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

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Review

Stem cell therapy in coronavirus disease 2019: current evidence and future potential

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ABSTRACT

The end of 2019 saw the beginning of the coronavirus disease 2019 (COVID-19) pandemic that soared in 2020, affecting 215 countries worldwide, with no signs of abating. In an effort to contain the spread of the disease and treat the infected, researchers are racing against several odds to find an effective solution. The unavailability of timely and affordable or definitive treatment has caused significant morbidity and mortality. Acute respiratory distress syndrome (ARDS) caused by an unregulated host inflammatory response toward the viral infection, followed by multi-organ dysfunction or failure, is one of the primary causes of death in severe cases of COVID-19 infection. Currently, empirical management of respiratory and hematological manifestations along with anti-viral agents is being used to treat the infection. The quest is on for both a vaccine and a more definitive management protocol to curtail the spread. Researchers and clinicians are also exploring the possibility of using cell therapy for severe cases of COVID-19 with ARDS. Mesenchymal stromal cells are known to have immunomodulatory properties and have previously been used to treat viral infections. This review explores the potential of mesenchymal stromal cells as cell therapy for ARDS.

Introduction

The latter half of 2019 saw a sudden rise in pneumonia or severe respiratory infection in Wuhan, Hubei Province, China, secondary to a novel coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The infectivity of SARS-COV-2 surpassed the pace of finding an effective treatment or preventive option, and as of October 27, 2020, there are 43,341,451 confirmed positive cases, with a mortality rate of 2.6% and a recovery rate of 73% (www.WHO.int).

A pathogen's basic reproduction number (R0) denotes the average number of people who can be infected by an infected individual. Though the R0 of coronavirus disease 2019 (COVID-19) differs between countries, it is higher than 1, suggesting an exponential infectivity potential of the virus, which has led to this pandemic [2,3]. The R0 of COVID-19 (2–3) and that of Spanish influenza is similar but higher than that of H1N1 influenza (1.46–1.52) and Middle East respiratory syndrome (0.3–0.8) [4–6].

Although a majority of patients with COVID-19 infection are asymptomatic, symptoms can range from mild to severe [7–9]. Pneumonia, respiratory distress, multi-organ dysfunction, sepsis, septic shock, loss of speech and movement are signs of severity [10]. The elderly and immune-compromised and those with comorbidities have a higher risk of developing severe symptoms with a fatal outcome [11,12]. The virus-induced cytokine storm results in COVID-specific acute respiratory distress syndrome (ARDS), multi-organ dysfunction syndrome and eventual death [13].

Currently, severely affected patients are being treated with anti-viral and anti-inflammatory drugs, besides supportive measures such as invasive and non-invasive mechanical ventilation [14]. Acute progressive renal injury, an early marker of multi-organ dysfunction syndrome, requires renal replacement therapy in advanced disease [15]. Horby *et al.* [16] found that dexamethasone reduced mortality in patients receiving invasive ventilation but not in those without any respiratory support. Although treatment with several anti-virals did not lead to any improvement [17,18], patients receiving remdesivir, an RNA polymerase inhibitor, demonstrated significant clinical improvement [19]. Over 50 clinical trials have been registered at ClinicalTrials.gov for investigating the safety and efficacy of the anti-viral favipiravir for COVID-19 treatment.

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The usage of chloroquine and hydroxychloroquine for COVID-19 treatment remains inconclusive [20,21]. Anakinra, an IL-1 receptor antagonist, has shown beneficial effects in moderate to severe COVID-19 infections [22,23]. Tocilizumab and sarilumab, both IL-6 receptor antagonists, used in small cohorts, have alleviated clinical symptoms without oxygen supplementation [24]. Ongoing trials will clear ambiguity on tocilizumab dosage and mortality post-treatment. Janus kinase signal inducer pathway inhibitors ruxolitinib and baricitinib are also being investigated [25,26]. Convalescent plasma therapy also has potential, but safety and efficacy have to be established with larger studies [27–29].

With an increasing number of infections worldwide, there is a pressing need to find a method of prevention and treatment for COVID-19. Vaccines are being developed, with one from Oxford University in collaboration with AstraZeneca in a phase 3 trial [30,31]. Although 300 clinical trials for investigating anti-viral drugs and 163 for anti-inflammatory drugs are ongoing, it is imperative to look for newer and alternate modalities to treat COVID-19 patients. Researchers have explored the role of stem cells in suppressing ARDS during the cytokine storm since mesenchymal stromal cells are known to play an immunomodulatory role [1,32].

SARS-CoV-2 belongs to the Coronaviridae family, has a 5% genetic association with the SARS virus [33] and was given the nomenclature of COVID-19 by the Director General of the World Health Organization on January 30, 2020 [34]. The spike protein on the virus recognizes the spike protein present on angiotensin-converting enzyme 2 (ACE-2), making it the port of entry into the host cells [35]. The ACE-2 receptor is present ubiquitously and predominantly in the alveolar cells, making the lungs the most vulnerable to infection [36]. ACE-2 receptors have not been detected in bone marrow, lymph nodes, thymus, spleen, lymphocytes or macrophages [37]. Transmembrane protease serine 2 also plays a decisive role in viral entry into the host cells [38].

The overdrive that occurs in the host immune system in response to the virus also adversely affects the host cells [39]. Pro-inflammatory cytokines such as IL-7, IL-6, Il-2, tumor necrosis factor (TNF), MIP1A, interferon gamma-induced protein 10 and granulocyte colony-stimulating factor and chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9 and CXCL10 are released during the infection [40,41]. The inflammatory response of the host can cause dysfunctional air exchange, pulmonary edema, cardiac injury and ARDS, eventually leading to death. Such an effect is called a cytokine storm and is reported in graft-versus-host disease during graft failure as well as in advanced stages of COVID-19 infection [42]. It has been reported to occur with a short median time of 8 days from the appearance of the first symptom to ARDS [43]. Hence, trials of multiple treatment modalities and strategies are being used, including anti-viral therapy, hydroxychloroquine, neutralizing antibodies, convalescent plasma therapy, repurposed anti-viral medications and blockers of ACE-2 receptor with antibodies [44,45].

