

# Stem Cell Therapy for SARS-CoV-2 and Influenza Virus Infections

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## Abstract

The emergence of infectious diseases, including viral zoonoses, has allowed intensive research into novel therapeutic approaches. Stem cell therapy, mostly using mesenchymal stem cells (MSCs), has garnered significant attention due to the immunomodulatory properties and tissue repair capabilities. MSCs have demonstrated promise in treating severe COVID-19 cases and several clinical trials have revealed that MSC therapy improves 28-day survival rates, reduces mortality, and accelerates recovery. These cells effectively mitigate a cytokine storm, relieve pulmonary symptoms, and positively influence organ recovery, including the liver and kidneys. Bioanalytical readings return to normal following MSC administration, emphasizing the potential in managing COVID-19-induced complications. MSC therapy offers a potential solution for infection with the influenza virus, which is responsible for historical pandemics and epidemics, and remains a global health concern. MSCs inhibit immune cell-mediated responses and reduce lung damage in animal models, and despite antiviral drugs, influenza-induced manifestations persist. MSCs, with an ability to counteract inflammation and promote lung tissue repair, hold promise for managing influenza infections. While MSCs offer therapeutic benefits, certain challenges remain. Specifically, ethical considerations, regulatory hurdles, and scalability are some of the challenges that hinder widespread adoption. However, ongoing systematic reviews and meta-analyses provide real-time insight that support the security and effectiveness of MSC therapy.

## Keywords

Cytokine storm, immunomodulatory properties, stem cells, viral infections.

## Introduction

In recent decades the emergence of infectious diseases has captured global attention [1, 2]. These diseases carry a significant threat to public health given the virulence, mortality rates, modes of transmission, and effect on patients' quality of life [2]. Emerging infectious diseases are those infectious diseases that show signs of first occurring in a community or rapidly increasing in frequency or geographic spread according to the World Health Organization (WHO) [3]. Infectious diseases have remained the leading cause of morbidity and mortality throughout the 1970s, as demonstrated by the development of severe acute respiratory syndrome coronavirus (SARS-CoV-2) in 2019 and acquired immunodeficiency syndrome (AIDS) in 1978 [4]. Zoonotic transmission accounts for approximately 60% of emerging infectious diseases with 70% originating in wildlife [5]. Notably, some infectious agents that were once deemed inconsequential to public health have resurged, resulting in severe effects on the global

population [6]. Moreover, some pathogens have exhibited an increased incidence and prevalence worldwide that are driven by factors, such as mutation, therapeutic resistance, and pathogen evolution [7].

While advances in medical science and technology have equipped us with potent tools to combat these diseases, several limitations and challenges persist. The rapid mutation rates of some pathogens, such as influenza virus and HIV, pose significant hurdles in the development of effective and long-lasting vaccines [8]. In addition, the rise in antimicrobial resistance (AMR) has emerged as a formidable challenge, rendering many standard treatments ineffective and complicating the management of common infectious diseases [9]. The socioeconomic disparities across different geographic regions further exacerbate infectious disease control because limited access to healthcare services and insufficient infrastructure hinder timely diagnosis and treatment [10]. Moreover, the global interconnectedness facilitated by modern travel and trade accelerates the spread of infectious agents, which complicates

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containment efforts [11]. Addressing these challenges requires a multidisciplinary approach involving advances in biomedical research and robust public health strategies, international collaboration, and policy interventions.

## The ongoing challenge of emerging infectious diseases

The 21st century has witnessed the emergence of several epidemic- and pandemic-level viral infections without even including the disturbing SARS-CoV-2 (COVID-19) pandemic [12]. Despite the lessons learned from the lethal 1918 influenza outbreak, the world was ill-prepared for the SARS-CoV-2 outbreak given the prior warnings from the SARS-CoV (2003) and Middle East respiratory syndrome coronavirus [MERS-CoV] (2012) epidemics, which clearly indicated the heightened risk of such strains flowing in bats [1, 12, 13]. Nevertheless, remarkable progress in basic virology, cell biology, biochemistry, and immunology research has accelerated the development of antiviral products and novel vaccines, although the global distribution of these medical interventions remains a difficult task [14]. Concurrently, the swift spread of rumours and half-truths has created misperception and eroded public assurance in these interventions, resulting in more harm than good [15]. The current SARS-CoV-2 pandemic has underscored the necessity of investing in preparedness for global outbreaks and developing diagnostic and intervention technologies [16]. Indeed, these technologies are essential in the development of therapeutics tailored to specific viral infections with high heterogeneity [1, 16].

## Mesenchymal stem cells as a promising therapeutic approach

Mesenchymal stem cell (MSC) therapy offers a favourable approach for mitigating the adverse effects of infectious viral diseases [7]. MSCs belong to a diverse subset of self-renewing progenitor cells that can be derived from many adult tissues, including umbilical cord blood, amniotic fluid, dental pulp, bone marrow, menstrual blood, foetal liver, Bichat's fat pad, abdominal fat pad, and endometrium [1, 17]. This amazing versatility allows researchers and clinicians to harness the regenerative potential of these cells, making MSCs a suitable candidate for treating a wide spectrum of diseases. Upon invasion of a virus, MSCs respond to damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) by transforming into a pro-inflammatory phenotype (MSC1), which produces inflammatory chemokines that attract circulating leukocytes to the inflamed tissues. MSCs thereby regulate the activities of various immune cells involved in the antiviral response, such as dendritic cells (DCs), macrophages, natural killer (NK) cells, B lymphocytes, CD4+ T helper cells,

and cytotoxic T lymphocytes (CTLs). Interferons (IFNs) produced by MSCs influence the cytotoxic functions of NK cells and CTLs, enhance the antigen-presenting capabilities of DCs and macrophages, regulate cytokine production in CD4+ T helper cells, and control antibody production in B cells, all of which are crucial for the effective elimination of virus-infected cells. During the tissue repair phase, MSCs adopt anti-inflammatory phenotypes and release a variety of immunoregulatory molecules, such as transforming growth factor-beta (TGF- $\beta$ ), indoleamine 2,3-dioxygenase (IDO), interleukin (IL)-10, interleukin-1 receptor antagonist (IL-1Ra), and prostaglandin E2 (PGE2). These molecules help suppress the overactivation of immune cells, thus preventing the development of a cytokine storm and the subsequent harmful systemic inflammatory response.

