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Review

Mesenchymal stromal/stem cells (MSCs) and MSC-derived extracellular vesicles in COVID-19-induced ARDS: Mechanisms of action, research progress, challenges, and opportunities

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ABSTRACT

In late 2019, a novel coronavirus (SARS-CoV-2) emerged in Wuhan city, Hubei province, China. Rapidly escalated into a worldwide pandemic, it has caused an unprecedented and devastating situation on the global public health and society economy. The severity of recent coronavirus disease, abbreviated to COVID-19, seems to be mostly associated with the patients' immune response. In this vein, mesenchymal stromal/stem cells (MSCs) have been suggested as a worth-considering option against COVID-19 as their therapeutic properties are mainly displayed in immunomodulation and anti-inflammatory effects. Indeed, administration of MSCs can attenuate cytokine storm and enhance alveolar fluid clearance, endothelial recovery, and anti-fibrotic regeneration. Despite advantages attributed to MSCs application in lung injuries, there are still several issues –foremost probability of malignant transformation and incidence of MSCs-related coagulopathy– which should be resolved for the successful application of MSC therapy in COVID-19. In the present study, we review the historical evidence of successful use of MSCs and MSC-derived extracellular vesicles (EVs) in the treatment of acute respiratory distress syndrome (ARDS). We also take a look at MSCs mechanisms of action in the treatment of viral infections, and then through studying both the dark and bright sides of this approach, we provide a thorough discussion if MSC therapy might be a promising therapeutic approach in COVID-19 patients.

1. Introduction

At the end of 2019, the novel coronavirus infection (COVID-19) pandemic was originated in Wuhan, Hubei province, China, and it was confirmed to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As the rate of mortality has been growing dramatically each day, with no dedicated therapeutic agent, COVID-19 has become to be a global public health issue that demands new

Abbreviations: ACE2, Angiotensin-Converting Enzyme 2; AD-MSC, Adipocyte-Derived MSC; AFC, Alveolar Fluid Clearance; ALI, Acute Lung Injury; ALT, Alanine Aminotransferase; Ang-1, Angiopoietin-1; ARDS, Acute Respiratory Distress Syndrome; AST, Aspartate Aminotransferase; AT II, Type II Alveolar Epithelial; BDNF, Brain-Derived Neutrophilic Factor; BM-MSC, Bone Marrow MSC; COPD, Chronic Obstructive Pulmonary Disease; CRP, C-Reactive Protein; CT, Computerized Tomography; DC, Dendritic Cell; DIC, Disseminated Intravascular Coagulation; EV, Extracellular Vesicle; GVHD, Graft-Versus-Host Disease; hESC, Human Embryonic Stem Cell; HGF, Hepatocyte Growth Factor; HIF1-α, Hypoxia-Induced Factor 1-A; IFN, Interferon; IMRC, Immunity and Matrix-Regulatory Cell; IPF, Idiopathic Pulmonary Fibrosis; ISG, Interferon-Stimulated Genes; IV, Intravenous; **KGF**, Keratinocyte Growth Factor; **LDH**, Lactate Dehydrogenase; **LIF**, Leukemia Inhibitory Factor; **LPS**, Lipopolysaccharide; **MERS-CoV**, The Middle East Respiratory Syndrome Coronavirus; **MIP-2**, Macrophage Inflammatory Protein-2; **MOD**, Multiple Organ Dysfunction; **MSC**, Mesenchymal Stromal/Stem Cell; **MVB**, Multi Vesicle Body; **NGF**, Nerve Growth Factor; **NK cell**, Natural Killer Cell; **PDGF**, Platelet-Derived Growth Factor; **PGE2**, Prostaglandin E2; **ROS**, Reactive Oxygen Species; **SARS-CoV**, Severe Acute Respiratory Syndrome Coronavirus; **SPA**, Surfactant Protein A; **SPC**, Surfactant Protein C; **TGF-β**, Transforming Growth Factor-B; **Th**, T Helper; **TMPRSS2**, Transmembrane Protease Serine 2; **TNF- α**, Tumor Necrosis Factor- A; **UC-MSC**, Umbilical Cord MSC; **VEGF**, Vascular Endothelial Growth Factor; **WBC**, White Blood Cell.

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strategies from all around the world. SARS-CoV-2 is genetically similar to two other beta groups of *coronaviruses*, named severe acute respiratory coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) with a mortality rate of 10% and 37%, respectively [1,2]. Despite the lower mortality rate of the novel coronavirus infection than the SARS and MERS epidemics [3,4], the longer incubation period made the SARS-CoV-2 more contagious with a much higher total number of deaths [5,6]. The clinical manifestations of COVID-19 vary from asymptomatic or mild sickness with fever, cough, or lack of breath to severe respiratory failure which requires mechanical ventilation support. Patients with severe COVID-19 are highly at the risk of acute respiratory distress syndrome, secondary infection, coagulopathy, septic shock, and also multiple organ dysfunction (MOD) [5,7,8]. Para-clinical findings in patients with COVID-19 demonstrate hyperactivation of the immune system, which in turn results in inflammatory hyper-response, cytokine-storm, and subsequently, damage of the pulmonary tissue, dysfunction of air exchange, and ARDS [9,10].

Due to immunomodulatory, anti-inflammatory, and other immune properties, mesenchymal stem cells (MSCs) –which according to 2019 ISCT suggestion should be expressed as mesenchymal stromal cells [11]– can play a key role in avoiding or alleviating the cytokine storm. Presently, MSCs are largely used in cell-based therapies and their safety and efficacy, especially for the treatment of immune-mediated inflammatory diseases, have been investigated in numerous clinical trials [12–15]. A large number of clinical trials introduced MSCs as the promising therapeutic approach toward improving the adverse effects of the SARS-CoV-2 infection via immunomodulatory effects, attenuating the cytokine storm, and exerting anti-inflammatory effects [16]. In this study, we review the historical evidence of successful use of MSCs for lung disease and highlight the therapeutic role of MSCs and their EVs such as immunomodulation, alveolar fluid clearance (AFC), endothelial recovery, and anti-fibrotic regeneration in the treatment of viral infections. Also, through discussing the advantage and disadvantage of this approach we deliberate if MSC therapy might be a promising therapeutic approach in COVID-19 patients.

2. An overview of MSCs in viral infections; historical evidence

In 2004, the first inclusive report on MSCs clinical implementation was published, in which allogeneic bone marrow MSCs (BM-MSCs) were injected for pediatric graft-versus-host disease (GVHD), leading to 1-year-survival of the patient [15]. Afterward, MSCs have been widely examined as a valuable treatment option for a wide spectrum of tissue/organ damage especially for immune-mediated inflammatory diseases such as GVHD, inflammatory bowel disease (IBD), Crohn's disease, rheumatoid arthritis, and ARDS [17,18]. This is attributed to their ease of isolation and large *ex vivo* expansion capacity, as well as the ability to interact with other immune cells via secretion of paracrine factors and exerting their immunomodulatory effects [14]. As the lungs are in direct contact with the external environment, they are prone to different infections including viral diseases. Over the past decade, a considerable number of studies shed light on the therapeutic effects of MSCs for lung diseases, such as ARDS [19–23], chronic obstructive pulmonary disease (COPD) [24–28], Asthma [29–42], and idiopathic pulmonary fibrosis (IPF) [43–48].

Despite the limited data from clinical studies, numerous reports suggest the therapeutic function of MSCs in preclinical models of respiratory virus-induced lung infections. A report by Chan et al. showed that the MSCs remarkably diminished the impairment of alveolar fluid clearance caused by the avian influenza virus (H5N1) *in vitro* and reduced A/H5N1-associated acute lung injury (ALI) *in vivo* [49]. Similarly, another study indicated that umbilical cord MSCs (UC-MSCs) may effectively restore alveolar fluid clearance in A/H5N1-associated ALI [50]. Furthermore, a study in a pig model provided interesting evidence showing that extracellular vesicles from MSCs may attenuate influenza virus-induced ALI [51]. Based on the results of a recent study showing that MSCs could improve the survival rate of H7N9-induced ARDS in both preclinical and clinical studies, the authors suggested that the MSC-based therapy could also be an ideal option for treatment of COVID-19 as they share similar complications such as ARDS and ALI [52]; however, in the other two *in vivo* studies in mice infected with A/H1N1, no improvement in inflammation or survival was seen [53,54]. Besides, MSCs are themselves at the risk of being infected with the influenza virus [55,56]. Future studies are needed to clarify the safety and efficacy of MSC's therapeutic role in influenza virus infections. The history beyond the therapeutic effects of MSCs in lung injuries caused by viral infections is summarized in Fig. 1.