Mesenchymal stromal cells as a potential therapeutic strategy

Mesenchymal stromal cells (MSCs) are multi-potent adult stem cells with immunomodulatory properties [46]. They are found in bone marrow, adipose tissue, dental pulp, umbilical cord, placenta, Wharton's jelly, amniotic fluid, skin, foreskin, salivary gland and cord blood (Figure 1) [47]. The versatility of the differentiation potential of MSCs is based on the tissue-specific source of the cells [46]. According to the International Society for Cell & Gene Therapy, MSCs are characterized by their ability to adhere to plastic surfaces as well as their expression

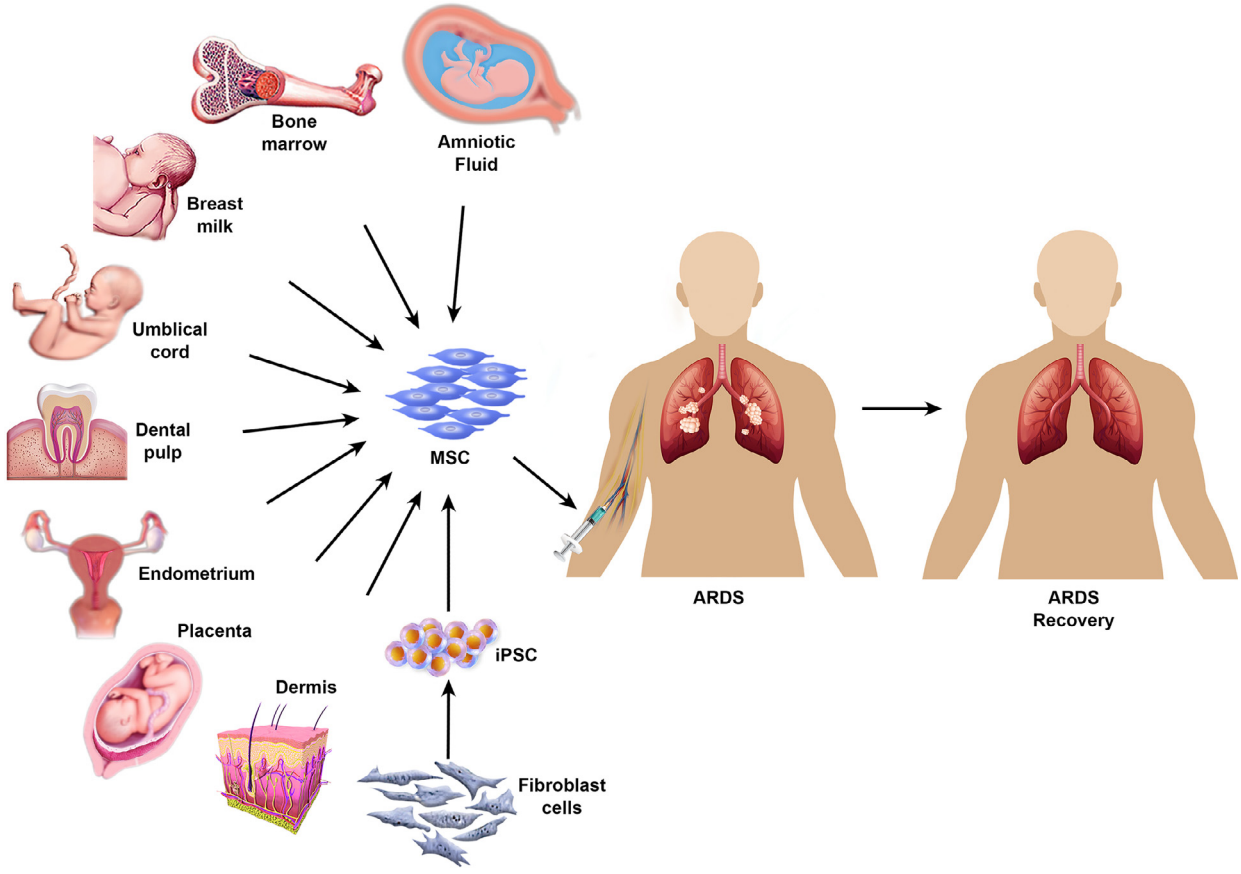

Fig. 1. Sources of MSCs and mode of MSC infusion in clinical trials. The diverse sources of MSCs and their application in ARDS recovery are shown. iPSCs, induced pluripotent stem cells. (Color version of figure is available online).

of CD105, CD73 and CD90 and lack of CD45, CD34, CD14, CD11b, CD79, CD 19 and HLA-DR [48,49]. The multi-potency of MSCs is validated by their ability to differentiate into adipocytes, chondroblasts and osteoblasts [49]. They have been widely used to aid in the regeneration of damaged neurons or muscle fibers and to suppress immune reactions via anti-inflammatory macrophages and regulatory T cells [50]. MSCs express low levels of major histocompatibility complex class I but lack major histocompatibility complex class II on their surface [44]. They exert an anti-microbial role by dynamically balancing pro- and anti-inflammatory responses, secreting anti-microbial peptides and molecules such as indoleamine 2,3-dioxygenase and IL-17, in addition to their autocrine and paracrine functions [51,52].

Bone marrow-derived MSCs (BM-MSCs) have been widely used, followed by umbilical cord-derived MSCs (UC-MSCs) and adipose-derived MSCs (AD-MSCs), for cytokine storm rescue. Apart from stromal vascular fraction cells and adipose-derived stromal cells (ADSCs), the stromal vascular fraction obtained after lipoaspirate contains endothelial cells, macrophages and pericytes, fulfilling the MSC definition described by the International Society for Cell & Gene Therapy [53,54]. ADSCs have high immunomodulatory, anti-inflammatory, proliferation, differentiation and regenerative potential compared with BM-MSCs [55]. They express fatty acid translocase marker CD36 but lack cell adhesion marker CD106 compared with BM-MSCs [56]. The paracrine effects of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and fibroblast growth factor 2 (FGF2) released by ADSCs aid in resolving the lung injury caused by COVID-19 infection by promoting type 2 alveolar cell regeneration and angiogenesis [57]. The immunomodulatory effects of ADSCs are driven primarily by anti-inflammatory cytokine IL-10 and conversion of inflammatory macrophage M1 to the anti-inflammatory and wound healing M2 type [55]. The extracellular matrix is maintained by ADSCs by regulating the levels of matrix metalloproteinase and tissue inhibitor matrix metalloproteinase. Ease of harvest, along with higher yield, longer life span and shorter doubling time, makes ADSCs a more preferred source of MSCs compared with BM-MSCs and UC-MSCs.

MSCs in viral infections

MSCs have been widely used in the management of both infectious and non-infectious etiologies owing to their immunomodulatory and regenerative potential.

