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Review Article

Update on the Use of Mesenchymal Stem Cells in the Treatment of Various Infectious Diseases Including COVID-19 Infection

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Abstract

Mesenchymal Stem Cells (MSCs) have antimicrobial, anti-inflammatory, immunomodulatory, and regenerative potentials. Additionally, utilization of MSCs in the clinical arena has been shown to be safe and well tolerated. Hence, this form of cellular therapy has gained particular attention in the treatment of several infectious disorders and their complications.

MSCs have been successfully used in the treatment of the following infections and their complications: bacterial infections including complicated sepsis; viral infections including Human Immunodeficiency Virus (HIV), hepatitis B and C viruses, and Coronavirus disease (COVID-19) complicated by acute respiratory distress syndrome; parasitic infections including schistosomiasis, malaria, and Chagas disease; and mycobacterial infections including tuberculosis. The use of MSCs derived from certain sources and Extracellular Vesicles (ECVs) derived from MSCs has improved their efficacy and reduced their side effects. However, the clinical application of MSCs in the treatment of several infectious diseases still faces real challenges that need to be resolved. The current status of MSCs and the controversies related to their utilization in various infections will be thoroughly discussed in this review.

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Introduction

MSCs are heterogeneous, non-hematopoietic, adult multipotent stromal progenitor cells that are capable of self-renewal and differentiation into multiple lineages and various cell types [1-3]. MSCs can be obtained from various body tissues and organs and they have characteristic features and surface markers on flow cytometry as shown in Table 1 [1-5]. MSCs have several antimicrobial, anti-inflammatory, and regenerative properties which make them suitable candidates for use in the treatment of various infections and their complications. These properties include: (1) inhibition of biofilm formation; (2) excessive recruitment of neutrophils to the sites of infection or inflammation; (3) reduction of tissue damage and release of paracrine factors that direct tissue regeneration and wound healing; (4) detection and elimination of invading pathogens and release of antimicrobial factors that are needed for clearance of pathogens and reducing their load as shown in preclinical models of sepsis, cystic fibrosis and Acute Respiratory Distress Syndrome (ARDS); (5) having the capacity to enhance antibacterial activity by interaction with the host innate immune system; (6) activation of phagocytosis and reprogramming of macrophages and neutrophils towards a more anti-inflammatory phenotype; (7) activation of the immune responses by induction of proinflammatory responses and downregulation of proinflammatory cytokines; (8) secretion of antimicrobial peptides, molecules, and proteins such as: interleukin (IL)-17, indoleamine 2,3 dioxygenase, β-defensins, lipocalin-2, and cathelicidin LL-37; (9) inhibition of inflammation and regulation of multiple inflammatory networks; and (10) changing the microenvironment at the site of infection and inhibition of T-cell proliferation at the site of tissue injury [2,3,5-7].

Table 1: Sources and characteristic features and surface markers of MSCs.

Sources of MSCs	Characteristic features of MSCs	Surface markers of MSCs
1. Bone marrow 2. Peripheral blood 3. Umbilical cord (UC) blood 4. Wharton's jelly of UC 5. Placenta 6. Amniotic fluid 7. Menstrual blood 8. Breast milk 9. Adipose tissues 10. Dental pulp 11. Palatal tonsils 12. Salivary glands 13. Lung and liver tissues	1) Differentiation into osteoblasts, adipocytes, and chondrocytes. 2) Adherence to the plastic vessel under optimal culture conditions. 3) Having characteristic surface markers on flow cytometry.	**Characteristically positive:** CD 105 CD 73 CD 90 **Characteristically negative:** CD 45 CD 34 CD 14 CD 11b CD 19 CD 79a HLA-DR

- MSCs: Mesenchymal Stem Cells
- HLA: Human Leukocyte Antigen

MSCs have demonstrated potent antimicrobial effects through direct and indirect mechanisms against the major classes of human pathogens including bacteria, viruses, fungi, and parasites across a wide range of infection models. The immunomodulatory and antibacterial activity of MSCs can be enhanced by various forms of preconditioning protocols [1,8]. Currently, more than 80 Clinical Trials (CTs) are investigating the use of MSCs in the treatment of various infections including sepsis, local bacterial infections, and viral infections such as COVID-19 [1,9]. The completed CTs on the use of MSCs in difficult-to-treat infectious diseases have demonstrated safety, tolerability, as well as potential efficacy as adjuvant therapy in complex or resistant infections [1]. The use of ECVs of MSCs is a promising cell-free treatment strategy that allows for solving problems associated with the safety of cell therapy and increasing its effectiveness. Hence, MSCs and their ECVs can be a promising tool for the treatment of various infectious diseases, particularly in combination with antimicrobial agents [2,4].