3. Plausible mechanisms of MSCs in viral infections

3.1. MSCs and modulation of the immune system

The principle mechanism by which MSCs exert their therapeutic functions is interaction with immune cells either via direct cell–cell contact or with the secretion of soluble immune factors (cytokines, chemokines, growth factors, angiogenic factors, and EVs). Indeed, MSC-regulated immunomodulation affects both innate and adaptive immunity by regulating the activity of neutrophils, monocytes, macrophages, dendritic cells (DC), T cells, B cells, and natural killer (NK) cells. MSCs modulate the T cell functions including inhibition of T helper (Th17) response, generation of regulatory T cells, shifting from Th1 to Th2 subset, and finally decreasing inflammation. Not only do MSCs restrain the proliferation of $CD4^+$ and $CD8^+$ T cell subsets [57,58] they can also significantly influence DC development through prostaglandin E2 (PGE2) production, which eventually leads to the production of anti-inflammatory Th2 subset via differentiation of DCs to the plasmacytoid subset [59]. Apart from the modulation of the T cell responses, MSCs inhibit the proliferation of B cells and prevent their differentiation into plasma cells resulting in a reduction of immunoglobulin secretion [60,61]. MSCs can also hamper oxidative burst in neutrophils, diminish the extracellular release of elastase and myeloperoxidase, and eventually weaken neutrophil infiltration and damage [62]. Concerning the immunomodulatory effects of these cells on innate immunity, Dayan et al. reported that MSCs could also decrease M1-type macrophages that possess a significant pro-inflammatory effect, while they increase alternatively activated M2-type macrophages via down-regulation of IL-1β and IL-6 levels [57]. Indeed, the anti-inflammatory properties of MSCs are mainly mediated by the paracrine pathways. They decrease the secretion of the pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-12, and IFN-γ while elevating the level of the anti-inflammatory IL-10 mediator [63]. Taken together, all these findings reveal that MSCs could hamper the inflammatory responses, at least partly, through polarization of immune cells to the subsets which possess prominent anti-inflammatory characteristics.

3.2. MSCs and alveolar fluid clearance (AFC)

In the case of ARDS, MSCs play a role in clearing alveolar fluid which is disturbed due to cytokine storm in the lungs [64]. It has been reported that human UC-MSCs could improve the AFC impairment by producing a large amount of Angiopoietin-1 (Ang-1) [65] and hepatocyte growth factor (HGF) [50]. Ang-1 serves as a ligand for the Tie2 receptor and plays a key role in vascular stabilization due to its effects on endothelial permeability by inhibiting leukocyte-endothelium interactions and upregulating a tight-junction [66]. HGF, on the other hand, inhibits epithelial apoptosis and also regulates motility, cell growth, and morphogenesis via interaction with the c-Met receptor. Ang-1 and HGF both are considered significant mediators in the restorative properties of UC-MSCs on AFC in A (H5N1)-induced ARDS [50]. Accordingly, it has been reported that HGF could restore lung permeability via inhibition of endothelial apoptosis as well as the protection of tight junctions in a bacterial ALI model [67].

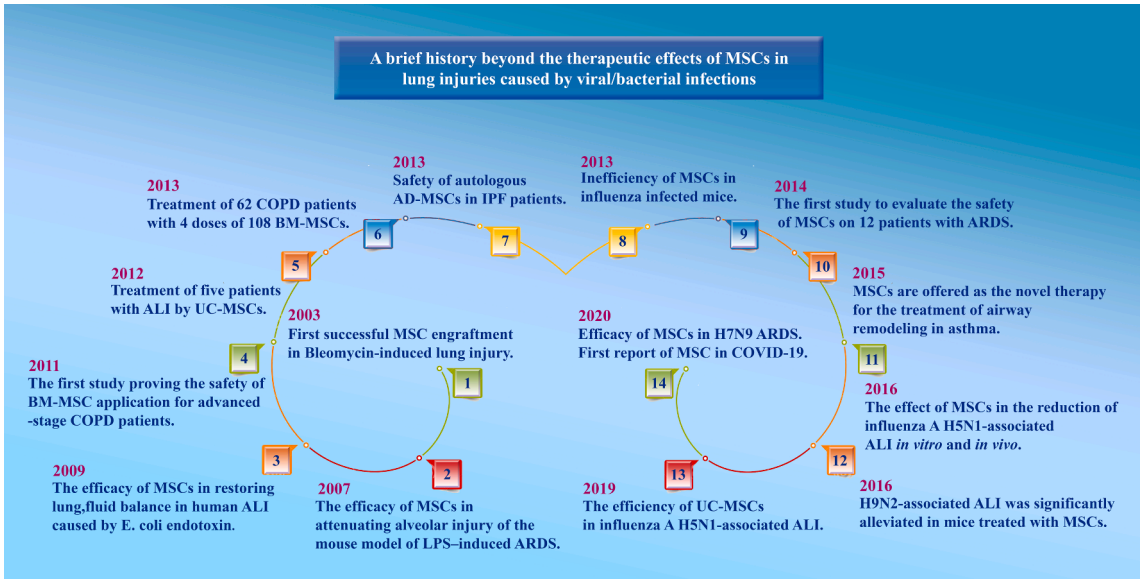

Fig. 1. A glance at the history beyond the application of MSCs in lung injuries. MSC: Mesenchymal stem cell; **LPS:** Lipopolysaccharide; **ARDS:** Acute respiratory distress syndrome; **ALI:** Acute lung injury; **BM:** Bone marrow; **COPD:** Chronic obstructive pulmonary disease; **UC:** Umbilical cord; AD-MSC: Adipocyte-derived MSC; **IPF:** Idiopathic pulmonary fibrosis.

3.3. MSCs and regeneration

Given the fact that MSCs can secret a variety of growth factors including HGF, keratinocyte growth factor (KGF), and vascular endothelial growth factor (VEGF), they have significant ability to play essential roles in tissue regeneration in lung injuries via diminishing collagen accumulation and fibrosis [68]. HGF and VEGF can also restore pulmonary capillary permeability and stabilize the pulmonary endothelial barrier [69]. In a study by Aguilar et al., administration of MSCs expressing KGF resulted in the reduction of bleomycin-induced fibrosis,