Because of the strong immunomodulatory properties, MSCs are being extensively studied in numerous experimental settings as a potential new therapeutic approach for treating viral diseases. Furthermore, the insightful immunomodulatory capabilities not only allow tissue repair but also offer exciting prospects for mitigating inflammatory responses and enhancing immune regulation, underscoring a focal role for MSCs in the future of regenerative medicine and disease management.

## Understanding emerging viral zoonoses

Some viral zoonoses are categorized as “evolving infectious diseases” due to the recent recognition and substantial changes in epidemiologic features and geographic distribution of these zoonoses [1, 18]. The primary basis for virus emergence is the increased interaction between viruses and wild animals, which results in the transmission of viruses from non-human hosts to new human hosts [19, 20]. Climate changes also contribute to the rise in viruses. Variants of newly evolving viruses can cause severe epidemics and appear in drug-resistant forms, which are referred to as “re-emerging viruses.” Indeed, the relationship between climate changes and the emergence of viruses is a subject of intense significance in the virology domain. Evidentiary strands have unravelled over the years, underscoring the unquestionable influence of shifting environmental dynamics on the viral landscape. One cannot overlook the research that elucidates how alterations in temperature, humidity, and precipitation patterns can provide fertile ground for the resurgence of dormant viruses or the amplification of existing viruses. Furthermore, the ramifications extend beyond mere viral reactivation because these climatic variations can also catalyse the evolution of viral strains into hitherto unseen variants. Such variants with genetic novelties possess an alarming potential to unleash severe epidemics. This finding was exemplified by the emergence of the SARS-CoV-2 virus pandemic, which is believed to have zoonotic origins influenced by changing environmental conditions that brought humans into closer contact with animal reservoirs [1]. The spectre of drug-resistant “re-emerging viruses” looms ominously on

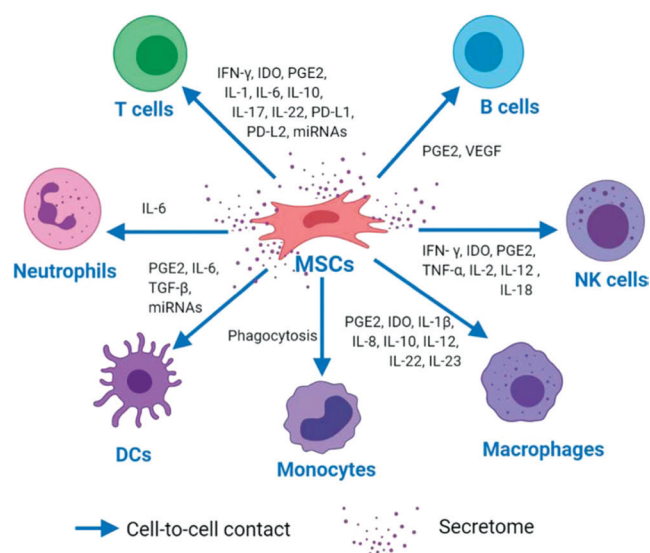
the horizon as well and the selective pressures exerted by a changing climate can hasten the development of resistance mechanisms in viruses against antiviral drugs. The ongoing battle against antibiotic-resistant bacteria highlights the possibility that a similar scenario is plausible in the virosphere, which has been further substantiated by the growing body of evidence documenting the evolution of drug-resistant strains of HIV, and influenza and hepatitis viruses [1].

## Versatility of stem cell therapy

Stem cell therapy has tremendous potential for treating a wide range of human diseases, including neurodegenerative disorders, amyotrophic lateral sclerosis, Alzheimer’s disease, Parkinson’s disease, autoimmune diseases, rheumatoid arthritis, type 1 diabetes mellitus, cardiovascular diseases, and cancers [21, 22]. A major increase in registered clinical studies using MSCs has occurred over the past 10 years. East Asia, especially China, has been leading this trend, followed by North America and Europe [6]. The distinctive feature of stem cells is in the permanent self-renewal and ability to differentiate into specialized adult cell types. MSCs can be categorized as pluripotent stem cells, which have the capacity to develop into any cell type, and multipotent stem cells, which have limitations in differentiation potential [23]. The ease with which MSCs are isolated from various tissues and the capacity to differentiate into multiple lineages make MSCs a smart option for treating various clinical conditions, including viral infections [24]. The vast stem cell therapeutic array is a testament to the potential stem cells hold in the field of regenerative medicine. Pluripotent stem cells, represented by embryonic stem cells and induced pluripotent stem cells, constitute the pinnacle of versatility within this spectrum because pluripotent stem cells possess the remarkable ability to criss-cross the developmental continuum, following the trajectory of embryogenesis itself [23]. With the potential to regenerate damaged or degenerated tissues and organs, pluripotent stem cells have ignited an enthusiasm for scientific exploration and ventured into uncharted territories of curing previously intractable diseases. Moreover, pluripotent stem cells offer a glimmer of hope to individuals afflicted by a myriad of medical conditions, including neurodegenerative disorders and heart diseases. In contrast, multipotent stem cells, although somewhat less all-inclusive in differentiation capabilities when juxtaposed with pluripotent counterparts, remain an option in the biomedical field. These cells, found in various tissues, such as bone marrow, adipose tissue, and the umbilical cord, harbour the inherent potential to transform into a more limited repertoire of cell types, typically within a specific tissue or organ system. The importance of this differentiation potential should not be underestimated because multipotent stem cells are endowed with the capacity to replenish and regenerate tissues, thereby having pivotal roles in maintaining homeostasis and repairing local injuries [23]. Clinically, multipotent stem cells have shown great promise in the domain of tissue engineering and regenerative therapies and offer practical solutions for ailments, such as orthopaedic injuries and haematologic disorders.