Human immunodeficiency virus

Despite highly active anti-retroviral therapy and reduction in viral load, some HIV patients are vulnerable to opportunistic infections. These patients are categorized as non-immune responders (NIRs) [58]. In a pilot open-label clinical trial, Zhang *et al.* [59] administered three doses of UC-MSCs to seven NIR patients, and six NIRs served as controls. The results revealed an increase in circulating naive and central memory CD4 T-cell counts along with HIV-1-specific interferon γ and IL-2 generation. However, MSCs have been shown to reactivate latent HIV in macrophages and T-helper lymphocytes through PI3 kinase and nuclear factor kappa light chain enhancer of activated B-cell pathways using *in vitro* models [60]. Clinical trials with AD-MSCs (NCT02290041) and UC-MSCs (NCT01213186) are ongoing to evaluate the safety, efficacy and optimal dosage for reconstituting CD4 T cells. It has been shown that MSCs obtained from HIV patients harbor defective differentiation potential, thereby limiting the usage of autologous MSC transplantation [61]. Further studies are needed to determine the role of MSCs in immune restoration in NIR as well as HIV patients and whether MSCs can be administered as monotherapy or in combination with anti-viral therapy.

Hepatitis B virus

Liver disease is a major complication of chronic hepatitis B virus (HBV) infection, and orthotopic liver transplantation remains the only therapeutic strategy in end-stage disease, with artificial liver support systems serving as a temporary measure [62]. Although Xie *et al.* [63] found BM-MSCs to be resistant to HBV infection, Ma *et al.* [64] showed that BM-MSCs of HBV patients can be a virus reservoir. A single dose of autologous BM-MSCs in 53 patients with liver failure caused by HBV has been shown to be well tolerated, but the improvement is short-lived [65]. Zhong *et al.* [66] found that BM-MSCs of HBV patients had deranged proliferative capacity. A comparative study to investigate the differentiation ability and resistance to HBV was conducted by Wang *et al.* [67] in BM-MSCs and AD-MSCs. Both differentiated well into hepatocytes; however, only AD-MSCs were resistant to HBV. Phase 2 clinical trials by Ling *et al.*(NCT01223664) and Bingliang *et al.* (NCT01221454) are comparing the safety and efficacy of allogeneic BM-MSC transplantation in liver failure induced by chronic hepatitis in comparison to conventional treatment. In addition, Bingliang *et al.*are studying the effect of three different dosages of BM-MSCs (2×10^5 cells/kg, 1×10^6 cells/kg and 5×10^6 cells/kg) (NCT01322906). Gao *et al.*are evaluating the role of combination treatment with UC-MSCs and plasma exchange therapy for acute-on-chronic liver failure (NCT01724398) and investigating the short- and long-term outcomes of autologous BM-MSC transplantation in liver failure patients (NCT00956891). Jasirwan *et al.*(NCT04357600) and Fan *et al.* (NCT03826433) are evaluating the safety and efficacy of UC-MSCs in patients with liver failure due to chronic HBV infection. Multi-centric clinical trials with MSCs from different sources and long-term follow-up will help to obtain clarity on the safety and efficacy of MSCs in liver failure secondary to chronic HBV infection.

Clinical trials for cell therapy in COVID-19 management

The initial reports of stem cells as a therapeutic strategy for COVID-19 came from China, with the injection of human UC-MSCs into a 65-year-old woman on ventilation. After the second injection of 50 million MSCs, the patient showed improvement and received three infusions of MSCs 3 days apart. Serum bilirubin, liver function enzymes and C-reactive protein levels decreased, and CD3+ T cells, CD4+ T cells and CD8+ T cells increased to normal levels. The patient was weaned from the ventilator and 2 days after the third infusion tested negative for COVID-19 [68]. Seven more patients (one critically ill, four severely ill, two mildly ill) were injected intravenously with clinical-grade MSCs, and three severely ill COVID-19 patients were treated with placebo in a hospital in Beijing, China [69]. They were given a single injection of 1×10^6 stem cells/kg of weight and followed up for 14 days. Lung function improved on the second day, and C-reactive protein, CXCR3+CD4+T cells, CXCR3+CD8+T cells and CXCR3 plus natural killer cells decreased over a week post-injection. Regulatory dendritic cells CD14+CD11c+CD11b and IL-10 increased in the MSC-injected group. The study also revealed that MSCs did not express ACE-2 or transmembrane protease serine 2. The plausible mechanism by which the MSCs might have worked was by reducing the molecules that induce inflammation and triggering those that dampen inflammation.

The US Food and Drug Administration has allowed the use of MSCs as an investigational drug [70–72]. Over 50 clinical trials using MSCs or their products for COVID-19 are registered at ClinicalTrials.gov. The highest number of ongoing clinical trials are in the USA (18), followed by China (nine). Intravenous injection of MSCs ranging from 0.5×10^6 cells/kg to 750×10^6 cells/kg is being used in these clinical trials. Three trials have employed MSC-derived exosome vesicles, of which two used aerosols. Most trials are using MSCs derived from allogeneic umbilical cord (twenty one), followed by bone marrow (ten), adipose (ten), Wharton's jelly (six), dental pulp (two), olfactory mucosa (one) and unknown (six). Mount Sinai Hospital injected MSCs obtained from Mesoblast Ltd, an Australian biotech company,

in 12 ventilator-dependent ARDS patients, with encouraging results. This prompted a randomized, double-blind, placebo-controlled trial with 300 patients [73,74] using an intravenous infusion of BM-MSCs 2×10^6 cells/kg (NCT4371393). Mesoblast is extending the use of MSCs to children from 2 months to 15 years of age [75]. The ongoing clinical trials are listed in Table 1.

Intramuscular injection of placenta-derived mesenchymal-like cells cured six severely ill COVID-19 patients in a trial conducted by Pluristem Therapeutics Inc, an Israel-based biotech firm [76]. A randomized, double-blind, placebo-controlled, multi-center (USA and Israel), parallel assignment phase 2 trial with 140 patients is being conducted by Pluristem Theapeutics Inc, comparing high and multiple doses of intramuscular injections of MSCs (300×10^6 cells) with placebo treatment (NCT04389450). Novellus, Inc, and Citius Pharmaceuticals, Inc, propose to use MSCs derived from reprogrammed messenger RNA induced pluripotent stem cells generated from fibroblasts of a single individual (NoveCite MSCs). A randomized, placebo-controlled, dose-inducing study followed by a dose level expansion to assess the safety and efficacy of NoveCite MSCs in subjects with ARDS due to COVID-19 is in the pipeline [77]. An induced pluripotent stem cell bank would help overcome the scarcity or unavailability of MSCs.

Athersys, Inc, completed a phase 1/2 clinical trial of intravenous injection of their innovative product MultiStem in COVID-19 patients [78]. Phase 1, with a small initial dose, confirmed the safety, and phase 2, with a larger dosage, was a double-blind, placebo-controlled, randomized trial. A total of 36 patients were included in the study wherein six patients were treated with a small dose of MultiStem cells, 20 were intravenously injected with 900×10^6 MultiStem cells and 10 were treated with a placebo. The treatment group had lower mortality and lesser intensive care unit days, without any adverse reactions [79]. The group is now conducting a phase 2/3 clinical trial to investigate the safety and efficacy of MultiStem in COVID-19 patients with ARDS (NCT04367077) by recruiting 400 patients. The study will have two arms: experimental and placebo.