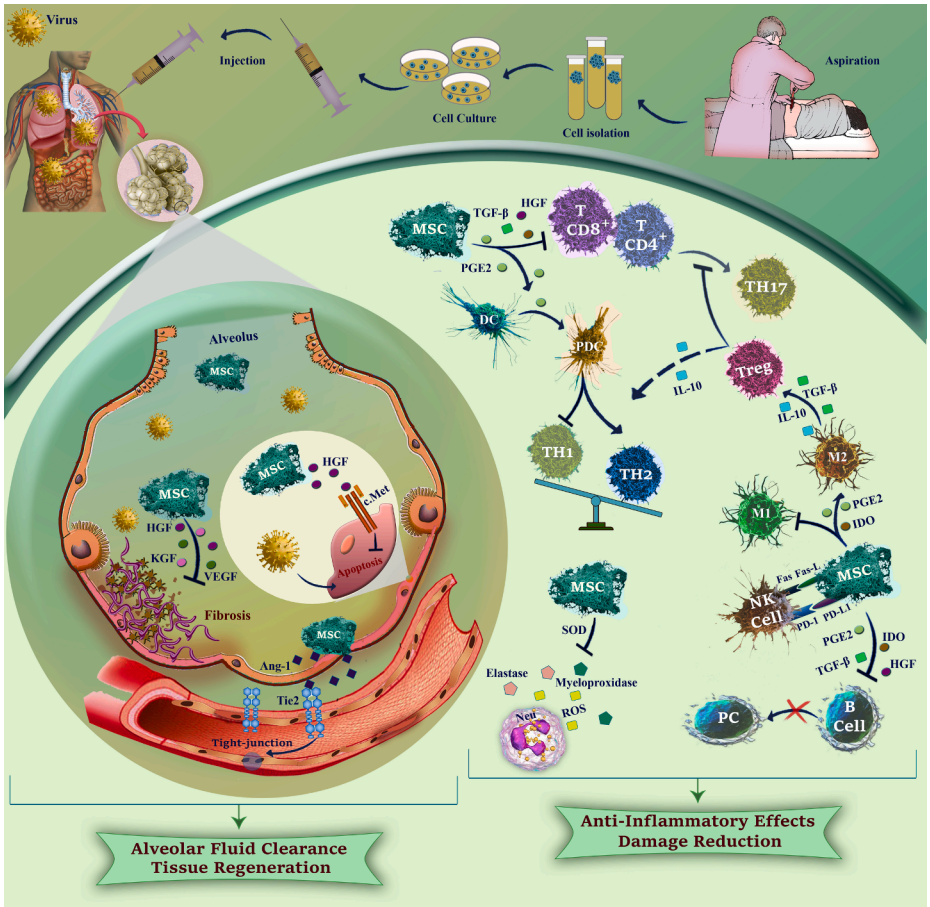

Fig. 2. A schematic overview of the potential mechanisms of action of MSCs against viral infections. MSCs can promote tissue regeneration and enhance alveolar fluid clearance through secretion of HGFs, KGFs, VEGFs, and Ang-1 which reduce fibrosis and facilitate injured endothelium repair. Also, MSCs may attenuate cytokine storm by regulating the immune cells in the inflammatory environment through secretion of anti-inflammatory factors leading to Treg induction, as well as TH2, PDC, and M2 macrophage polarization. Soluble factors from MSCs can prevent oxidative burst in neutrophils and reduce tissue damage via inhibition of extracellular release of elastase and myeloperoxidase.**Ang-1:** Angiopoietin-1; **HGF:** Hepatocyte growth factor; **KGF:** Keratinocyte growth factor; **VEGF:** Vascular endothelial growth factor; **PGE2:** Prostaglandin E2; **TGF- β:** Transforming growth factor-B; **TH:** T Helper; **Treg:** Regulatory T cell; **IDO:** Indoleamine 2,3-dioxygenase; **NK cell:** Natural killer cell; **PD-1-PD-L1:** Programmed death receptor and ligand; **DC:** Dendritic cell; **PDC:** Plasmacytoid DC; **PC:** Plasma cell; **ROS:** Reactive oxygen species; **SOD:** Superoxide dismutase; **Neu:** Neutrophil.

as well as decreasing collagen buildup and maintaining normal alveolar structure [70]. It has been also reported that HGF and KGF from MSCs stabilize B cell lymphoma 2 (Bcl-2), suppress hypoxia-induced factor 1-A (HIF1-α) protein expression, and diminish reactive oxygen species (ROS) production; resulting in an anti-apoptotic effect on the alveolar epithelial cells [71]. To provide a well-conceptualized prospect, we summarized the plausible mechanisms of MSCs in viral infections in Fig. 2.

3.4. MSCs and production of extracellular vesicles

Extracellular vesicles (EVs) are membrane-bound vesicles about 40–1000 nm in size, produced by a variety of human cells. Exosome, microvesicles, and apoptotic bodies are three kinds of EVs. Microvesicles are separated directly by budding from the cell membrane, while exosomes are formed within the endosomal network of multi-vesicular bodies (MVBs) and their fusion with the plasma membrane [72]. MSC-derived EVs mimic many of the beneficial impacts of MSCs and transport a wide range of bioactive factors such as proteins and lipids, as well as transcription factors, mRNA, microRNA, long non-coding RNA, DNA, and signal transduction molecules [73]. Released EVs are the integral component of the cell-to-cell communication network, and upon transfer to the recipient cells, they can modulate downstream signaling. Compared with their parents, EVs administration is safer because they cannot replicate and form a tumor, they are non-immunogenic, and finally, they do not lead to emboli formation. Also, EVs are more stable and viable at − 80 °C for a longer time [74].

Termed as cell-free therapy, EVs have attracted special interest for their clinical application. MSC-derived EVs have been investigated in ARDS due to their ameliorating function in ALI by reducing inflammation, improving edema clearance, enhancing macrophages phagocytosis, and attenuating the severity of cytokine storm, and also tissue repair through the direct mitochondrial transfer of host cells [23,75–78]. In the study by Zhu et al., intratracheal administration of MSC-derived microvesicles was effective for pulmonary edema in the treatment of endotoxin-induced injury in mice by reducing extravascular lung water, restoring lung protein permeability, and reducing the influx of neutrophils and macrophage inflammatory protein-2 (MIP-2) levels through the expression of KGF mRNA in the injured alveolus [23]. In another study, Intratracheal administration of MSC EVs showed the same results by alleviating lung inflammation and restoring alveolar-capillary permeability in LPS-induced ALI mice. Notably, the effect was partly mediated by Ang1 mRNA, which is considered an important vascular-stabilizing factor [79]. Microvesicles derived from human MSCs could also improve the survival of mice injured with bacterial pneumonia by secreting KGF and decreasing the influx of inflammatory cells, cytokines, protein, and increasing the macrophage phagocytosis [76]. Mitochondrial transfer from BM-MSC carrying microvesicles to pulmonary alveoli ensued protective effects against LPS-induced ALI in mice [78,80]. Moreover, the transfer of functional mitochondria from EVs was responsible for the elevation of macrophage phagocytosis through the promotion of oxidative phosphorylation [80]. Apart from ARDS, MSC-derived EVs have been also studied as a potential therapy in the management of other lung injuries including idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, pulmonary arterial hypertension, asthma, and silicosis [81–84]. All in all, MSC-derived EVs due to their advantages over their parents could be considered as an ideal candidate for the clinical application in a wide variety of viral infections, including COVID-19. Fig. 3 provides a schematic representation of the plausible