## MSC mechanisms of action in viral infections

Human MSCs are non-hematopoietic stem cells identified by unique cell surface markers and differentiation clusters (CD29, CD44, CD73, and CD90) [25]. These cells can develop into three lineages, as follows: endodermal (hepatocytes); mesodermal (osteocytes, adipocytes, and chondrocytes); and ectodermal (neurocytes). MSCs have a crucial role in the innate and adaptive immune systems. MSCs exert immunomodulatory effects primarily through interactions with immune cells via direct cell-to-cell contact and the release of paracrine factors (Figure 1) [26]. MSCs interact with various immune cells, including T cells, B cells, NK cells, and macrophages [27]. *In vitro* studies have demonstrated that MSCs suppress naive and memory T-cell responses by interacting with antigen-presenting cells (APCs) [27]. This interaction involves the upregulation of intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, which are essential for T-cell activation and recruitment of leukocytes (WBCs) to sites of inflammation [28]. Further research has shown that co-culturing bone marrow-derived (BM)-MSCs with activated T cells induces lymphocytes that produce IL-17A [29]. MSCs co-cultured with CD4+ T cells have been shown to activate the Notch1/forkhead box P3 (FOXP3) pathway, increasing the percentage of CD4+CD25+FOXP3+ regulatory T cells (Tregs) [30]. Knockdown of Galectin-1, a protein abundantly expressed in MSCs that affects T lymphocytes and cytokine secretion, results in the loss of MSC



**Figure 1** The figure depicts MSCs modulating immune cells through direct contact and secreted factors. MSCs influence T cells by secreting molecules, such as IFN-γ, IDO, PGE2, various interleukins, PD-L1, PD-L2, and miRNAs. For B cells, MSCs release PGE2 and VEGF to aid in proliferation and antibody production. NK cells are regulated by MSCs through factors, such as IFN-γ, IDO, PGE2, TNF-α, IL-2, IL-12, and IL-18, to enhance cytotoxicity. MSCs also modulate macrophages, dendritic cells (DCs), monocytes, and neutrophils with factors, including PGE2, IDO, IL-1β, IL-6, IL-8, IL-10, TGF-β, and miRNAs, which balance immune responses and prevent excessive inflammation. Source [26].



immunomodulatory properties and restores CD4+ and CD8+ T-cell proliferation [31]. BM-MSCs express high levels of Toll-like receptors (TLRs) 3 and 4, which are responsible for nuclear factor kappa B (NF- $\kappa$ B) activity and cytokine production. Expression of these TLRs in MSCs can restore efficient T-cell responses during infection [26].

Human placenta MSCs (PMSCs) have been shown to express high levels of programmed-death ligand (PD)-1 and -2, which inhibit T-cell proliferation by arresting the cell cycle [32]. *In vivo* mouse models have provided further insight into immune regulation between MSCs and T cells. For example, in a syngeneic orthotopic mouse model of ovarian cancer, compact bone (CB)-derived MSCs have shown anti-tumor effects when combined with a fusion protein (VIC-008) that activates CD4+ and CD8+ T cells and inhibits Tregs in the tumor microenvironment (TME) [33]. In foetal abortion models, MSCs have enhanced the suppressive regulation of T cells and macrophages [34]. Conversely, MSCs primed by activated T cells derived from interferon-gamma knockout (IFN- $\gamma$   $-/-$ ) mice exhibit a significantly reduced ability to suppress T-cell proliferation, which highlights the importance of cell-to-cell contact in MSC immunosuppressive function [35].

In addition to T cells, MSCs also impact B cells through direct contact. Adipose (A)-derived MSCs have been shown to enhance the survival of quiescent B cells via contact-dependent mechanisms and facilitate B-cell differentiation independently of T cells [36]. A-MSCs also inhibit caspase 3-mediated apoptosis of B cells by upregulating vascular endothelial growth factor (VEGF) [37] and inhibit B-cell proliferation by blocking the cell cycle in the G0/G1 phase through activation of the p38 mitogen-activated protein kinase (MAPK) pathway [38]. MSCs also interact with cells of the innate immune system through direct contact. Tracking studies have revealed that infused umbilical cord (UC)-derived MSCs briefly reside in the lungs before being rapidly phagocytosed by monocytes, which then migrate to other body sites. This phagocytosis induces phenotypic and functional changes in monocytes, which subsequently modulate adaptive immune cells and have a crucial role in mediating the immunomodulatory effects of MSCs [26]. Co-culture studies with different NK cell lines (KHYG-1 and NK-92) have shown differential crosstalk between MSCs and cytotoxic NK cells with granule polarization either suppressed or induced [39]. A-MSCs can also switch activated M1-like inflammatory macrophages to an M2-like phenotype via PGE2 and prevent neutrophil death through an ICAM-1-dependent mechanism, thereby exerting tissue-protective effects [26, 40].