Cynata Therapeutics has initiated an open-label, randomized controlled clinical trial to evaluate the safety and efficacy of their Cymerus MSCs. These MSCs are derived from mesenchymal angioblasts. Using their proprietary technology, induced pluripotent stem cells are generated using transgene-, viral- and feeder-free techniques by de-differentiation of donated blood. These stem cells are further differentiated to mesenchymal angioblasts for the derivation of MSCs used in the infusion (NCT02923375). Of the 24 intensive care unit patients recruited, 12 random patients will be infused with Cymerus MSCs in addition to standard of care, and the other 12 receiving standard of care would serve as controls. The endpoint would be improvement in hypoxia at day 7 and safety/tolerability in 28 days [80].

Sanchez-Guijo *et al.* [81] treated 13 COVID-19 patients with AD-MSCs post anti-viral and anti-inflammatory treatment. Two patients received a single dose, 10 received double the dose and another received a single dose of 0.98 cells/kg body weight. The clinical analysis revealed improvement in the beneficial immune cell profile, with no adverse effects of the infusion (NCT04348461). Hope Biosciences is conducting three clinical trials using AD-MSCs in an attempt to address the dose-scaling effect of MSC infusion, starting with 50×10^6 cells/kg and going up to 200×10^6 cells/kg over 4–5 intravenous infusions, and to evaluate safety and efficacy in a phase 2 trial (NCT04362189, NCT04349631, NCT04348435). The START study (STem cells for ARDS Treatment) recently published a phase 2 safety administration trial with a single dose of intravenous MSCs [82]. Bari *et al.* [83] and Sanap *et al.* [84] advocate the use of MSC secretome as a cell-free treatment modality for COVID-19 patients with ARDS.

Protective mechanisms of MSCs in ARDS

Migration of MSCs is stimulated by the pro-inflammatory marker TNFα [85] and by the binding of ligands CD106 and CD62E with integrin $\alpha4/\beta1$ (CD49δ/CD29) and CD44 receptors, respectively [86,87]. Trophic factors such as epithelial growth factor, transforming growth factors α and β, basic FGF2, HGF, insulin-like growth factor 1, VEGF, stem cell factor and stem cell-derived factor 1 and immunomodulatory factors such as prostaglandin E2, inducible nitric oxide synthase, indoleamine 2,3-dioxygenase, CCL2, IL-10 and IL-6 are some of the molecules released by MSCs [88,89]. The cytokine secretion profile of dendritic cells and macrophages is modulated by MSCs [90]. The anti-proliferative properties of MSCs play a role in limiting the proliferation of T lymphocytes, B cells, natural killer cells and microglial cells [91]. MSCs have been successfully transplanted in graft-versus-host disease and in multiple system atrophy [92,93].

MSCs have immunomodulatory functions, direct cell-to-cell interactions and secrete growth factors and extracellular vesicles. During inflammation, impaired barrier properties of epithelial cells are associated with an increase in the permeability of endothelial cells in the lungs [94]. It has been shown that intratracheal MSC administration in lipopolysaccharide-induced inflammatory conditions in mouse models leads to a reduction in inflammation [95]. This study also demonstrated that through the paracrine process MSCs can induce IL-10 via prostaglandin E2 and other secretory factors, such as granulocyte-macrophage colony-stimulating fact and granulocyte colony-stimulating factor, which help to recover the barrier properties of the lungs. Additionally, MSCs secrete anti-inflammatory factors IL-10 and IL-4 and suppress the activation of lymphocytes and inflammatory cytokines IL-1-α, IL-1-β, IL-6, IL-17, TNFα, TNFγ and interferon γ [96]. It has also been described that MSCs reduce the excessive secretion of neutrophil extracellular traps at the site of infection, thereby preventing further damage to lung tissues [97]. MSCs have the ability to reduce the excessive production of neutrophils that causes tissue damage and increase neutrophil-mediated phagocytosis in bacterial infections [98]. MSCs play a role in differentiating macrophages into M1 and M2 phenotypes. M1 activates phagocytosis, which has a pro-inflammatory function and aids in bacterial clearance, and M2 supports tissue repair by resolving inflammation at the infection site [99,100]. MSCs also suppress the proliferation of effector T cells and promote regulatory T cells, thereby reducing the immune response and resolving lung damage in ARDS [101].

In a sepsis mouse model, MSCs were shown to have transcriptional responses via the downregulation of Toll-like receptor-mediated nuclear factor kappa light chain enhancer of activated B cells and along with a simultaneous upregulation of the nuclear factor of activated T cells, calcium and calcineurin gene families regulating the transcription of cytokine genes [102]. In a lipopolysaccharide-induced acute lung injury mouse model, BM-MSCs established cell-to-cell contact with connexin 43 gap junction channels. The attached MSCs released mitochondria-containing microvesicles into alveolar epithelial cells. The mitochondrial transfer increased adenosine triphosphate concentrations in epithelial cells, thereby repairing alveolar epithelial and endothelial barriers in acute lung injury [103]. In addition, an *Escherichia coli* pneumonia model demonstrated that mitochondrial transfer from MSCs to macrophages partially occurs through tunneling nanotube-like structures [104]. The mitochondrial transfer enhances phagocytic activity, which establishes a mechanism for anti-microbial effect through cell-to-cell contact. MSCs also play a paracrine role by secreting soluble molecules.

In a rat ventilator-induced lung injury model, the MSC secretome (MSC-conditioned medium) reversed the lung injury via keratinocyte growth factor (KGF). KGF repairs epithelial cells by enhancing Na-K-ATPase, anti-inflammatory cytokine (IL-1α, matrix metallopeptidase 9) and macrophage activity via granulocyte-macrophage colony-stimulating factor [105,106]. Overexpression of certain MSC factors, such as PDGFβ, VEGF, basic FGF, angiogenin 1 and PDGF, induces cell proliferation and brings about lung repair [107]. In various studies, the overexpression of angiogenin 1, KGF, ACE-2, CXCR4 and HGF has reduced endotoxin-induced lung injury, edema formation, collagen

Table 1
List of clinical trials on MSCs in COVID-19 from ClinicalTrials.gov.