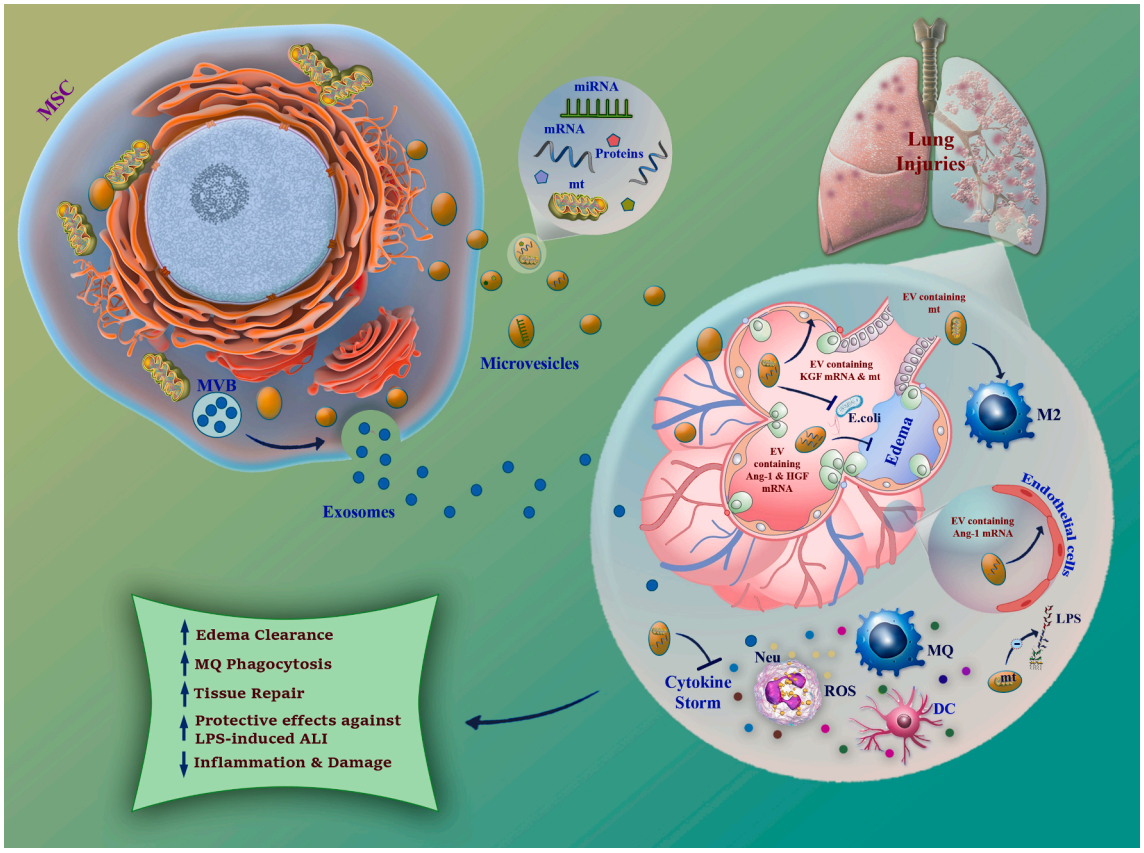

Fig. 3. A Schematic representation of the role of MSC-derived EVs in lung injuries. Microvesicles and exosomes transfer miRNA, mRNA, protein, and mitochondria from their parents to the injured alveolus. EVs containing mitochondria and the mRNAs of KGF, HGF, and Ang-1 can decrease lung edema and enhance the tissue repair process. Mitochondrial transfer not only may hamper LPS-lung injury also inhibit cytokine storm by its modulatory effect on a variety of immune cells. **EV:** Extracellular vesicle; **MVB:** Multi-vesicular Bodies **Mt:** Mitochondria; **Ang-1:** Angiopoietin-1; **HGF:** Hepatocyte growth factor; **KGF:** Keratinocyte growth factor; **LPS:** Lipopolysaccharide; **DC:** Dendritic cell; **Neu:** Neutrophil; **MQ:** Macrophage.

mechanisms of MSC-derived EVs in lung injuries.

4. MSCs as the potential therapy for COVID-19

SARS-CoV-2 viruses are enveloped with positive-stranded RNA of about 26 to 32 kb in length [85]. After entering the lungs, as the first organ exposed to the virus due to its way of transmission, the virus attaches to its functional receptor angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) through the specific recognition of its surface spike (S) protein. A very similar structure also exists in the SARS virus, however, with a lower affinity binding (10–20 times) compared to the S protein of SARS-CoV-2. Notably, this binding capacity indicated the high transmission power of SARS-CoV-2 [86]. RNA is then released into the host cell and uses the replicate machinery of the infected cells [87]. The ACE2 receptor is abundantly distributed not only in alveolar epithelial cells also in the kidneys, liver, heart, and digestive organs; the fact explains why beyond ARDS, patients might go through organ damage, shock, and death from MOD [9]. Inside the host cell, the virus can trigger a "cytokine storm". Indeed, deleterious unrestrained widespread inflammatory response arising from an excessive secretion of pro-inflammatory cytokines finally leads to deadly clinical manifestations of ARDS. The pathophysiology of SARS-CoV-2 has been largely discussed in several recent studies [88–90]. Previous studies indicated that MSCs could be at the risk of various viral infections such as influenza virus [56], hepatitis B virus [91], and human herpesvirus [92]. On the other hand, not only the lack of ACE2 receptors on MSCs may probably make their recognition by SARS-CoV-2 impossible [63] but the expression of interferon-stimulated genes (ISGs) could also induce resistance in MSCs [93]. Inline, RNA-sequence analysis for infused MSCs showed these cells do not express both ACE2 and TMPRSS2, which means MSCs cannot carry risks for cross-contamination of SARS-CoV-2. Infused MSCs also express high levels of type II alveolar epithelial (ATII) specific surfactant protein A (SPA) and surfactant protein C (SPC), indicating the potency of these cells for generating ATII cell [94]. Apart from these interesting characteristics, anti-inflammatory factors such as TGF-β, HGF, leukemia inhibitory factor (LIF), FGF, VEGF, and nerve growth factor (NGF) were highly expressed in MSCs that make these cells applicable candidates in COVID-19 treatment [63].

4.1. Therapeutic roles of MSCs and MSCs-derived EVs in COVID-19

4.1.1. Bone marrow MSCs (BM-MSCs) and umbilical cord MSCs (UC-MSCs)

To date, there have been several clinical studies publishing data regarding the use of MSCs as the novel treatment for SARS-CoV-2 cases. In the first reported study, a total of ten patients was enrolled. The intravenous (IV) administration of clinical-grade BM-MSCs was done for seven patients, while the remaining three patients served as the control group. They were closely followed for 14 days, no adverse effects were observed after MSC injection in seven cases, and MSC therapy could nearly improve all the patients' symptoms. The results of this interesting study revealed that BM-MSCs inhibit the over-activation of the immune system and prevent cytokine storm. Besides, an increase in the regulatory DC population has been observed [63].

Liang et al. have shown the safety and efficacy of treatment with UC-MSC in the modulation of the immune response and recovery of the injured tissue of a 65-years-old female severely ill COVID-19 patient. In this reported case study, a patient with a fever, fatigue, cough, and shortness of breath was treated with glucocorticoid and antiviral drugs which were ineffective. After diagnosis as a critically ill-type COVID-19 with ARDS, she was treated with triple IV infusion of 5×10^7 UC-MSCs. Following the second infusion, besides clinical improvement, white blood cell (WBC) counts and neutrophils decreased to a normal level, and lymphocytes elevated to normal range [95]. The results published by Shu et al. support that human UC-MSCs can be considered as a priority treatment option for severe COVID-19 cases. In the indicated study, a total of 41 patients were divided into 2 groups: 29 patients assigned to the placebo group and 12 assigned to the UC-MSC group. The patients were followed for 2 weeks after hUC-MSC injection. In the hUC-MSC treatment group no invasive ventilation occurred, no mortality was observed, and the patients' clinical symptoms, including shortness of breath, chest tightness, and fatigue were remarkably improved [96]. Meng et al. also conducted a clinical trial for evaluation of the safety of human UC-MSCs in the treatment of moderate and severe cases of COVID-19 in which 9 patients received 3 cycles of UC-MSCs on days 0, 3, and 6. After treatment, the PaO2/FiO2 ratio was improved, and computerized tomography (CT) scans reported improvement of lung injuries. The lung lesions were controlled for six days and completely disappeared within 2 weeks with no serious UC-MSCs infusion-associated adverse events [97]. In a case series, 8 critically ill patients on mechanical ventilation received PLX-PAD, a placenta-derived mesenchymal-like cell therapy. Despite the little sample size and the uncontrolled study design, the clinical status of patients including respiratory variables, kidney function, and positive end-expiratory pressure were improved [98]; further supporting the therapeutic efficacy of UC-MSCs in COVID-19 patients especially those with the critically ill status.

4.1.2. MSCs from other sources

Wu et al. reported IV delivery of a cell population derived from human embryonic stem cells (hESCs), termed immunity and matrix-regulatory cells (IMRCs), could hamper both fibrosis and pulmonary inflammation in a mouse model of lung tissue damage. With regards to the crisis of SARS-CoV-2 disease, IMRCs were administrated to 2 critically ill COVID-19 patients. Within 14 days following IV injection, both patients significantly recovered from pneumonia and tested negative for SARS-CoV-2. Notably, IMRCs may probably be superior to primary UC-MSCs due to stronger immunomodulatory effects, higher consistency in quality, and anti-fibrotic function [99]. Sanchez-Guijo et al. has tested the safety and efficiency of allogenic AD-MSCs for 13 patients with COVID-19 being under mechanical ventilation and treated with anti-inflammatory and anti-viral therapies. Ten out of 13 patients received two doses, 2 patients were treated with a single dose and 1 patient received 3 doses of AD-MSCs (0.98×10^6 cell/kg). Clinical improvement was seen in 69.2% of the patients and 7 patients were extubated and discharged. No adverse effect related to cell therapy was observed and the treatment resulted in the reduction of inflammatory factors including CRP, lactate dehydrogenase (LDH), ferritin, IL-6 as well as an increase in B and T lymphocytes [100]. In another clinical study by Chen et al., menstrual blood-derived MSCs were given to 25 patients with the median age of 70 years in a single, double, and triple infusion of 1×10^6 cells/kg. After treatment, abnormal signs of CT scan were improved in 16 cases, both PO_2 and SO_2 were increased while the levels of IL-6 and CRP were decreased. While no patients died during hospitalization, three cases underwent treatment-associated side effects, specifically heart failure, liver dysfunction, and allergic rash [101]. To provide a well-conceptualized overview, we summarized the results of previous studies that investigated the therapeutic roles of MSCs in COVID-19 in Table 1.