MSCs also exert immunomodulatory properties through secretion of multifunctional molecules via paracrine mechanisms [41]. This secretome includes a diverse array of cytokines, growth factors, and chemokines, such as TGF- $\beta$ 1, tumor necrosis factor-alpha (TNF- $\alpha$ ), PGE2, interferon-gamma (IFN- $\gamma$ ), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), IDO, and nitric oxide (NO) [26]. These paracrine factors are encapsulated in extracellular vesicles (EVs) secreted by cells, which are classified into exosomes, micro-vesicles (MVs), and apoptotic bodies based on size and origin [42, 43]. MSCs influence the

adaptive immune system, particularly T cells, through paracrine secretion. MSCs inhibit T helper (Th)17 cell differentiation by inducing IL-10 and PGE2 production while inhibiting IL-17, IL-22, and IFN- $\gamma$  [43]. However, the mechanisms underlying MSC-Th17 interactions are not fully understood. *In vitro* and *in vivo* studies using IL-25 knockdown have shown that MSCs suppress Th17 responses through the IL-25/STAT3/PD-L1 axis [44]. MSC-secreted IDO induces Tregs, which are responsible for kidney allograft tolerance [45]. Additionally, exosomes derived from BM-MSCs transfected with plasmids encoding shFas and anti-miR-375 and co-cultured with peripheral blood mononuclear cells (PBMCs) suppress immune responses in immunodeficient mouse models by inhibiting PBMC proliferation and enhancing Treg function [46]. MSCs also secrete PD-1 ligands, including PD-L1 and PD-L2, to exert immunosuppressive effects directly on T-cell behaviour by suppressing CD4+ T-cell activation [47].

Within the innate immune system, MSCs interact with NK cells by inhibiting IL-2-induced NK cell proliferation [48] and modulating cytotoxic activity or cytokine production via IDO and PGE2 secretion [49]. MSCs enhance the ability of IL-12- and IL-18-stimulated NK cells to secrete IFN- $\gamma$ , potentially improving infection defence at injury sites and influencing tissue regeneration [50]. MSC-derived IL-6 protects neutrophils from apoptosis, preserving neutrophils within the bone marrow niche [51]. MSC-derived exosomes augment neutrophil viability, while MSC-conditioned media (CM) increase neutrophil function, demonstrating the usefulness of MSC-derived exosomes and CM in enhancing immunity by modulating neutrophils [52]. Lipopolysaccharide (LPS)-stimulated MSCs enhance neutrophil anti-microbial functions by releasing IL-8 and macrophage migration inhibitory factor (MIF), which contributes to the resolution of infections and inflammation [53]. MSC-EVs also have a crucial role in macrophage polarization, enhancing the formation of anti-inflammatory M2 macrophages over M1-like inflammatory macrophages by downregulating IL-23 and IL-22 [54]. BM-MSCs activated by LPS or TNF- $\alpha$  reprogram macrophages by releasing PGE2, which acts on macrophages through PG EP2 and EP4 receptors [55]. Human PMSCs transform macrophages from an inflammatory M1 into an anti-inflammatory M2 phenotype via soluble IL-10, IL-1 $\beta$ , IL-12, MIP-1 $\alpha$ , and glucocorticoid and progesterone receptors [56].

Importantly, IFN-stimulated gene (ISG) expression equips these cells with resistance to viral entrance by aiming at various stages of the viral lifecycle, including genome integration, transcription, and translation [1, 57]. Notable ISGs include PMAIP1, ISG15, IFI6, IFITM3, SAT1, p21/CDKN1A, SERPINE1, and CCL2 [57]. ISGs have been shown to suppress the infection of various viruses *in vitro* and some directly affect the susceptibility of specific viruses [58]. MSCs regulate the host tissue microenvironment by modulating immune responses, inhibiting NK and T cells, and downregulating inflammatory cytokines while upregulating regulatory cytokines [22]. TLRs, especially TLR3 and TLR4 on the surface of MSCs, have a crucial role in immunomodulatory action in response to RNA viruses, thereby preventing a cytokine storm [59, 60]. MSCs release

anti-inflammatory chemicals, such as NO, PGE2, TGF- $\beta$ 1, HGF, IDO, and IL-10 in response to this hyperimmune response [61, 62].

## Efficacy of MSCs in treating COVID-19

Clinical trials have recognised the safety and efficacy of MSCs in the treatment of COVID-19, which demonstrated that MSCs possess the remarkable ability to mitigate inflammation, release protective substances, offer antioxidant effects, reduce cell mortality, and enhance the overall immune response. As of June 2022, 104 clinical trials involving stem cells were registered and documented for COVID-19 therapy. Several studies have validated and shown that MSC therapy considerably lowers the incidence, frequency, and mortality of critically ill patients [63]. For example, Shu et al. [63] reported no mortality in the MSC therapy group, while Xu et al. [64] found significantly higher survival rates in MSC-treated patients compared to those receiving standard treatment. The harm inflicted on the respiratory system by COVID-19 arises from a combination of the inherent pathogenicity of the virus and the immune reaction to virus. A study piloted by Shi et al. [65] discovered that COVID-19-infected patients exhibit elevated levels of proinflammatory cytokines [65]. However, patients who required admission to intensive care units (ICUs) displayed a decrease in the levels of MCP1, MIP-1 $\alpha$ , GCSF, IP10, and TNF- $\alpha$  when compared to non-admitted individuals. This shift in cytokine levels points to the occurrence of a cytokine storm within the lungs of infected individuals. Such alterations in cytokine levels have been linked to a cascade of immune responses and extensive lung damage following pulmonary inflammation. This combined effect ultimately contributes to a heightened risk of mortality. Patients treated with MSCs exhibit significantly improved 28-day survival rates and a reduced likelihood of death compared to the control group [66]. Moreover, MSC therapy accelerates COVID-19 recovery and improves pulmonary function [65]. After MSC delivery, several analytical parameters reverted to normal, including C-reactive protein (CRP), alanine aminotransferase (ALT), creatinine, and serum ferritin (SF) levels, as well as platelet counts [67]. MSCs improved the healing of other organs, such as the liver and kidneys, in addition to reducing pulmonary symptoms [67]. MSCs have a vital role in mitigating lung injuries caused by Coronaviridae family members by targeting the cytokine storm and promoting lung tissue repair and restoration [62].