Factors that affect the outcome of mesenchymal stem cell therapies

Recent studies have suggested that factors such as age, gender, route of administration, infused stem cell dose, as well as biological sources of MSCs, have a significant impact on the outcome of MSC therapies [10-14]. Also, studies have shown that: (1) it is preferable to use MSCs obtained from Bone Marrows (BMs) of young healthy donors or derived from Umbilical Cords (UCs) directly after birth; and (2) administration of MSCs that are compatible with the biological gender of the recipient can avoid gender-specific immunological complications [12]. Although similar, MSCs derived from different sources possess distinct characteristics, advantages, and disadvantages, including their differentiation potential and proliferation capacity, which influence their clinical applicability [15]. However, the preferred source may vary according to the clinical indication. Examples are: MSCs derived from BM, adipose tissue, and dental tissues are preferable for use in oral and dental regeneration while MSCs obtained from UC and other perinatal tissues are preferable in COVID-19 infections [16-20].

Mesenchymal stem cells in bacterial infections

Chronic bacterial infections associated with biofilm formation are often difficult to treat without extended courses of antibiotic therapy [21]. The antimicrobial activity of MSCs relies on direct effects and indirect effects by secreting paracrine factors to inhibit bacterial growth [6]. In animal models, the combination of activated MSCs and antibiotic therapy may become a promising approach to treating infections caused by drug-resistant bacteria and accelerate the healing of infected tissues [22,23]. In patients with sepsis or pneumonia, administration of MSCs has been shown to inhibit bacterial growth and enhance survival by improving clearance of pathogenic bacteria [24,25]. So, MSCs should be considered as novel therapeutic strategies to control chronic infections and infections caused by multi-drug resistant organisms [6,21].

Sepsis and septic shock are life-threatening disorders that are associated with high rates of morbidity and mortality [26,27]. Recently, due to the failure of conventional therapies, research has been focused on innovative treatments such as cellular therapies [26]. The antimicrobial, immunomodulatory, anti-inflammatory, anti-apoptotic, and regenerative properties of MSCs can protect against organ failure caused by sepsis and septic shock. Consequently, MSCs have been extensively utilized in preclinical as well as clinical trials in various infectious diseases [26,27]. However, the mechanisms involved in the way MSCs exert their beneficial effects to control inflammation and prolong survival in septic conditions remain unclear [28]. Based on their immunomodulatory and antimicrobial properties, adult MSCs represent an emerging therapeutic strategy to treat sepsis and sepsis-induced organ dysfunction or failure [29,30]. Adult MSCs have been shown to reduce mortality in experimental models of sepsis [7]. Three phase I CTs, that included small numbers of patients, on the use of MSCs in the treatment of patients having septic shock have shown safety and positive impact of MSC therapy on survival rates of patients during the early phase of sepsis. However, there is an urgent need to perform phase II as well

as randomized phase III CTs to determine the role of MSC therapies in patients with septic shock [31-33]. Additionally, ECVs of MSCs have therapeutic effects that are similar to the parent MSCs and they can protect against sepsis-induced organ dysfunction [27]. Studies in animal models have shown that the use of ECVs obtained from BM-derived MSCs was associated with less organ damage in comparison to ECVs derived from MSCs obtained from other sources [34]. Additionally, ECVs derived from MSCs have shown a superior safety profile as well as the ability to be stored safely without loss of function compared to the parent cells. Hence, MSC-ECVs may be used as a novel alternative to MSC-based therapy in sepsis [27].

Mesenchymal stem cells and viral infections

The interplay between MSCs and viruses can be described as a double-edged sword as MSCs have been found to be highly susceptible to viral infections in vitro [35]. Upon encountering certain viruses, MSCs appear to produce deleterious effects and they act as viral transmitters and this may raise concerns about their therapeutic efficacy. On the other hand, MSCs provide beneficial effects such as allowing the proliferation and function of specific antiviral effector cells instead of suppressing them thus they may serve as an ideal tool to study viral pathogenesis and protect hosts against viral challenges by using their antimicrobial activity [35-37]. Additionally, MSCs express receptors that are used by HIV, hepatitis B virus (HBV), and herpes viruses for their interaction with target cells. Hence, MSCs are permissive for these viruses and could transmit them to recipients of allogeneic stem cell transplantation [38]. As the clinical efficacy of MSC infusion may be impaired by some destructive outcomes, MSCs should be screened for HIV, HBV, herpes, and other viruses prior to transplantation in order to prevent the evolution of viral-associated diseases and to ensure the safety of MSC therapy [35,38].