4.1.3. MSC-derived EVs

In an open-label randomized cohort study conducted by Sengupta et al., the efficiency and safety of allogenic BM-MSC-derived exosomes (ExoFlo™) have been investigated for the first time for patients with COVID-19. A single dose of ExoFlo (15 ml via the IV route) was infused into 24 critical patients with COVID-19. They showed that MSC-derived exosomes can downregulate cytokine storm, restore oxygenation, and reconstitute immunity in hospitalized patients with severe conditions. No adverse effects were attributed to the treatment and significant reduction of CRP, ferritin, and D-dimer were seen. Also, the absolute neutrophil/lymphocyte count and oxygenation were improved [102]. Up to now, 8 clinical trials using MSC-derived EVs to treat COVID-19 are

Table 1
A summary of the studies that investigated the therapeutic roles of MSCs in COVID-19.

	Severity	Dose and route	No.	Aim and outcome	Ref
BM-MSCs					
	ARDS	A single dose of 1 × 10^6 cells/kg; IV	20	Assessment of the PaO2/FiO2 ratio, oxygen saturation, sequential organ failure assessment, duration of ICU stay and hospitalization, Oxygen therapy-free days, and alterations of inflammatory parameters.	[103]
	Moderate/severe	A single dose of 10 × 10^6 cells/kg; IV	60	Resulted in a fewer number of organ failure-free days, a higher oxygenation index, and a greater decrease of plasma Ang-2.	[104]
	Moderate/severe	Single doses of 1 × 10^6 cells/kg; IV	10	Improved pulmonary function, decreased level of CRP, TNF-α, cytokine storm, and increased regulatory DC population.	[63]
UC-MSCs					
	ARDS	Three doses of 5 × 10^7 cells; IV	1	WBC count, neutrophils, and lymphocytes changed to normal, and inflammation symptoms relieved.	[95]
	Moderate/severe	Three doses of 3 × 10^7 cells; IV	18	Decreased the level of IL-6, improved Pao2/Fio2, and ameliorated lung CT scan.	[97]
	Severe/critical	A single dose of 5 × 10^6 cells; IV	41	Improved clinical symptoms, including fatigue, oxygen saturation, and shortness of breath, reduced CRP and IL-6 level, WBC count returned to the normal range, and lung inflammation improved.	[96]
	ARDS	Two doses of 0.7 × 10^6 cells/kg; IV A single dose of 0.3 × 10^6 cells/kg; IT	1	Improved hypoxemia and electrolyte, reduced level of CRP, and improved chest X-ray.	[105]
	ARDS	Two doses of 100 ± 20 × 10^6; IV	24	Inflammatory cytokines were significantly decreased, higher survival rate with shorter time of recovery	[106]
	ARDS	A single dose of 400 × 10^6 cells; IV	60	The incidence of serious adverse events, oxygenation Index, PaO2/FiO2 ratio, and sequential organ failure, length of ICU and hospital stay, and mortality rate were assessed.	[107]
	Severe/critical	A single dose of 1 ×		Increased SpO_2 to the normal range,	[108109]
	ARDS	10^6 cells/kg; IV	1	improved lung CT scan, neutrophils and lymphocytes returned to normal range, and decreased levels of ALT, AST, and CRP. Reduced serum levels of TNF-α, CRP, IL-6, and INF-γ, and resulted in remarkable signs of recovery in lung CT scan.	
		Three doses of 200 × 10^6 cells, IV	11		
Placenta-derived MSCs					
	ARDS	One to two doses of 3 × 10^8 cells; IV	8	Decreased CRP level, and improved positive end-expiratory pressure and PaO2/FiO2 ratio.	[98]
IMRCs					
	ARDS	Single-dose; IV	2	Recovery from pneumonia, a decrease of pro-inflammatory cytokines (TNF-α, TGF-β), improvement of survival rate in a dose-dependent manner, and reduction of inflammation and lung fibrosis.	[99]
AD-MSCs					
	Severe/critical	Three doses of 0.98 × 10^6 cells/kg; IV	13	Reduced CRP, IL-6, ferritin, LDH, and D-dimer levels, and increased lymphocyte count.	[100]
Menstrual blood-derived MSCs					
	Severe/critical	Three doses; IV	2	Increased $CD4^+$ T cells, decreased IL-6 and CRP levels, and improved partial pressure and O2 saturation.	[110]
	Severe/critical	Three doses of 0.3 × 10^7cells, IV	44	Decreased rate of mortality, and significantly improved dyspnea.	[111]

BM: Bone marrow; **MSC:** Mesenchymal stem cell; **ARDS**: Acute respiratory distress syndrome; **IV**: Intravenous; **IT:** Intratracheal**; PaO2/FiO2**: arterial oxygen partial pressure to fractional inspired oxygen; **Ang-2:** Angiopoietin 2; **UC:** Umbilical cord; **WBC**: White blood cell; **CT**: Computerized tomography; **INF:** Interferon; **IMRCs:** Immunity and matrix-regulatory cell; **CRP**: C-reactive protein; **Spo2:** Peripheral oxygen saturation; **ALT:** Alanine aminotransferase; **AST:** Aspartate aminotransferase; **TNF-α:** Tumor necrosis factor-A; **TGF-β:** Transforming growth factor- B; **LDH:** Lactate dehydrogenase; **DC:** Dendritic cell.

registered in clinicaltrials.gov, among which 4 are still in progress (Table 2). Fig. 4 provides a summary of the therapeutic roles of MSCs and MSCs-derived EVs in COVID-19.

4.2. Optimizing the MSC therapy regimes

Several key points in MSC therapy should be considered to improve the capacity of MSCs in treating COVID-19, including administration route, the period window of administration, optimal dose, source of administration, and last but not least, dose frequency. IV infusion seems to be the most favorable mode of MSC delivery in ARDS and COVID-19 in the majority of clinical trials. It is the least invasive in comparison to intra-arterial or tissue injection. More importantly, due to the trapping property of MSCs, most of the cells injected via the IV route remain in

Table 2
Ongoing clinical trials using MSC-derived extracellular vesicles for treatment of COVID-19.

Dose	Route	No.	Phase	Status	Location	Primary Outcome Measures	Identifier
20 doses 0.5–2 × 10^{10} of exosomes	Inhalation	90	2	Enrolling by invitation	Russia	1. Safety assessments such as adverse events will be registered and monitored during all trials. 2. Safety assessments such as adverse events during the inhalation procedures.	NCT04602442
5 doses of 2 × 10^{8} nanovesicles	inhalation	24	1	Completed	China	1. Adverse events assessment within 28 days. 2. Efficiency evaluation within 28 days, including the time to clinical improvement.	NCT04276987
20 doses of 0.5–2 × 10^{10} exosomes	Inhalation	30	1|2	Completed	Russian	1. Safety assessments such as adverse events will be registered and monitored during all trials. 2. Safety assessments such as adverse events during the inhalation.	NCT04491240
1 dose of 2–20 × 10^{8} nanovesicles	inhalation	27	1	recruiting	China	Safety evaluation within 7 days after the first treatment, including frequency of adverse reactions.	NCT04313647
2 doses of 1 × 10^{8} MSCs + 2 doses of EV	IV	60	2|3	Recruiting	Iran	1. Adverse events assessment within 28 days. 2. Blood oxygen saturation.	NCT04366063
NA	IV	60	2	Not yet recruiting	USA	1. All-cause mortality. 2. Median days to recovery.	NCT04493242
3 doses of 0.5–1 cc secretome	IM	48	2	Recruiting	Indonesia	NA	NCT04753476
4 doses of 2–8 × 10^{10} exosomes	IV	55	1|2	Not yet recruiting	USA	1. Adverse events assessment within 90 days. 2. Quality efficacy of exosome therapy within 90 days.	NCT04798716

MSCs: Mesenchymal stem cells; **AT-MSCs**: Adipocyte Tissue-MSCs; **IV:** Intravenous; **EV**: Extracellular vesicle; **IM:** Intramuscular; **NA**: Not available.