## Influenza viruses and the potential of MSC therapy

Influenza viruses are frequent culprits leading to pandemics and epidemics, with the emergence of H1N1 influenza

in 1918 setting a historical precedent [68]. The 21<sup>st</sup> century has witnessed sporadic outbreaks of avian influenza virus (AIV) subtypes, such as H5N1, H7N9, and H9N2, which have caused high mortality rates in humans [69]. In spite of antiviral drugs as the primary therapeutic approach against influenza-induced manifestations, antiviral drugs often fail to repair damaged lung tissues, which has led researchers to explore alternative treatments involving human bone marrow-derived mesenchymal stromal cells (BM-MSCs) [70]. These cells have demonstrated promise in countering the impact of H5N1 virus infection on human alveolar epithelial cells. Specifically, BM-MSCs contribute to a reduction in enhanced alveolar protein permeability (APP) and an elevation in alveolar fluid clearance (AFC). The mechanisms underlying this process involve the secretion of human keratinocyte growth factor (KGF) and angiopoietin (Ang)-1 by BM-MSCs and *in vivo* experiments have underscored the significant anti-inflammatory properties of BM-MSCs, highlighting the ability of BM-MSCs to increase the population of M2 macrophages [1]. These specialized immune cells have a vital role in producing various cytokines and chemokines, including IL-1 $\beta$ , IL-4, IL-6, IL-8, and IL-17 [1]. MSCs have also shown promise in ameliorating lung injury caused by influenza viruses by restoring alveolar epithelial cell function, decreasing inflammation, and controlling the immune response [71, 72]. Furthermore, MSCs have been shown to inhibit the release of proinflammatory cytokines and multiplication of virus-specific CD8 + T cells, ultimately improving survival of influenza virus patients [73].

## Comparison of efficacy of MSCs in treating COVID-19 versus influenza

Numerous clinical trials have demonstrated the promising potential of MSCs in addressing COVID-19 and its complications (Table 1) [74]. Over 100 registered clinical trials have explored MSCs for COVID-19 treatment, with many focusing on severely ill patients [75]. A phase I clinical study confirmed the safety of high and low doses of DW-MSC infusion in non-severe COVID-19 patients [76]. However, to firmly establish the therapeutic efficacy of MSCs, large-scale randomized controlled trials are necessary. Shu et al. [63] reported that patients treated with UC-MSCs had improvement in clinical symptoms, such as weakness, fatigue, shortness of breath, and the oxygenation index, within 3 days of treatment. Prenatal MSCs from UC-MSCs or placental (PL-MSC) tissues have been used in critically ill COVID-19 patients with ARDS, resulting in reduced dyspnoea and an increased SpO<sub>2</sub> within 2–4 d after an initial infusion in 64% of the patients [74, 67]. A multicentre randomized, double-blind trial revealed a significant increase in the PaO<sub>2</sub>:FiO<sub>2</sub> ratio in the UC-MSC group compared to the placebo group in COVID-19-associated acute respiratory distress syndrome (ARDS) [77]. A clinical trial using human menstrual blood-derived mesenchymal stromal cells for severe and critically ill COVID-19

**Table 1** Clinical Trials Exploring the Potential of MSC Infusions in COVID-19 Patients (Adapted from [74])

No	Study Title	Trial ID NO	Phase	Indications	Source of MSCs	Country
1	Safety of DW-MSC infusion in patients with low clinical risk COVID-19 infection: a randomized, double-blind, placebo-controlled trial	NCT04535856	Phase 1	Low clinical risk COVID-19	Allogenic UC-MSC	Indonesia
2	Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells	ChiCTR2000031494	Phase 1	Severe/critical COVID-19	Human umbilical cord	China
3	Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: a case series	IRCT20200217046526N2	Phase 1	ARDS in COVID-19	Allogeneic umbilical cord/placenta	Iran
4	Treatment of COVID-19-associated ARDS with mesenchymal stromal cells: a multicenter randomized double-blind trial	NCT04333368	Phase 2	ARDS in COVID-19	Umbilical cord	France
5	Evaluation of the safety and efficacy of using human menstrual blood-derived mesenchymal stromal cells in treating severe and critically ill COVID-19 patients: An exploratory clinical trial	ChiCTR2000029606	Phase 1	Severe and critical COVID-19	Allogenic menstrual blood	China
6	Mesenchymal stromal cell therapy for COVID-19-induced ARDS patients: a successful phase 1, control-placebo group, clinical trial	IRCT20160809029275N1	Phase 1	ARDS in COVID-19	Allogenic Umbilical cord	Iran
7	Conquering the cytokine storm in COVID-19-induced ARDS using placenta-derived decidual stromal cells	IRCT2017010531786N1	Phase 1/2	ARDS in COVID-19	Placenta	Iran
8	Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial	NCT04355728	Phase 1/2a	ARDS in COVID-19	Allogeneic umbilical cord	USA
9	Bone marrow-derived mesenchymal stromal cell therapy in severe COVID-19: preliminary results of a phase I/II clinical trial	NCT04445454	Phase 1/2	Severe COVID-19	Bone marrow	Belgium
10	Umbilical cord mesenchymal stromal cells as critical COVID-19 adjuvant therapy: A randomized controlled trial	NCT04457609	Phase 1	ARDS in COVID-19	Allogenic umbilical cord	Indonesia
11	Safety and efficacy study of allogeneic human menstrual blood stromal cell secretome to treat severe COVID-19 patients: clinical trial phase I & II	IRCT20180619040147N6	Phase 1/2	Severe COVID-19	Allogeneic human menstrual blood	Iran
12	Human mesenchymal stem cell therapy in severe COVID-19 patients: 2-year follow-up results of a randomized, double-blind, placebo-controlled trial	NCT04288102	Phase 2	Severe COVID-19	Allogenic umbilical cord	China
13	Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial	NCT04252118	Phase 1	Moderate and severe COVID-19	Allogeneic umbilical cord	China
14	Nebulized exosomes derived from allogenic adipose tissue mesenchymal stromal cells in patients with severe COVID-19: a pilot study	NCT04276987	Phase 2a	Severe COVID-19	Allogeneic adipose tissue	China
15	Safety and long-term improvement of mesenchymal stromal cell infusion in critically COVID-19 patients: a randomized clinical trial	U1111-1254-9819	Phase 1/2	Critical COVID-19	Allogeneic umbilical cord	Brazil
16	Allogenic mesenchymal stromal cells and their extracellular vesicles in COVID-19 induced ARDS: a randomized controlled trial	IRCT20200217046526N2	Phase 2	ARDS in COVID-19	Allogenic perinatal tissue	Iran
17	The systematic effect of mesenchymal stem cell therapy in critical COVID-19 patients: a prospective double controlled trial	NCT04392778	Phase 1/2	Critical COVID-19	Umbilical cord	Turkey
18	Cell therapy in patients with COVID-19 using Wharton's jelly mesenchymal stem cells: a phase 1 clinical trial	IRCT20190717044241N2	Phase 1	Severe COVID-19	Umbilical cord	Iran
19	Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial	NCT04288102	Phase 2	Severe COVID-19	Umbilical cord	China
20	Safety and efficacy assessment of allogeneic human dental pulp stem cells to treat patients with severe COVID-19: structured summary of a study protocol for a randomized controlled trial (phase I/II)	NCT04336254	Phase 1/2	Severe COVID-19	Allogeneic dental pulp	China

