loss of airway epithelial cells caused by infection and viral replication suggests another possibility for the lack of cell regeneration considering that regenerating cells and stem cells can be equally lost or infected [95].

### Final Considerations

Anti-inflammatory therapies for patients with ARDS have been developed using stem cells offering a great promise for managing ARDS [70, 97, 98]. MSCs related cell-therapies demonstrate high efficacy in preclinical data allowing their clinical usage [99]. For COVID-19 research and headStartclinical trialsheadEnd, it is important to consider the blood biomarkers involved in the pathophysiology of the disease which provide therapeutic targets and thus improve the clinical care. Moreover, it is essential to understand the role of endogenous lung progenitor cells during the repair of lung injury and also



the mechanism of lung development for developing novel therapeutic strategies [100, 101]. Han et al. [102] mentioned some obstacles in clinical practice that must be considered for COVID-19 as, for example, the low mobilization of transplanted MSCs at the injury site and their low survival rate. The comprehensive interaction between MSCs and the host tissue is a key to the successful therapeutic application whereby experimental studies play a major role in developing lung diseases in clinical translation [37].

Since we know that the mitochondrial disorder caused by the overactivation of Nlrp3 inflammasome is determinant to the pathogenesis of SARS-CoV-2, Nlrp3 inflammasome inhibitors must be taken into account regarding their therapeutic applicability [87–89, 92]. An example for this inhibitory potential is the MCC950 molecule which could affect the binding of SARS-CoV-2 to cells and inhibit the amplification of the intracellular virus, and also the ComC inhibitors that assist in modulating the activity of the innate immune system [93]. Another possible inhibition therapy against SARS-CoV-2 is the use of ACE2 + MSC-derived small extracellular vesicles (sEVs) overexpressed, as suggested by Inal [103].

Regarding the combat against the cytokine storm in the lungs during viral pneumonia, some studies highlighted that the leukemia inhibitor factor (LIF) released by the MSCs may not be expressed enough to supply the damage caused by the disease [104, 105]. As an innovative and technological alternative, there are MSCs with “LIFNano”, nanotechnology that represents a 1000-fold increase in power compared to not using nanotechnology. “LIFNano” acts on damaged tissues and reduces the cytokine storm. Therefore, it represents a therapeutic agent ready to act beneficially against viral pneumonia [106].

Significant advances have been made in three-dimensional (3D) cell culture to develop organoids. These are able to recapitulate the complexity and functionality of different organs. Human lung organoids and bud tip progenitor organoids are composed of cells that are highly similar to the developing human lung. They are ideal for studying developmental biology and tissue engineering. Considering that the cells are specific to the patient’s genetics, the organoids that mimic lung disease may be critical for designing personalized medicine and screening for therapeutic responsiveness [107].

## Conclusion

With the COVID-19 boom, many headStartclinical trialsheadEnd are being carried out using different sources with an emphasis on MSCs. We look forward to the results of the ongoing headStartclinical trialsheadEnd to find a treatment for the disease. Researchers around the world are joining forces to

help fight COVID-19. Stem cells used in the current clinical studies are a new therapeutic promise for COVID-19 where pharmacological treatments seem insufficient.

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## Compliance with Ethical Standards

**Conflicts of Interest** The authors declare that they have no conflict of interest.

**Research Involving Human Participants and/or Animals** Not applicable.

**Informed Consent** Not applicable.

**Abbreviations** ACE 2, Angiotensin-convertingenzyme 2; ALI, Acute lung injury; ARDS, Acute respiratorydistress syndrome; CoV, Coronavirus; MSCs, Mesenchymal stemcells; iPSCs, Induced PluripotentStem Cells; ESCs, Embryonic Stem Cells; HSPCs, hematopoieticstem/progenitor cells; IFITM, Interferon InducedTransmembrane Family; ISGs, Interferon-StimulatedGenes; KGF, keratinocyte growthfactor; MERS, Middle EastRespiratory Syndrome; SARS, Severe acuterespiratory syndrome; TMPRSS2, TransmembraneProtease Serine 2

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