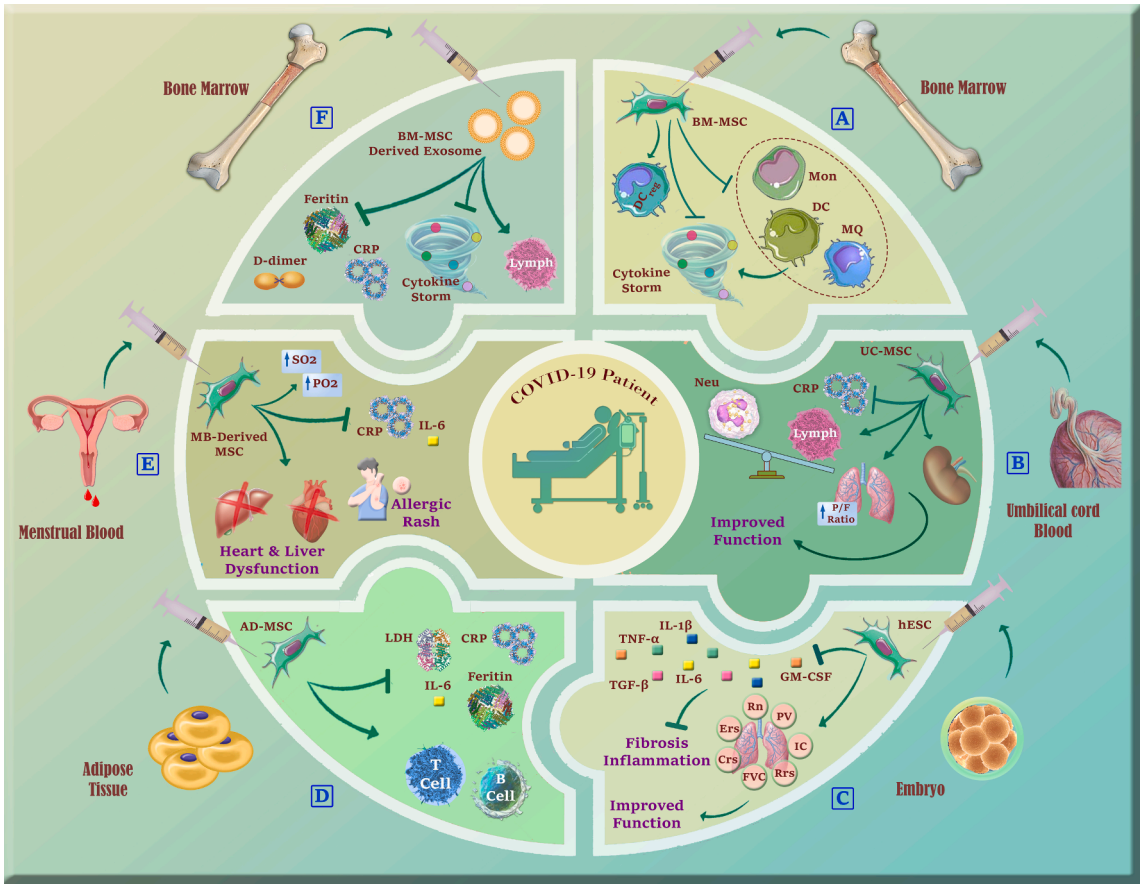

Fig. 4. A schematic summary of clinical application of MSCs and their EVs from different sources in COVID-19 patients. A) BM-MSCs could modulate inflammation via downregulation of cytokine storm induced by the overactivation of pro-inflammatory immune cells. **B)** Administration of UC-MSCs could return immune cells to the normal range, decrease CRP level, and improve lung and kidney function. **C)** Human embryo-derived stem cells not only could improve lung function also prevent fibrosis and pulmonary inflammation. **D)** AD-MSC therapy resulted in a decreased level of inflammatory factors and increased B and T cell populations. **E)** Following menstrual blood-derived MSCs injection, the inflammatory factors were decreased, however, the patients underwent several treatment-associated side effects. **F)** Administration of BM-MSC-derived exosomes could improve the outcome of the disease through their significant attenuating effect on D-dimer, inflammation, and cytokine storm.**Mon:** Monocyte; **DC:** Dendritic Cell; **MQ:** Macrophage; **UC-MSC:** Umbilical cord MSC; **CRP:** C- reactive protein; **Neu:** Neutrophil; **P/F ratio:** Arterial oxygen partial pressure to fractional inspired oxygen; **hESC:** Human embryonic stem cell; **GM-CSF:** Granulocyte-macrophage colony-stimulating factor; **TNF- α:** Tumor necrosis factor-A; **TGF- β:** Transforming growth factor-B; **AD-MSC:** Adipocyte-derived MSC; **LDH:** Lactate dehydrogenase.

the lungs that is the main organ affected mostly in ARDS and COVID-19. Also, IV administrated MSCs might be beneficial for the recovery of other organs as severe cases might suffer from MOD syndrome. However, the safety issues should be considered during IV delivery of MSCs in COVID-19 patients because of high pro-coagulant tissue factor (TF/CD142) expression in MSC products. Anticoagulation issues might have less significance in other routes of delivery such as intramuscular leading the cells into the extravascular space directly [112].

The most frequent doses for transfusion of human MSCs range from one-two million cells/kg and never exceed a dose of twelve million cells/kg. The median dose is 1×10^8 cells/patient in the IV route, however, the efficiency dose–response results have shown a narrower minimal effective dose between 100 and 150 million, and less efficacy is attributed to either higher or lower doses [13,113]. The timing of MSC administration is also significant as the life-threatening cytokine storm, ARDS, and organ failure occur quickly. It was suggested that when symptoms are progressively getting worse, it is the optimum time for MSCs transplantation [63].

There is a preference for allogeneic transplantation of MSCs over the autologous one in the case of COVID-19 due to the time limitation for treatment, especially in severe cases [114]. On the other hand, MSC capacities are affected by age of the donor. It has been reported that MSCs received from older donors have shown a lower proliferation rate, poor homing, reduced immunomodulatory properties, and a higher percentage of apoptotic cells [115]. This means that autologous alternative is questionable in the elderly due to their liability to suffer severe COVID-19. MSCs from different sources also vary in their biological properties. According to a systematic review study by McIntyre et al., BM-MSCs and UC-MSCs are more effective in the treatment of acute lung disease [116]. However, because of the relatively low count of MSCs from BM, it might not be sufficient for the systematic disease caused by the SARS-CoV-2 virus, and among other available sources, MSCs obtained from umbilical cord –which has a higher concentration of stem cells and also obtained by a non-invasive method – seems the most desirable. Moreover, UC-MSCs have a fast doubling time and they could be expanded faster in culture, providing enough cells for multi-organ damage in COVID-19 cases. UC-MSCs have a gene expression profile similar to embryonic MSCs; they have a higher proliferation speed, more plasticity, and unlike ESCs, possess no tumorigenic effects [117–119]. Taken together, adjusting the safe production of MSCs, in addition to settling an agreement on clinical trials concerning MSCs source and dose, administrative time, and mode of delivery might be pivotal for an effective and safe MSC-based therapy in COVID-19. Notably, pre-clinical animal data recommend the augmented MSCs either by the cytokine pre-activation, genetic engineering, or reprogramming to boost their threats potency [120], and future investigations should focus to develop modified MSCs that could safely and efficiently exert therapeutic effects.

4.3. Ongoing clinical trials of MSC therapy in COVID-19

Several clinical and pre-clinical studies have investigated the role of MSCs and their extracellular vesicles in the treatment of SARS-CoV-19 disease. Although the results of preliminary reports are promising, further trials in a larger cohort of patients are required to validate the definite safety and efficiency of MSCs and MSCs-derived EVs in mollifying symptoms associated with the COVID-19 infection. As per the time of submission of this review - April 2021, there are 74 ongoing studies related to the use of MSCs from various sources in the treatment of COVID-19 that are registered on clinicaltrial.gov. (Table 3).

5. MSC therapy in the dark and bright side

Within the past decade, MSC-based therapies have gained interest among researchers because of their promising therapeutic roles in the treatment of inflammatory diseases. However, in regards to COVID-19, most of the clinical trials are yet ongoing and research concerning MSCs and their EVs is in its infancy. There have been only a few published results from clinical trials using MSCs for COVID-19 with none of them enrolled a large group of patients and with a detailed report of adverse effects. Therefore, despite the mentioned advantages attributed to MSCs application in lung injuries including COVID-19, there are still issues requiring to be resolved for the successful application of these cells. One of them involves the clinical-grade production of MSCs in this pandemic situation since a growing number of people are being infected with SARS-CoV-2, many of whom might be eligible for cell-based therapy meaning that we require to have a product ready-to-use on the shelf. Moreover, there are plenty of concerns regarding the stability of MSCs preparation. During *ex vivo* culture and passaging, MSCs go through cellular and molecular shifts [121]. The changes affect the proliferation, differentiation, homing to the site of injury, secretion of paracrine factors, the exhibition of morphological changes, and even probability of malignant transformation [122]. Previous studies reported that, in a specific vision, SCs may be compared to malignant cells as they can proliferate for a long period, suppress antitumor immunity, and escape apoptosis. Besides, pro-angiogenic factors such as platelet-derived growth factor (PDGF), VEGF, HGF, and Ang-1 released by MSCs can trigger angiogenesis [123]. This means the long-term evaluation of patients who received MSC therapy may be necessary to follow-up their tumorigenic capacity, especially in elder cases with compromised antitumor immunity.