Sl. No.	Clinical trial no.	Number of patients	Study						Source of biological material
			Arms	Type	Phase	Design	Purpose	Country	
1	NCT04276987	30	Conventional plus aerosol inhalation of MSC-derived exosomes	Interventional	I	Single group treatment	Treatment	Spain	Allogeneic AD-MSC exosomes
2	NCT04400032	9	Experimental with escalating dose (25×10^6 cells/kg, 50×10^6 cells/kg, 90×10^6 cells/kg) and three infusions	Interventional	I	Single group treatment	Dose-escalating safety	Canada	BM-MSCs
3	NCT4341610	40	Experimental: 100×10^6 cells/kg Control: normal saline	Interventional	I–II	Double-blind, randomized, placebo-controlled	Treatment	Denmark	Allogeneic AD-MSCs
4	NCT04445220	24	Experimental: 1, low dose, 250×10^6 cells/kg 2, high dose, 750×10^6 cells/kg Control: sham In patients with acute kidney injury, MSC infusion by integration with continuous renal replacement therapy	Interventional	I–II	Randomized, multi-center, double-blind, sham-controlled	Safety, treatment and tolerability	USA	Allogeneic MSC
5	NCT04466098	30	Experimental: 300×10^6 cells/kg (three times) Control: placebo	Interventional	II	Randomized, multi-center, placebo-controlled	Treatment	USA	Allogeneic MSC
6	NCT04299152	20	Experimental: stem cell educator therapy Control: conventional therapy Patient blood separated by apheresis, and patient immune cells co-cultured with cord blood stem cells, followed by putting the educator immune cells back in patients	Interventional	II	Partially masked and single center	Safety, feasibility and efficacy	USA	Human multipotent UC-MSCs
7	NCT04333368	40	Experimental: 1×10^6 cells/kg (three times) Control: normal saline	Interventional	I–II	Randomized parallel assignment	Treatment	France	UC Wharton's jelly
8	NCT04491240	90	Experimental: 1, exosome inhalation (first type) 2, exosome inhalation (second type) Control: placebo inhalation	Interventional	I–II	Randomized parallel assignment	Safety and treatment	Russia	AD-MSCs
9	NCT04447833	9	Experimental: 1, MSC infusion 1×10^6 cells/kg 2, MSC infusion 2×10^6 cells/kg	Interventional	I	Open-label dose escalation study of advanced therapy investigational medicinal product	Safety	Sweden	Allogeneic BM-MSCs
10	NCT04437823	20	Experimental: MSC infusion 5×10^5 cells/kg (three times) Control: standard of care	Interventional	II	Randomized open-label	Treatment	Pakistan	UC
11	NCT04269525	16	Experimental: 3.3×10^7 cells/kg	Interventional	II	Single group assessment	Prevention and treatment	China	UC
12	NCT04389450	140	Experimental: high dose (once and twice) and low dose (once) MSC infusion Control: placebo infusion (once and twice)	Interventional	II	Randomized, multi-center, double-blind	Treatment	Israel	Placental mesenchymal-like adherent stromal cells
13	NCT03042143	18 (phase 1) and 60 (phase 2)	Experimental: 1, CD362-enriched MSCs, 100×10^6 cells/kg, 200×10^6 cells/kg, 400×10^6 cells/kg 2, highest dose of experimental arm 1. Control: placebo	Interventional	I–II	Open-label dose escalation pilot study. Phase 1 double blind, randomized, placebo controlled. Phase 2 clinical trial	Treatment	UK	UC
14	NCT04361942	24	Experimental: 1×10^6 cells/kg Control: placebo	Interventional	II	Double-blind, randomized, placebo-controlled	Treatment	Spain	Allogeneic MSC
15	NCT04398303	70	Experimental: 1, MSC infusion 1×10^6 cells/kg plus conventional treatment 2, conditioned medium plus conventional treatment Control: conventional treatment plus placebo	Interventional	I–II	Randomized, placebo-controlled	Safety and treatment	USA	Allogeneic human UC-MSCs
16	NCT04467047	10	Experimental: MSC infusion 1×10^6 cells/kg	Interventional	I	Open-label, single group assignment	Safety and feasibility	Brazil	BM-MSCs

(*continued on next page*)

Table 1 (*Continued*)

Sl. No.	Clinical trial no.	Number of patients	Study						Source of biological material
			Arms	Type	Phase	Design	Purpose	Country	
17	NCT04392778	30	Experimental: MSC infusion 3×10^6 cells/kg (three times) with ventilator Sham comparator Saline infusion (three times) with ventilator Untreated without ventilator	Interventional	I–II	Randomized, double-blind, parallel assignment	Treatment	Turkey	Allogeneic UC
18	NCT04390139	30	Experimental: MSC infusion 1×10^6 cells/kg Placebo comparator	Interventional	I–II	Randomized, double-blind, parallel assignment	Safety and treatment	Spain	Wharton's jelly MSC
19	NCT04492501	600	Experimental: 1, therapeutic plasma exchange 2, therapeutic plasma exchange plus MSC infusion 2×10^6 cells/kg or remdesivir 3, MSC infusion 2×10^6 cells/kg and/or remdesivir and/or tocilizumab (all alone or in combination)	Interventional	I–II	Non-randomized, open-label, factorial assignment, case–control study	Treatment	Pakistan	BM-MSCs
20	NCT04345601	30	Experimental: MSC infusion 1×10^8 cells/kg (twice) Control: standard of care	Interventional	I	Randomized, open-label, parallel assignment	Treatment	USA	BM-MSCs
21	NCT4377334	40	Experimental: MSC infusion Control: no intervention	Interventional	II	Randomized, open-label, parallel assignment	Treatment	Germany	BM-MSCs
22	NCT04397796	45	Experimental: MSC infusion Control: placebo	Interventional	I	Randomized, double-blind, placebo-controlled	Safety and treatment	USA	BM-MSCs
23	NCT04494386	60	Experimental: 1, MSC infusion 100×10^6 cells/kg (phase 1, open-label, one or two infusions) 2, MSC infusion (randomized, one or two infusions) 3, placebo infusion (one or two infusions)	Interventional	I–II	Open-label, non-controlled trial Randomized, placebo-controlled trial	Safety and treatment	USA	UC-MSCs
24	NCT04371393	300	Experimental: MSC infusion 2×10^6 cells/kg (remestemcel-L) plus standard of treatment Control: placebo plus standard of treatment	Interventional	III	Randomized, double-blind, parallel assignment, placebo-controlled	Safety and treatment	USA	BM-MSCs
25	NCT04452097	9	Experimental: MSC infusion 0.5×10^6 cells/kg, 1×10^6 cells/kg, 1.5×10^6 cells/kg, BX-U001	Interventional	I	Non-randomized, open-label, single arm, dose-escalating	Safety	USA	UC-MSCs
26	NCT04390152	40	Experimental: MSC infusion 50×10^6 cells/kg (twice) plus hydroxychloroquine plus lopinavir/ritonavir or azithromycin Control: placebo plus hydroxychloroquine plus lopinavir/ritonavir or azithromycin	Interventional	I–II	Randomized, double-blind, parallel assignment	Safety and treatment	USA	Wharton's jelly-derived MSCs
27	NCT04362189	100	Experimental: MSC infusion 100×10^6 cells/kg (four infusions) Control: saline (four infusions)	Interventional	II	Randomized, double-blind, placebo-controlled	Safety and treatment	USA	AD-MSCs
28	NCT04348461	100	Experimental: MSC infusion 1.5×10^6 cells/kg (twice) Control: standard of treatment	Interventional	II	Randomized, two-treatment, multi-center, controlled	Safety and treatment	Spain	AD-MSCs
29	NCT04371601	60	Experimental: MSC infusion 1×10^6 cells/kg (four infusions) plus standard of care Control: standard of care	Interventional	I	Randomized, parallel assignment, open-label	Safety and treatment	China	UC
30	NCT04461925	30	Experimental: MSC infusion 1×10^6 cells/kg (twice) plus standard of care Control: standard of care	Interventional	I–II	Non-randomized, open-label, parallel assignment	Safety and treatment	Ukraine	Placenta and UC
31	NCT04355728	24	Experimental: MSC infusion 100×10^6 cells/kg (twice) plus standard of care plus heparin Control: standard of care plus vehicle plus heparin	Interventional	I–II	Randomized, double-blind, parallel assignment	Safety and treatment	USA	UC