Table 1 (continued)

No	Study Title	Trial ID NO	Phase	Indications	Source of MSCs	Country
21	Human placenta-derived mesenchymal stem cells transplantation in patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 (phase I clinical trial): safety profile assessment	IRCT20200621047859N4.	Phase 1	ARDS in COVID-19	Allogenic placenta	Iran
22	Nebulization therapy with umbilical cord mesenchymal stem cell-derived exosomes for COVID-19 pneumonia	ChiCTR2000030261	Phase 1	Pneumonia in COVID-19	Umbilical cord	China
23	A randomized trial of mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome from COVID-19	NCT04371393	Phase 3	ARDS in COVID-19	Allogenic bone marrow	USA

patients showed significant improvement in dyspnoea, the SpO<sub>2</sub>, and the PaO<sub>2</sub>, and notably lower mortality in the MSC group compared to the control group [74, 64]. Farkhad et al. [78] found that mesenchymal stromal cell therapy improved the SPO<sub>2</sub>:FIO<sub>2</sub> ratio in COVID-19-induced ARDS patients. Lanzoni et al. [66] reported improved patient survival and faster recovery after two rounds of intravenous allogeneic UC-MSC administration in ARDS patients. In a phase I/II study, survival rates were higher in the MSC group 28 and 60 d post BM-MSC treatment [79]. An Indonesian randomized controlled trial showed a survival rate 2.5-fold higher in the UC-MSC group than the control group among critically ill COVID-19 patients [80]. Fathi-Kazerooni et al. [81] reported a significantly higher survival rate in severe COVID-19 patients treated with human mesenchymal stromal cells compared to placebo treatment.

Many inflammatory biomarkers and cytokines are closely associated with severe and critical COVID-19. Meng et al. [82] reported improved PaO<sub>2</sub>:FiO<sub>2</sub> ratios and a decline in inflammatory cytokines, such as IL-6, IFN-γ, TNF-α, MCP-1, IP-10, IL-22, IL-1RA, IL-18, IL-8, and MIP-1, after three rounds of UC-MSC treatment. Fathi-Kazerooni et al. [81] reported notably lower CRP levels on day 5 in severe COVID-19 patients treated with human mesenchymal stromal cells compared to placebo, with significant reductions in CRP, LDH, D-dimer, and SE levels in the treatment group. Sadeghi et al. [83] demonstrated significant reductions in IL-6 and CRP levels in COVID-19-induced ARDS patients treated with placenta-derived decidual stromal cells. A pilot study showed that aerosol inhalation of exosomes from human adipose-derived MSCs (haMSC-Exos) in COVID-19 patients increased lymphocyte counts and decreased CRP, LDH, and IL-6 levels [74, 84].

In COVID-19 patients, common CT findings include ground-glass opacification, infiltration, consolidation, pneumonia, and emphysematous changes [85]. Many clinical trials have shown that MSC treatment improves lung changes in COVID-19 patients. Shu et al. [63] reported faster lung inflammation absorption on CT imaging in severe COVID-19 patients treated with UC-MSC compared to the control group. A case series trial showed significant recovery indications, such as reduced ground-glass opacities or consolidations, in COVID-19-induced ARDS patients [74]. Meng et al. [82] observed complete fading of lung lesions within 2 weeks in moderate COVID-19 patients after a UC-MSC transfusion. A phase 2 randomized, double-blind, placebo-controlled trial showed a significant reduction in solid component lesion volume proportions in the UC-MSC group compared to the placebo group in COVID-19-induced ARDS patients [74]. A randomized clinical trial showed a decrease in lung damage extent 4 months after 3 rounds of a mesenchymal stromal cell infusion in critically ill COVID-19 patients [86]. A pilot study reported varying degrees of pulmonary lesion resolution after aerosol inhalation of haMSC-Exos in COVID-19 patients [84]. Xu et al. [64] detected a significant difference in the improvement rate of chest CT findings between experimental and control groups in the first month following MSC infusion in severe and critically ill COVID-19 patients. Fathi-Kazerooni et al. [81] demonstrated significant pulmonary involvement improvement in



severe COVID-19 patients treated with human mesenchymal stromal cells secretome. Sadeghi et al. [83] showed complete disappearance of pulmonary infiltrates in COVID-19-induced ARDS patients treated with placenta-derived decidual stromal cells.