Last but not least, it is reported that some cases of critically ill COVID-19 are highly prone to disseminated intravascular coagulation (DIC) and thromboembolism due to their pro-coagulant state. On the other hand, MSC products from various sources, especially AT-derived MSCs, express high levels of tissue factor (TF). TF is recognized as one of the crucial determinants of cell product hemocompatibility which can trigger instant blood-mediated inflammatory reaction (IBMI) following activation of the host innate immune cascade systems, including complement and coagulation by infused MSCs [124]. Being aware of the risk of lethal thrombotic complication, especially for the reactivated patients, alternative non-IV regimes, standardized hemocompatibility testing for new applied MCs, and administration of anticoagulant before application of high doses of MSCs should be seriously considered [125,126]. All in all and taking all these concerns into account, we propose that MSCs-based therapeutic strategies should apply for COVID-19 cases only when its significant medical justifications and safety concerns are determined.

6. Conclusion and future perspective

Millions of people have been influenced with COVID-19 with no verified treatment available. Currently, supportive therapies, as well as non-specific anti-viral drugs, are mainly used for this purpose; however, MSC therapy seems to be a promising answer to this pandemic. ARDS, the major cause of respiratory failure that is characterized by injury to both the pulmonary endothelium and alveolar epithelium, is the most common complication of COVID-19 cases requiring mechanical ventilation and ICU support. IV-infused MSCs migrate directly to the lungs and secret a wide variety of factors to diminish pro-inflammatory cytokines, reduce pulmonary edema, elevate the rate of AFC, and inhibit cellular apoptosis. MSC-derived EVs has been also shown to down-regulate cytokine storm, restore oxygenation, and reconstitute immunity in hospitalized COVID-19 patients with a severe condition. Notably, compared with their parents, exosomes seem to be safer because they cannot replicate and form a tumor, they are non-immunogenic, and they do not lead to emboli formation. Despite the safety and efficacy of MSCs in cell-based therapies have been shown in Phase I and Phase II of numerous clinical trials and several tens of them already made their way to Phase III, this field is in its infancy in COVID-19 and further studies regarding the ideal source and dose, optimum route of administration, and the time window of MSCs administration remains to be done.

Table 3
Registered clinical trials on the Clinicaltrials.gov administrating MSCs to treat COVID-19.

SC source	Dose and Route of administration	No.	Phase	Status	Location	Study design	Identifier
BM-MSCs							
BM-MSCs	A single dose of 1–2 × 10^6 cells/kg, IV	9	1	Recruiting	Sweden	Interventional, Single Group Assignment, Open-Label Masking	NCT04447833
BM-MSCs	Three times of 1.5–3 × 10^6 cells/kg, IV	20	1|2	Recruiting	Belgium	Single Group Assignment, Open Label	NCT04445454
BM-MSCs	Two doses of 2 × 10^6 cells/kg, IV	20	2	Recruiting	Pakistan	Randomized, Parallel Assignment, Open Label	NCT04444271
BM-MSCs	Gp 1: Three doses of 25 × 10^6 cells/kg, IV Gp 2: Three doses of 50 × 10^6 cells/kg, IV Gp 3: Three doses of 90 × 10^6 cells/kg, IV	9	1	Recruiting	Canada	Non-Randomize, Interventional, Sequential Assignment, Open Label	NCT04400032
BM-MSCs	NA	45	1	Recruiting	USA	Randomized, Parallel Assignment, Quadruple Masking	NCT04397796
BM-MSCs	NA	10	NA	Not yet recruiting	UK	Observational, Case-Only, Prospective	NCT04397471
BM-MSCs	NA	40	2	Not yet recruiting	Germany	Randomized, Parallel Assignment, Open Label	NCT04377334
BM-MSCs	Two doses of 2 × 10^6 cells/kg, IV	223	3	Active, not recruiting	USA	Randomized, Parallel Assignment, Triple Masking	NCT04371393
BM-MSCs	A single dose of 1 × 10^6 cells/kg, IV	20	1|2	Not yet recruiting	China	Randomized, Parallel Assignment, Single Masking	NCT04346368
BM-MSCs	Four doses of 1 × 10^8 cells/kg, IV	30	1	Not yet recruiting	USA	Single group, Parallel Assignment, Open Label	NCT04345601
BM-MSCs	A single dose of 1 × 10^6 cells/kg	10	1	Not yet recruiting	Brazil	Single Group Assignment-Open Label	NCT04467047
BM-MSCs	A single dose of 2 × 10^6 cells/kg	600	NA	Completed	Pakistan	Non-Randomized, Factorial Assignment, Open Label	NCT04492501
BM-MSCs	Two doses, IV	40	2	Recruiting	USA	Randomized, Parallel Assignment, Quadruple Masking, double-blind	NCT04780685
UC-MSCs							
UC-MSCs	A single dose, IV	40	1	Completed	USA	Randomized, Single Group Assignment, Triple Masking	NCT04573270
UC-MSCs	Two doses of 10 × 10^7 cells, IV	60	1|2	Recruiting	USA	Randomized, Parallel Assignment, Triple Masking	NCT04494386
UC-MSCs	Two doses of 10 × 10^7 cells, IV	21	1|2	Not yet recruiting	USA	Randomized, Parallel Assignment, Double Masking	NCT04490486
UC-MSCs	A single dose of 1 × 10^6 cells/kg, IV	40	1	Recruiting	Indonesia	Randomized, Interventional, Parallel Assignment, Triple Masking	NCT04457609
UC-MSCs	Single-dose of 0.5, 1, 1.5 × 10^6 cells/kg, IV	39	1|2	Not yet recruiting	USA	Non-Randomized, Sequential Assignment, Open Label	NCT04452097
UC-MSCs	5 × 10^5 cells/kg, IV	20	2	Recruiting	Pakistan	Randomized, Parallel Assignment, Open Label	NCT04437823
UC-MSCs	A single dose of 1 × 10^6 cells/kg, IV	30	2	Not yet recruiting	Colombia	Randomized, Parallel Assignment, Triple Masking	NCT04429763
UC-MSCs	1 × 10^6 cells/kg, IV	10	2	Recruiting	Mexico	Allocation: Non-Randomized, Parallel Assignment, Open Label	NCT04416139
UC-MSCs	Three doses of 1 × 10^6 cells/kg	30	1|2	Recruiting	USA	Randomized, Single Group Assignment, Quadruple Masking	NCT04399889
UC-MSCs	A single dose of 1 × 10^6 cells/kg	70	1|2	Not yet recruiting	USA	Randomized, Parallel Assignment, Double Masking	NCT04398303
UC-MSCs	Three doses 3 × 10^6 cells, IV	30	1|2	Recruiting	Turkey	Randomized, Parallel Assignment, Quadruple Masking	NCT04392778
UC-MSCs	Two doses of 50 × 10^6 cells, IV	40	1|2	Not yet recruiting	Colombia	Randomized, Parallel Assignment, Quadruple Masking	NCT04390152
UC-MSCs	Four doses of 1 × 10^6 cells, IV	60	1	Active, not recruiting	China	Randomized, Parallel Assignment, Open Label	NCT04371601
UC-MSCs	NA	106	2	Recruiting	Spain	Randomized, Parallel Assignment, open-label	NCT04366271
UC-MSCs	Two doses of 100 × 10^6 cells, IV	24	1|2	Completed	USA	Randomized, Parallel Assignment, Triple Masking	NCT04355728
UC-MSCs	Three doses of 4 × 10^7 cells, IV	100	2	Completed	China	Randomized, Parallel Assignment, Quadruple Masking	NCT04288102
UC-MSCs	Four doses of 5 × 10^6 cells, IV	48	NA	Not yet recruiting	China	Randomized, Parallel Assignment, Open Label	NCT04273646
UC-MSCs	Four doses of 9.9 × 10^7 cells, IV	16	2	Recruiting	China	Non-randomized, Single Group Assignment, Open Label	NCT04269525
UC-MSCs	Three doses of 3 × 10^7 cells, IV	20	1	Recruiting	China	Non-Randomized, Parallel Assignment, Open Label	NCT04252118
UC-MSCs	Two doses of 1 × 10^6 cells/kg, IV	30	1|2	Recruiting	China	Randomized, Parallel Assignment, Triple Masking	NCT04339660
UC-MSCs	A single dose of 4 × 10^8 cells, IV	75	1|2	Recruiting	UK	Randomized, Parallel Assignment, Quadruple Masking	NCT03042143
UCWJ-MSCs	Three doses of 1 × 10^6 cells, IV	47	1|2	Active, not recruiting	France	Randomized, Interventional, Parallel Assignment, Triple Masking	NCT04333368
CB-MSCs	NA, IV	70	1	Recruiting	USA	Randomized, Parallel Assignment, Open Label	NCT04565665
PLX-PAD	High and low doses, IV	140	2	Recruiting	USA	Randomized, Parallel Assignment, Quadruple Masking	NCT04389450
PLX-PAD	A single dose of 3 × 10^8 cells, IV	40	2	Recruiting	Israel	Randomized, Parallel Assignment, Open Label	NCT04614025
Placenta-MSCs	Three doses of 1 × 10^6 cells/kg, IV	30	1|2	Recruiting	Ukraine	Non-Randomized, Parallel Assignment, Open Label	NCT04461925
Embryonic SCs	1 × 10^6 cells	9	1|2	Recruiting	China	Interventional, Open Label	NCT04331613
WJ-MSCs							
WJ-MSCs	Three doses of 10^6 cells/kg	30	2	Not yet recruiting	Spain	Randomized, Single Group Assignment, Quadruple Masking	NCT04625738