(*continued on next page*)

Table 1 (*Continued*)

Sl. No.	Clinical trial no.	Number of patients	Study						Source of biological material
			Arms	Type	Phase	Design	Purpose	Country	
32	NCT04490486	21	Experimental: MSC infusion 100×10^6 cells/kg (twice) Control: placebo	Interventional	I	Randomized, double-blind, placebo-controlled	Safety and treatment	USA	UC
33	NCT04302519	24	Experimental: MSC infusion 1×10^6 cells/kg (dose scaling)	Interventional	I	Open-label, single center, single arm	Safety and treatment	China	Dental pulp
34	NCT04352803	20	Experimental: MSC infusion 5×10^5 cells/kg plus standard of care Control: standard of care	Interventional	I	Non-randomized, open-label, sequential assignment, unmatched control	Safety and treatment	USA	Adipose tissue
35	NCT04457609	40	Experimental: MSC infusion 1×10^6 cells/kg plus standard of treatment Control: standard of treatment	Interventional	I	Randomized, double-blind, parallel assignment, controlled trial	Safety and treatment	Indonesia	UC
36	NCT04349631	56	Experimental: MSC infusion (five times)	Interventional	II	Open-label, single center clinical trial	Safety and treatment	USA	Adipose tissue
37	NCT04428801	200	Experimental: MSC infusion 200×10^6 cells/kg (three times) Control: placebo	Interventional	II	Randomized, double-blind, multi-center, placebo-controlled	Treatment	USA	Adipose tissue
38	NCT04339660	30	Experimental: MSC infusion 1×10^6 cells/kg plus standard of treatment Control: placebo plus standard of treatment	Interventional	II–III	Randomized, double-blind, parallel assignment	Treatment	China	UC
39	NCT04366063	60	Experimental: 1, MSC infusion 100×10^6 cells/kg (twice) 2, MSC infusion 100×10^6 cells/kg (twice) plus exosome vesicles (two infusions) Control: standard of treatment	Interventional	II	Randomized, parallel assignment	Safety and treatment	Iran	NA
40	NCT04348435	100	Experimental: 1, MSC infusion 200×10^6 cells/kg (five times) 2, MSC infusion 100×10^6 cells/kg (five times) 3, MSC infusion 50×10^6 cells/kg (five times) Control: placebo (five infusions)	Interventional	I–II	Randomized, double-blind, placebo-controlled	Safety and treatment	USA	Adipose tissue
41	NCT04382547	40	Experimental: MSC infusion plus standard of treatment Control: standard of treatment	Interventional	II	Non-randomized, parallel assignment, open-label		Belarus	Olfactory mucosa
42	NCT04273646	48	Experimental: MSC infusion 0.5×10^6 cells/kg (four times) plus standard of treatment Control: placebo plus standard of treatment	Interventional	I–II	Randomized, parallel assignment, open-label	Safety and treatment	China	UC
43	NCT04288102	100	Experimental: MSC infusion 4×10^7 cells/kg (three times) plus standard of treatment Control: placebo plus standard of treatment	Interventional	II	Randomized, multi-center, double-blind, placebo-control	Safety and treatment	China	UC
44	NCT04346368	20	Experimental: MSC infusion 1×10^6 cells/kg plus standard of treatment Control: placebo plus standard of treatment	Interventional	I–II	Randomized, parallel assignment, open-label	Safety and treatment	China	BM
45	NCT04336254	20	Experimental: MSC infusion 3×10^7 cells/kg (three times) plus standard of treatment Control: saline plus standard of treatment	Interventional	I–II	Randomized, parallel assignment, open-label	Safety and treatment	China	Dental pulp
46	NCT04313322	5	Experimental: MSC infusion	Interventional	I	Open-label, direct study	Safety and treatment	Jordan	Wharton's jelly
47	NCT04252118	20	Experimental: MSC infusion 3×10^7 cells/kg plus standard of treatment Control: standard of treatment	Interventional	I	Non-randomized, parallel assignment, open-label	Safety and treatment	China	NA
48	NCT04366271	106	Experimental: MSC infusion Control: standard of treatment	Interventional	II	Randomized, multi-center, parallel assignment, open-label	Treatment	Spain	UC
49	NCT04366323	26	Experimental: MSC infusion 80×10^6 cells/kg (twice) Control: no intervention	Interventional	I–II	Randomized, multi-center, parallel assignment, open-label	Safety and treatment	Spain	Adipose tissue

(*continued on next page*)

Table 1 (*Continued*)

Sl. No.	Clinical trial no.	Number of patients	Study				Purpose	Country	Source of biological material
			Arms	Type	Phase	Design			
50	NCT04456361	9	Experimental: MSC infusion 1×10^8 cells/kg	Interventional	I	Open-label, pilot study, non-randomized, single group	Safety and treatment	Mexico	Wharton's jelly
51	NCT04315987	90	Experimental: MSC infusion 2×10^7 cells/kg (four times) Control: placebo (four infusions)	Interventional	II	Randomized, parallel assignment, double-blind	Treatment	Brazil	NA
52	NCT04429763	30	Experimental: MSC infusion 1×10^6 cells/kg plus standard of treatment Control: placebo plus standard of treatment	Interventional	II	Double-blind, controlled clinical trial, randomized, parallel assignment	Safety and treatment	USA	UC
53	NCT04416139	10	Experimental: MSC infusion 1×10^6 cells/kg Control: standard of treatment	Interventional	II	Non-randomized, parallel assignment, open-label	Treatment	Mexico	UC
54	NCT04444271	20	Experimental: MSC infusion 2×10^6 cells/kg (once or twice) plus standard of treatment Control: placebo plus saline plus standard of treatment	Interventional	II	Randomized, phase 2, parallel assignment, open-label	Treatment	Pakistan	BM

Details of clinical trials as listed on ClinicalTrials.gov as of July 25, 2020.
NA, not applicable.

depositionandfibrosis,inadditiontoenhancingthechemotacticandanti-inflammatory properties of MSCs [105,108–111]. The plausible mechanismbywhichMSCsresolveARDSisdepictedschematicallyinFigure2.