Upon infection, Lung Resident (LR)-MSCs mount an antiviral response and release a variety of immunomodulatory mediators which may have a biological impact on the pulmonary microenvironment [39]. During the early phase of viral infection, MSCs that are activated by viral antigens elicit strong immune responses by production of proinflammatory cytokines which enhance the antiviral properties of immune cells [38]. However, after the elimination of viral pathogens, MSCs produce immunoregulatory cytokines and trophic factors that support the prevention of overactivation of immune cells, as well as the repair and regeneration of injured tissues. Thus, MSCs orchestrate antiviral immune responses that crucially contribute to the elimination of infected cells [38].

MSCs display considerable promise in the treatment of severe viral pneumonia as they possess several relevant mechanisms of action and they have demonstrated safety profile in early phase studies [40]. IL-18, which is highly expressed in influenza-A H1N1-induced severe lung injury, is a promising cytokine that can prime UC-MSCs to improve the efficacy of precision therapy against viral-induced pneumonia such as COVID-19 [41]. Respiratory syncytial virus-mediated lung injury activates and stimulates the expansion of LR-MSCs which mount a transcriptional program related to the mechanisms of repair and regeneration [39]. Soluble mediators released from avian influenza A-H5N1 virus-infected alveolar epithelial cells impair alveolar fluid clearance and protein permeability by down-regulating alveolar sodium and chloride transporter proteins [42]. Studies have shown that (1) MSCs reduce the impairment of alveolar fluid clearance induced by influenza A H5N1 infection in vitro and prevent or reduce influenza A-H5N1-associated Acute Lung Injury (ALI) *in vivo*, (2) transplantation of IL-18 primed human UC-MSCs has significantly enhanced the inhibition of inflammation, viral load, fibrosis, and cell apoptosis in ALIs, (3) treatment with IL-18 primed human UC-MSCs has superior inhibitory effect on T-cell exudation and proinflammatory cytokine secretion in bronchoalveolar lavage fluid, (4) in animal models, BM-MSCs exert antiviral properties and they may have therapeutic potential in the treatment of influenza virus-induced pneumonia and ALI, and (5) MSCs have been shown to enhance antiviral immune responses and protect against lethal or generalized herpes viral infections [42-44]. Additionally, exosomes derived from human UC-MSCs have a broad antiviral role in the inhibition of viral replication and provide new insights into the development of antiviral agents by bioengineering these exosomes to target respiratory viruses [45].

Stem cell-based therapies represent innovative approaches to rebuild the damaged immune system and ultimately eliminate the virus from the body [37]. The potential of MSCs to treat viral infections is still in its infancy due to the limited number of studies on the use of these cells in the treatment of virus-associated diseases [46]. In HBV-related acute or chronic liver failure, transplantation of MSCs has been shown to: improve liver function, increase survival of patients, and decrease the incidence of severe infections [47,48]. Despite that MSCs appear to have the potential to contribute to the HIV-1 reservoir, the use of MSCs derived from adipose tissues and UC in 2 CTs performed in patients with acquired immunodeficiency syndrome has not been shown to be effective in recovering immunity or aiding immune reconstitution in an immune non-responder group of patients although safety of MSC therapy has been confirmed [36,49,50].

Ten systematic reviews and meta-analyses that included 129 CTs comprising 4391 patients on the use of MSCs in the treatment of COVID-19 infection and its complications have shown the following results: (1) MSCs can reduce the mortality

rates and increase overall survival in patients with COVID-19 infection; (2) MSCs can reduce the severity of COVID-19 pneumonia; (3) MSCs can induce remission of symptoms related to COVID-19 infection in the vast majority of studies included; (4) MSCs can reduce the duration of hospitalization and the requirement for invasive mechanical ventilation; (5) MSCs can improve lung function and radiological appearances in patients with COVID-19 pneumonia; and (6) MSCs can reduce the levels of inflammatory markers such as C-reactive protein and interferon-gamma in the majority of patients with severe COVID-19 infection [17,51-59]. Additionally, the included CTs have shown the safety of MSC therapy in COVID-19 infection without an increase in adverse effects [17,51-54,56-59]. In the CTs included: the commonest source of MSCs was the UC, intravenous infusion was the most common route of administration of MSCs, and the number of injections given ranged between 1 and 3 injections with variable MSC doses [17,18,52,56,58-60].