(*continued on next page*)

Table 3 (*continued*)

SC source	Dose and Route of administration	No.	Phase	Status	Location	Study design	Identifier
WJ-MSCs	A single dose of 10×10^7 cells, IV	9	1	Active, not recruiting	Mexico	Single Group Assignment, Open Label	NCT04456361
WJ-MSCs	10^6 cells, IV	30	1|2	Recruiting	Spain	Randomized, Parallel Assignment, Quadruple Masking	NCT04390139
WJ-MSCs	Four doses of 1×10^6 cells/kg, IV	5	1	Recruiting	Jordan	Single Group Assignment, Open Label	NCT04313322
AD-MSCs							
AD-MSCs	A single dose of 1×10^6 cells/kg, IV	20	1	Recruiting	Mexico	Randomized, Parallel Assignment, Open Label	NCT04611256
AD-MSCs	NA	10	1|2	Not yet recruiting	Korea	Single Group Assignment, Open Label	NCT04527224
AD-MSCs	four times 10×10^7 cells/time	6	1	Not yet recruiting	Japan	Single Group Assignment, Open Label	NCT04522986
AD-MSCs	NA, IV	20	1	Recruiting	USA	Interventional, Single Group Assignment, Open Label	NCT04486001
AD-MSCs	Five doses of 1×10^8 cells	20	2	Recruiting	USA	Interventional, Single Group Assignment, Open Label	NCT04349631
AD-MSCs	Three doses of 20×10^7 cells, IV	200	2	Not yet recruiting	USA	Randomized, Parallel Assignment, Double Masking	NCT04428801
AD-MSCs	Five doses of 2×10^8, 1×10^8, 5×10^7 cells, IV	100	2	Enrolling by invitation	USA	Randomized, Parallel Assignment, Quadruple Masking	NCT04348435
AD-MSCs	Two doses of 8×10^7 cells, IV	26	1|2	Active, not recruiting	Spain	Randomized, Parallel Assignment, Open Label	NCT04366323
AD-MSCs	5×10^7 cells/kg, IV	20	1	Not yet recruiting	USA	Non-Randomized, Sequential Assignment, Open Label	NCT04352803
AD-MSCs	Four doses of 1×10^8 cells, IV	100	2	Active, not recruiting	USA	Randomized, Parallel Assignment, Quadruple Masking	NCT04362189
AD-MSCs	Two doses of 1.5×10^6 cells/kg	100	2	Not yet recruiting	Spain	Randomized, Parallel Assignment-Quadruple Masking-Multi center	NCT04348461
AD-MSCs	$1–1.5 \times 10^6$ cells/kg	100	2	Not yet recruiting	USA	Randomized, Parallel Assignment, Double Masking	NCT04728698
AD-MSCs	Five doses, IV	56	2	Active, not recruiting	USA	Interventional, Single Group Assignment, Open Label	NCT04349631
Other Sources							
DP-MSCs	Three doses of 3×10^7, IV	20	1|2	Recruiting	China	Randomized, Interventional. Parallel Assignment, Triple Masking	NCT04336254
DP-MSCs	Three doses of 1×10^6 cells, IV	24	1	Not yet recruiting	China	Interventional, Single Group Assignment, Open Label	NCT04302519
LMSCs	Three doses of 1×10^8 cells, IV	70	1	Recruiting	USA	Randomized, Parallel Assignment, Double Masking	NCT04629105
Cymerus MSCs	2 million cells/kg, IV	24	1|2	Recruiting	Australia	Randomized, Parallel Assignment, Open Label	NCT04537351
RNA-engineered	NA	30	1|2	Recruiting	USA	Single Group Assignment, Open Label	NCT04524962
Olfactory MSCs	NA, IV	40	1|2	Enrolling by invitation	Belarus	Non-Randomized, Parallel Assignment, Open Label	NCT04382547
SCE	A single dose, IV	20	2	Not yet recruiting	China	Randomized, Parallel Assignment, Single Masking	NCT04299152
NHPBSCs	1×10^6 cells, IV	146	1|2	Completed	UAE	Randomized, Open-Label	NCT04473170
Progenitor	NA, IV	400	2|3	Recruiting	USA	Randomized, Parallel Assignment, Quadruple Masking,	NCT04367077
Undefined-MSCs							
MSCs	Three doses of 300×10, IV	30	2	Recruiting	USA	Randomized, placebo-controlled-parallel assignment, Triple Masking	NCT04466098
MSCs	250 to 750 million	22	1|2	Recruiting	USA	Randomized, Interventional, Parallel Assignment, Quadruple Masking	NCT04445220
MSCs	A single dose of 1×10^6 cells/kg	20	2	Recruiting	Spain	Randomized, Parallel Assignment, Double Masking	NCT04615429
MSCs	A single dose of 2.5,5 or 10×10^7 cells, IV	20	1	Recruiting	Brazil	Randomized, Parallel Assignment, Open Label	NCT04525378
MSCs	Four doses of 2×10^7 cells, IV	90	2	Not yet recruiting	Brazil	Interventional, Parallel Assignment, Quadruple Masking	NCT04315987
MSCs	Three doses of 1×10^6 cells/kg	21	NA	Completed	Turkey	Randomized, Parallel Assignment, Open Label	NCT04713878
MSCs	A single dose of 1×10^6 cells/kg, IV	24	2	Recruiting	Spain	Randomized, Parallel Assignment, Triple Masking	NCT04361942
DW-MSCs	Low dose gp: 5×10^7cells, IV High dose gp: 1×10^8 cells, IV	9	1	Recruiting	Indonesia	Randomized, Interventional, Parallel Assignment, Quadruple Masking	NCT04535856

MSC: Mesenchymal stem cell; **BM-MSC:** Bone marrow-MSC; **UC-MSC:** Umbilical cord-MSC; **CM:** Conditioned media; **AD-MSCs**: Adipocyte derived MSCs; **WJ-MSCs:** Warton jelly-MSC; **CB-MSC**: Cord blood-MSC; **IMRC**: immunity- and matrix-regulatory cell; **DP-MSCs**: Dental pulp MSCs; **LMSCs:** Longeveron MSCs; **SCE:** Stem cell educator; **NHPBSC:** Non-hematopoietic peripheral blood stem cells; g**p:** Group; **IV:** Intravenous; **NA:** Not available.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

Data sharing not applicable to this article as no datasets were

generated or analyzed during the current study.

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