In the case of influenza virus-induced lung injury, despite substantial evidence indicating the beneficial effects of MSC administration in preclinical models, some studies challenge the efficacy of MSCs as a therapeutic or prophylactic option for reducing pulmonary inflammation (Table 2) [87]. Research conducted by Darwish et al. [88] showed that MSC therapy does not lead to improved outcomes in severe experimental influenza. Similarly, Gotts et al. [89] reported no significant beneficial effects of MSCs on weight loss, survival, or lung injury. These findings highlight the importance of considering the timing, dose, route, and frequency of MSC administration when evaluating treatment efficiency. One potential reason for the observed lack of efficacy is that MSCs may have difficulty accessing the injured epithelial barrier and could potentially become infected by the influenza virus. Moreover, the short duration of preclinical models limits the ability to thoroughly investigate lung recovery processes following influenza-induced injury [88, 89].

Nevertheless, these experimental findings do not entirely rule out the potential of MSC therapy to contribute to long-term lung repair and the restoration of full lung function post-influenza infection. In addition to exogenously administered MSCs, tissue-resident MSCs have a significant role in tissue repair and regeneration [87]. Adult pulmonary tissue-resident MSCs exhibit similar phenotypes and functions to BM-MSCs [90]. Although few studies have examined the status of resident lung MSCs after virus-induced lung injury, there is some evidence suggesting that altered lung MSC function may have a role in bleomycin-induced pulmonary arterial hypertension (PAH). In mouse models, bleomycin treatment has been shown to lead to the loss of endogenous lung MSCs, which are critical for modulating the severity of the injury through an influence on the T cell response [91]. Transplantation of isolated lung MSCs has been shown to mitigate bleomycin-induced PAH, reduce the number of inflammatory cells, and inhibit T cell proliferation. These findings imply that lung MSCs are crucial for maintaining lung integrity post-injury, but the loss compromises this protective function [92]. Ye et al. [93] demonstrated that BM-MSCs influence endogenous lung stem cells (club cells) through the release of cytokines and vesicles, activating the Notch signalling pathway and affecting the proliferation of club cells in phosgene-induced lung injury. Another study

showed that BM-MSCs protect against LPS-induced lung injury by restoring alveolar bioenergetics through Cx43-dependent alveolar attachment and mitochondrial transfer [94]. These findings suggest that transplanted exogenous MSCs may create an important niche for various types of lung cells via different pathways.

The recent emergence of SARS-CoV-2, which has caused an outbreak of atypical viral pneumonia in patients, underscores the global public health risks posed by coronaviruses. Despite multiple occurrences of such viruses attacking humans, there are still limited specific strategies to address these virus-induced injuries [87]. Stem cells, including MSCs and LSCs, offer a potential therapeutic approach for treating virus-induced lung injuries. This potential has been explored from the perspectives of immune regulation and lung repair, although challenges remain. The number of clinical trials investigating stem cell therapy for virus-induced lung injury has been gradually increasing. Looking ahead, there is an expectation that stem cell therapy will become a viable treatment option for virus-induced lung injury.

## Challenges and future directions in MSC therapy

The potential of MSCs in various pre-clinical disease models is well-documented, yet the exact mechanisms underlying many observed effects remain elusive [95, 96]. Over the past 10 years, clinical trials for MSC-based therapies have been initiated for numerous medical conditions [97]. These clinical studies have consistently demonstrated that MSC applications are safe and feasible, although proving their efficacy has often been challenging as therapies progressed through clinical development stages. This challenge is reflected in the absence of MSC-based products in the European market, with only a few such products approved globally. South Korea is at the forefront, having registered two MSC products, with the first authorization granted in 2011 [95]. This noteworthy MSC approval is possibly due to the South Korean regulatory framework, which permits conditional marketing approval, allowing commercial sales under specific conditions while pivotal trials are ongoing. The European Union has a similar procedure under Regulation (EC) No 507/2006, although there are differences in the regulatory systems. In North America, Health Canada's Notice of Compliance with Conditions (NOC/c) allows for conditional marketing of MSC products, which is similar to the South Korean approach

**Table 2** Clinical Trials Exploring the Potential of MSC Infusions in Influenza Patients

No	Study Title	Trial ID NO	Phase	Indications	Source of MSCs	Country
1	Clinical study of mesenchymal stem cell treatment for acute respiratory distress syndrome induced by epidemic influenza A (H7N9) infection: A hint for COVID-19 treatment	ChiCTR-OCC-15006355	Completed	ARDS in Influenza	Menstrual blood derived MSCs	China
2	Using human menstrual blood cells to treat acute lung injury caused by H7N9 bird flu virus infection	NCT02095444	Unknown	No result posted	Menstrual blood stem cells	China



[95]. In the United States, the Food and Drug Administration (FDA) has stringent requirements for MSC-based therapies, requiring extensive pre-clinical and clinical data to demonstrate safety and efficacy [95]. Many studies involving MSC clinical applications often lack pre-clinical screening because only one active substance candidate is typically used. Evaluating the rationale behind using specific MSC cultures is essential if the clinical application does not require the same function as in the tissue of origin. MSC trials frequently aim to promote tissue regeneration or immunomodulation. Incorporating pre-clinical screening and selection, a standard part of conventional medicinal product development, should also apply to cell therapy. Techniques, such as modifying MSC populations with small compounds followed by expression or secretome profile screening, genetic modifications to enhance therapeutic effects, or comparing subpopulations from different origins, could be considered to improve study design and efficacy [98, 99].