Several studies have shown that the use of MSCs and their secretome in the treatment of severe COVID-19 infections has the following beneficial effects: (1) suppression of viral replication, viral shedding, and virus-induced damage to lung epithelial cells; (2) enhancement of the generation of regulatory Tcells that are suppressed by COVID-19; (3) MSCs shift the phenotype of antigen presenting cells including dendritic cells, B-lymphocytes, and macrophages; (4) MSCs modulate the proliferation and activation of naïve and effector T-cells, natural killer cells, and mononuclear cells; (5) MSCs prevent the formation of neutrophil extracellular traps that may have deleterious effects in patients with COVID-19 pneumonia and ARDS; (6) MSCs can inhibit the cytokine storm induced by COVID-19; (7) the secretome of MSCs including ECVs and exosomes has antiviral, antibacterial, and even analgesic effects; (8) reduction in pulmonary oedema associated with ARDS in COVID-19; (9) entrapment of intravenously infused MSCs in the lungs which is an advantage in patients with COVID-19 patients having pneumonia and ARDS; (10) enhancement of tissue regeneration and promotion of endogenous repair and healing in ALI induced by COVID-19; and (11) safety and efficacy of MSCs and their products provided good manufacturing practice guidelines and quality control measures of the whole process from harvesting till delivery are strictly applied [2,61-65].

Long-term follow-up of 65 patients having severe COVID-19, included in a CT, who received MSCs showed safety, but the efficacy of MSC treatment was not significantly sustained through the end of the 2-year follow-up period [66]. However, another CT that included 100 patients with COVID-19 infection on the use of UC-MSC treatment showed that UC-MSC administration achieved a long-term benefit in the recovery of lung lesions and symptoms after 1 year of follow-up [67]. Also, a third CT that included 17 patients with severe COVID-19 who required invasive mechanical ventilation in the intensive care unit showed that UC-MSCs infusion was safe and could play an important role in the chronic phase with a reduction in post-acute sequelae reduction in critically ill COVID-19 patients [68]. Additionally, MSC secretome could offer a new therapeutic approach to treating COVID-19 fibrotic lungs through its anti-inflammatory and antifibrotic factors [69].

Mesenchymal stem cells in mycobacterial infections

Recent studies have demonstrated that: (1) MSCs are present in and around the tuberculous granulomas which contain *Mycobacterium Tuberculosis* (MTB) bacilli, (2) MTB uses MSCs as a niche to evade host protective immune surveillance mechanisms and establish dormancy, (3) MSCs have the ability to restrict the growth of MTB to a certain extent and may be involved in the development of TB, (4) MSCs maintain antibacterial, immunomodulatory, anti-inflammatory, and regenerative properties during the regulation of TB immune responses, (5) MSCs express a large number of ATP-Binding Cassette (ABC) efflux pumps so that dormant MTB residing in MSCs are exposed to a suboptimal dose of drugs, and (6) MSCs represent the fifth element in cell-mediated immunity that is capable of regulating immune responses during TB infection [70-75]. Hence, it is highly likely that MSCs play significant roles in orchestrating: dormancy and reactivation of MTB, evasion of host immune responses, as well as resistance to anti-TB drugs [70,74,75]. Additionally, MSCs can be used as an immune target or immunotherapy agent for the treatment of TB and may provide a screening model for the development of new drugs or vaccines for TB [71].

Transplantation of MSCs and their exosomes has been used in the treatment of Multidrug-Resistant (MDR)-TB [73,76]. Three CTs; that included 135 patients; on the use of autologous MSCs to treat MDR-TB and extensively DR (XDR)-TB have shown the following results: (1) MSCs induced clinical and radiological improvements in 70% - 80% of patients; (2) MSC transplantation induced persistent remission and even cure in 53% - 56% of patients; and (3) the addition of autologous MSC transplantation to conventional anti-TB chemotherapy significantly enhanced the response rates in patients with MDR-TB and XDR-TB [77-79].

Mesenchymal stem cells in parasitic infections

Stem cells exert inhibitory effects on parasitic infections and they improve the functions of the tissues and organs involved [80,81]. Stem cell therapies are necessary in the treatment of parasitic infections because there are limited drug choices, and there is continuous emergence of drug resistance [80]. Stem cells including MSCs have been used in the treatment of various parasitic infections including leishmaniasis, trypanosomiasis, schistosomiasis, echinococcosis, malaria, and toxoplasmosis [80,81].