Experimental and pre-clinical evidence of the benefits of MSCs in immunomodulation of respiratory virus-induced lung injury is available, which may be helpful in the treatment of COVID-19. UC-MSCs are able to restore alveolar epithelial cell functions, as seen by increased alveolar fluid clearance and decreased protein permeability, in avian influenza virus (H5N1) lung injuries in mouse models [112]. MSCs are resistant to viral infections, and recently it has been established that intrinsically expressed interferon-stimulated genes (ISGs) protect stem cells against viral infection [113]. This study demonstrated that induction of intrinsic ISGs in human MSCs constitutively increased the expression of anti-virals (IFI6, ISG15, CCL2, SAT1, PMAIP1 and interferon-induced transmembrane protein 1 [IFITM1]). With regard to anti-viral mechanism, the IFITM family plays a major role in preventing the virus from crossing the lipid bilayer of cells. It has been demonstrated that IFITM prevents the entry of various viruses, including Ebola virus, dengue virus, influenza A virus, Rift Valley fever virus, reovirus and SARS-CoV, as well as replication in HIV-1 and hepatitis C virus [114,115]. Interestingly, it has been shown that SARS-CoV virus internalization is prevented by the host cell receptor ACE-2 in IFITM-expressing cells [114]. In the lungs, the ACE-2 receptor is expressed in alveolar type II cells and endothelial cells, and these cells play a role in preventing virus entry and reducing fibrosis and have anti-inflammatory and endothelial protective effects [116–118].

The COVID-19 mortality rate is higher in patients who have pre-existing systemic diseases, such as diabetes, renal disease and hypertension. In these conditions, the ACE-2 receptor plays an important role, as it is a major enzyme in the renin–angiotensin system, which has been localized in the apical surface area and glomeruli of the kidneys and in the acini and islets of the pancreas. In an *in vivo* mouse model, it was demonstrated that an ACE-2 deficiency can cause decreased insulin secretion, leading to diabetes [119]. Plasma ACE-2 levels are lower in chronic kidney disease patients undergoing dialysis [120]. Adult hypertensive rats show decreased expression of ACE-2 in the kidneys [121].

The potential benefits of overexpression of ACE-2 receptors by MSCs in relation to COVID-19 need further exploration. The details regarding the underlying mechanisms involved in resolving COVID-19 in patients with infusion of MSCs are still unknown. The authors have schematically represented the plausible mechanism by which MSCs reduce the adverse effects of ARDS caused by COVID-19 based on the existing knowledge (Figure 3).

Discussion

The emergence of the COVID-19 pandemic and its sequelae have prompted clinicians and researchers to explore all possible preventive and treatment modalities since existing strategies target symptoms, rather than the underlying pathology. Anti-virals, pulmonary and renal support systems and immunomodulators are being used to treat the cytokine storm, which causes respiratory depression and multi-organ dysfunction. Until effective vaccines and specific treatment options are available, the high infectivity rate of COVID-19 makes limiting disease progression a challenge. MSCs serve as a potential therapeutic candidate for combating the cytokine storm owing to their primordial cell lineage and multi-potent functions, such as immunomodulation and anti-inflammatory activity, and their ability to secrete various growth factors and soluble vesicles. Encouraging results from ongoing trials would expand the clinical applicability of MSCs and provide hope for patients suffering with ARDS due to COVID-19 infection.

Clarity is lacking regarding the best source of MSCs, the method of application or mode of infusion of the cells to the patient, the stage of