Though costly and perhaps less attractive for academic research, pre-clinical screening can be a cost-effective improvement for discovering new MSC therapy candidates, which would offer benefits, such as novel intellectual property acquisition. MSC product developers should start with the EMA scientific guidelines detailing quality, safety, efficacy, and pharmacovigilance for Cell Therapy Medicinal Products (CTMPs). Despite these guidelines, the variety of cell therapy products means a risk-based approach is necessary for development and evaluation. Directive 2001/83/EC encourages a risk-based approach for ATMPs to determine the extent of quality, non-clinical, and clinical data required for marketing authorization applications [95]. The risk analysis must cover the entire development process with relevant biological parameters, including cell viability and biodistribution investigation, in place of conventional pharmacologic tests. Given the lack of relevant animal models for cell therapy products, the regulatory evaluation will likely follow a risk-based approach until more products reach the market. Understanding these ethical issues and regulatory frameworks, which differ globally, is crucial for advancing MSC-based therapies. Solutions, such as adaptive licensing and a risk-based approach, could improve the efficiency and accessibility of these promising treatments. Nevertheless, the prolonged culture of stem cells may lead to chromosomal abnormalities and epigenetic changes, necessitating adherence to “Good Manufacturing Practices” (GMP), in which the standards for sustainable cell production can compromise the immune response and increase the susceptibility to infections [100, 101]. Moreover, concerns have arisen regarding the role of MSCs in promoting viral transmission and tumor growth [102, 103]. Therefore, it is imperative to homogenise therapeutic protocols, *ex vivo* preparations, and MSC isolation methods to enhance clinical outcomes. To address these ethical and regulatory challenges, a harmonized global regulatory framework could be developed incorporating best practices from different regions. Adaptive licensing, which allows for conditional approvals based on iterative data gathering and regulatory re-evaluation could be widely adopted among regulatory boards because this approach balances the need for timely access to therapies with the requirement for thorough safety and efficacy evaluations.

Enhancing international collaboration and sharing of clinical data could also improve the regulatory process, ensuring that MSC-based therapies meet high standards of safety and efficacy, while accelerating the availability to patients in need. Establishing clear guidelines for the ethical sourcing and use of MSCs, coupled with robust patient consent processes, can address ethical concerns and build public trust in these therapies.

## Conclusion and future directions

MSCs offer a multitude of advantages that make them attractive for therapeutic applications. First, MSCs can be harvested from various tissues, including BM, which is considered the most preferable source. MSCs can also be isolated from peripheral blood, AD tissues, oral tissues, and menstrual blood. Neonatal birth-related tissues, such as the PL, UC, Wharton’s jelly, and amniotic membrane or fluid, are effective sources of MSCs [104]. Once isolated, MSCs can be preserved for future therapeutic use. Second, MSCs are multipotent stem cells that possess the ability to self-renew and differentiate into multiple specialized cell types [104]. Third, MSCs can be expanded to large quantities in a relatively short time, allowing MSCs to be stored for repeated therapeutic interventions [104]. Importantly, clinical studies involving MSCs have not reported severe adverse reactions to allogeneic MSCs to date. Lastly, various clinical trials have confirmed the safety of MSCs in therapeutic applications [105].

Using MSCs for COVID-19 treatment presents several challenges that must be addressed to ensure efficacy and safety. Because MSC therapy is classified under stem cell treatments, it is imperative to adhere to the guidelines set by the International Society for Stem Cell Research (ISSCR). The ISSCR “Guidelines for the Clinical Translation of Stem Cells” outline the criteria for advancing stem cell-based treatments to ensure that the therapeutic potential is realized [104]. Key challenges include optimizing the expansion period, determining the required cell dose, and addressing issues related to cell culture and exposure to animal-derived products, which can significantly impact safety and efficacy. Long-term *in vitro* culture can lead to a loss of essential stem cell characteristics, such as stemness and plasticity, or even induce malignant transformation [106]. Another significant challenge is determining patient eligibility for MSC-based treatments, particularly for those with chronic conditions, cancer, autoimmune diseases, allergies, or those who are pregnant or breastfeeding. Many clinical trials using MSCs or derived exosomes for COVID-19 treatment are still in phase I/II trials and have yielded unsatisfactory results [104]. It is crucial to have robust evidence and verification of MSC safety and efficacy, which involves assessing potential adverse events and long-term consequences [107]. Another major challenge is the significant heterogeneity within MSC populations, which may contribute to inconsistent research findings. Moreover, recent studies indicate that MSCs might

not be as immunologically inert as previously believed [7]. This discovery necessitates further investigation to identify and isolate the “immune privileged” subpopulations within the diverse MSC pool for more reliable clinical applications. An alternative strategy to circumvent these issues is to explore cell-free therapies, such as MSC-derived exosomes [7]. These exosomes could offer significant advantages over MSCs, especially because the therapeutic effects of MSCs are largely attributed to paracrine activity. Given the limited research on MSC applications in virus-related diseases and the fact that most studies are still in early clinical phases, it is premature to draw definitive conclusions about efficacy. Therefore, it is essential to conduct well-designed, randomized controlled trials with larger sample sizes to thoroughly assess the safety and therapeutic effectiveness of MSC treatments over both short- and long-term periods [7].

Although the BM is the most common source of MSCs, the harvesting process is invasive and the yield is limited. ARDS can impair the immunomodulatory efficacy of BM-MSCs, complicating use for autologous transplantation [104]. While studies have explored the therapeutic

efficacy of MSCs from other sources in ARDS, it remains unclear which source provides the best outcomes. Determining the optimal cell injection dose is critical for clinical MSC treatments. Emerging and re-emerging infectious diseases have continued to challenge global healthcare systems, emphasizing the urgent need for pioneering therapeutic methods. Stem cell therapy, particularly with MSCs, holds immense promise in moderating the impact of these viral infections by exerting antiviral, anti-inflammatory, immunomodulatory, anti-fibrotic, anti-apoptotic, and angiogenic effects. Future clinical trials should focus on understanding these characteristics of stem cells in infectious environments and explore innate recognition mechanisms to enhance their antiviral potential. Standardization of MSC protocols and quality improvements are essential for addressing the challenges associated with graft rejection, graft-versus-host disease, and delayed immune reconstitution. The interface between viruses and stem cells thus remains a dynamic field ripe for further exploration, offering hope in the ongoing scuffle against infectious diseases.

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