In malaria, treatment with BM-derived MSCs showed the following effects: (1) improved the clearance of parasitized red blood cells, (2) increased the regeneration of hepatocytes and Kupffer cells, (3) increased the number of astrocytes and oligodendrocytes in the brain, (4) increased survival, and (5) decreased inflammation and malaria pigment accumulation in kidneys, lungs, and spleens of experimental animals [80,82]. Additionally, BM-derived MSCs are promising in the treatment of cerebral malaria as animal studies have shown that the combination of MSCs and adjuvant antimalarial treatment: protects against vascular damage, improves depression, and increases survival [82,83]. In experimental schistosomiasis, treatment with BM-derived MSCs significantly reduced the granuloma size as well as the expression of the fibrosis factor, alpha-smooth muscle actin, in hepatic cells [83]. Treatment with MSCs showed a significant reduction in the cutaneous lesions caused by Leishmania major, while in toxoplasmosis, experimental therapy with BM-derived MSCs combined with spiramycin, pyrimethamine, and folinic acid showed a significant decrease in the number and size of tissue cysts in the brains of mice [83].

In Chagas disease, unfortunately, more success has been achieved in animal or preclinical studies than in human studies [84]. In the murine model of Chagas disease, co-transplantation of MSCs and skeletal myoblasts has been shown to be effective in decreasing ventricular dysfunction [85]. In the Chagas disease model, cardiac MSCs have demonstrated potential as they exerted a protective effect on chronic Chagasic cardiomyopathy through immunomodulation but they neither reduced fibrosis nor contributed to cardiomyocyte formation [86]. Repeated injections of granulocyte colony-stimulating factor (G-CSF), which mobilizes stem cells from the BM, decreased inflammation and fibrosis in the hearts of mice having Chagas disease [80]. Also, G-CSF overexpression in MSCs potentiated the *in vivo* immunosuppressive effects of MSCs in chronic Chagas disease models [87].

The rising role of extracellular vesicles and exosomes of mesenchymal stem cells in the treatment of infectious diseases

Recently, studies have demonstrated that MSC-derived ECVs are at least partially responsible for the paracrine effects of MSCs including the transfer of molecules such as proteins/peptides, mRNA, microRNA, and lipids with immunoregulatory properties to recipient cells, and may offer specific advantages over the parent MSCs due to lower immunogenicity, storage without losing function, and superior safety profile [88,89]. ECVs can achieve their valuable roles in the treatment of infectious diseases through different mechanisms including elimination of the pathogen, regulation of immunity, modulation of drug resistance, repair of tissue damage, production of antimicrobial substances, inhibition of pathogen multiplication, and activating phagocytic activity of macrophages [90,91]. ECVs of MSCs have been extensively explored in treating various infectious diseases including respiratory tract infections, urinary tract infections, wound infections, sepsis, and intestinal infections [90,91]. MSC-ECVs have been shown to mimic MSCs in alleviating sepsis and protecting against sepsis-induced organ dysfunction and hence they may serve as an alternative to whole-cell therapy [88,89]. Thus, ECVs play a key role in infectious pathogenesis and hold great promise for developing innovative treatments [90].

Recent studies have shown that MSCs-derived exosomes may improve some complications of COVID-19 infection such as cytokine storm, ARDS, and ALI by suppressing inflammatory responses and regeneration of damaged tissues, and also serve as biomarkers, nanocarriers, and vaccines for the treatment of SARS-CoV-2 virus [92,93]. Nebulization of MSC-derived exosomes has been shown to be safe and effective, and administration of exosomes at the beginning of treatment of COVID-19 pneumonia may be more beneficial [94].

Conclusion and Future Prospects

MSCs have antimicrobial, anti-inflammatory, immuno-modulatory, and regenerative potentials that have enabled them to be used in the treatment of several bacterial, viral, mycobacterial, and fungal infections and their complications. The utilization of MSCs and their secretome have shown not only success and efficacy but also safety in the treatment of infections caused by MTB and COVID-19 infection and its complications in particular. Unfortunately, in MSC therapy for Chagas disease, more success has been achieved in animal or preclinical studies than in human studies.

Bioengineering of MSCs, and the use of MSCs obtained from certain sources, as well as the utilization of ECVs derived from MSCs have improved their efficacy and reduced their side effects. However, despite the progress achieved, the clinical application of MSCs in the treatment of several infectious diseases still faces real challenges that need to be resolved.

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