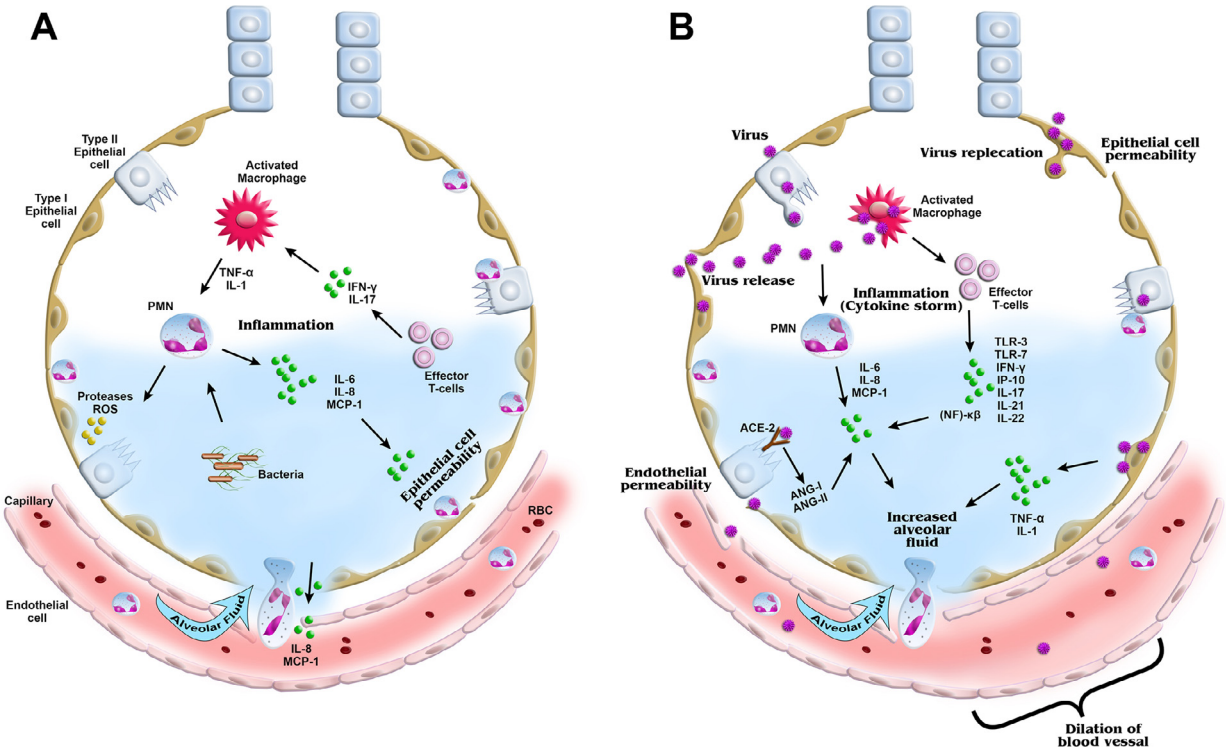

Fig. 2. Schematic representation of ARDS in non-viral and viral conditions. (A) In non-viral-induced ARDS, macrophages and effector T cells are activated and cytokines induced, which in turn activates neutrophils and causes secretion of further inflammatory cytokines and chemokines. (B) In viral-induced ARDS, additional cytokines are produced, leading to a cytokine storm. The released proteases and inflammatory cytokines damage the epithelial and endothelial layers of the alveoli, causing increased epithelial/endothelial permeability, fibrosis, edema formation and vasodilation. ANG, angiogenin; IP, interferon gamma-induced protein; MCP, monocyte chemoattractant protein; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; PMNs, polymorphonuclear cells; RBC, red blood cell; ROS, reactive oxygen species; TLR, Toll-like receptor. (Color version of figure is available online).

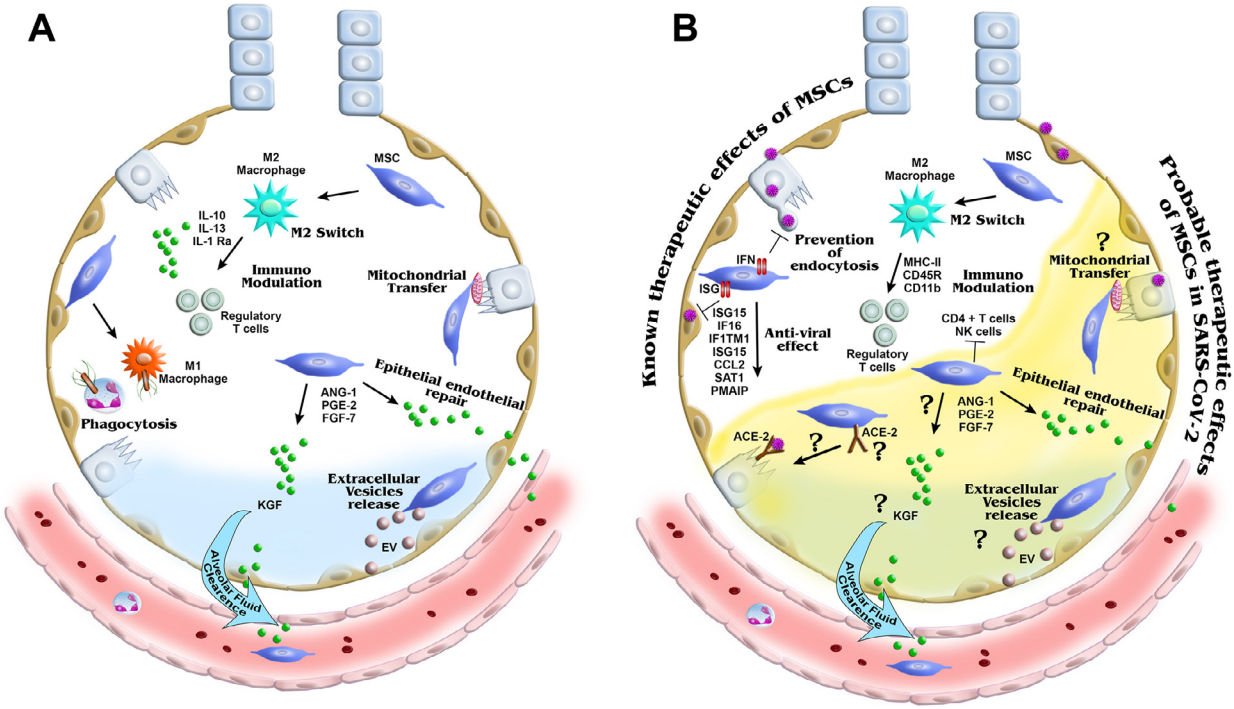

Fig. 3. Schematic representation of the mechanism of action of MSCs in ARDS. Potential therapeutic mechanisms of MSCs in non-viral and viral ARDS recovery are shown. MSCs promote differentiate of macrophages from type M1 to M2 to induce anti-inflammatory cytokines and M1 macrophages with phagocytic activity. MSCs reduce the infiltration of neutrophils by secreting anti-inflammatory cytokines and regulating effector T cells. These anti-inflammatory cytokines and other secreted factors reduce the epithelial/endothelial permeability and influx of alveolar fluid. (A) MSCs are known to directly transfer mitochondria through tunneling nanotubules and microvesicles to transfer RNA and proteins for tissue repair. In viral ARDS, few mechanisms are understood, suggesting that intrinsically expressed genes and proteins may have anti-viral effects. (B) For SARS-CoV-2 virus infection, cell-based therapy with MSCs is being explored. ANG, angiogenin; EV, extracellular vesicle; MHC, major histocompatibility complex; PGE2, prostaglandin E2; PMAIP1, phorbol-12-myristate-13-acetate-induced protein 1; PMNs, polymorphonuclear cells; RBC, red blood cell; ROS, reactive oxygen species; SAT, spermidine/spermine N1-acetyltransferase. (Color version of figure is available online).

disease at which MSCs would work with the highest efficiency, the timeline of results expected post injection, the age group of patients, etc. A combination treatment approach with MSCs and supportive drugs might work synergistically to restrict the infectivity of the virus, in addition to preventing the progression of the infection to a severe form. Another approach may be administration of anti-viral drugs carrying nanoparticles loaded on stem cells with an affinity for ACE-2 receptor-harboring alveolar cells. The means to generate high-clinical-grade MSCs is the need of the hour. Apart from cell-based therapy, exosome vesicles as well as the culture secretome of MSC might be explored as an alternative.

Future research toward a better understanding of MSCs resident in lung tissue could pave the way for developing the means to activate host-specific resident stem cells to resolve site-specific ARDS. This would eliminate the need for infusion of allogeneic cell therapy. The results of ongoing clinical trials would help provide guidelines for cell monotherapy or combination therapy with non-cell-based treatment, enabling clinicians worldwide to better manage severely infected COVID-19 patients. With the fear of a second wave of infection looming large, it is a race against time for researchers worldwide to fight the challenge posed by COVID-19.

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Declaration of Competing Interest

The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: RS and DD. Acquisition of data: MP, KC, CJ and DD. Analysis and interpretation of data: MP, KC, CJ and DD. Drafting or revising the manuscript: RS, DD, KC, HM, CJ and AG. All authors have approved the final article.

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