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Review

Stem Cell-Based Therapies for Sepsis

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ABSTRACT

Sepsis, a life-threatening condition triggered by the body's response to infection, presents significant healthcare challenges. This examines the potential of mesenchymal stem cells (MSCs) as a promising therapeutic strategy for sepsis, particularly for coronavirus disease 2019 (COVID-19), acute respiratory distress syndrome (ARDS), and neurological disorders. Preliminary clinical studies have demonstrated the safety and efficacy of MSC therapy for both COVID-19 patients and sepsis cases. However, inconsistencies in inclusion and exclusion criteria across studies highlight the need for further multicenter, randomized, controlled trials and long-term follow-up to identify the ideal patient population for MSC therapy. Mesenchymal stem cells possess anti-inflammatory and immune-modulatory properties, making them a justifiable treatment option for COVID-19-induced ARDS. Additionally, discusses the potential of MSCs to enhance bacterial clearance, reduce inflammation, and improve survival rates in sepsis. Furthermore, it explores the application of stem cell-based therapies in addressing neurological disorders associated with sepsis. The integration of combination therapies, including MSCs, holds promise for the treatment of sepsis and its associated complications. This chapter gives general information about the importance of ongoing research to address challenges such as cell tumorigenesis and the customization of MSC-based therapies for optimal clinical outcomes. Furthermore, it highlights the significant potential of MSC therapy in improving treatment outcomes for sepsis, COVID-19, ARDS, and neurological disorders. The utilization of MSCs in these conditions has shown promising results, including enhanced bacterial clearance, reduced inflammation, and increased patient survival rates. Through continuous research efforts, we aim to further understand and maximize the therapeutic benefits of MSC-based treatments in various medical contexts.

Keywords: Acute respiratory distress syndrome, cytokine storm, immunotherapy, SARS-CoV-2, sepsis, stem cell.

A life-threatening organ failure brought on by a host's defective reaction to infection" is what sepsis is described as. Although sepsis therapy has advanced significantly in recent years, sepsis incidence and mortality in clinical settings continue to rise. Additionally, since sepsis has so many different forms, diagnosing, treating, and managing sepsis patients continue to be extremely difficult tasks for clinicians.[1] Sepsis must be identified if all of the following criteria are met, including a likely or confirmed infection:

-Alteration in mental state

-Less than or equal to 100 millimeters of mercury for the systolic blood pressure, which is the first number in a blood pressure reading (mm Hg)

-Breathing more frequently than or equal to 22 times per minute.[2]

A stem cell is a structure that has the ability to renew itself in the living body of the root structure and can transform into different cell types by mitosis. Root junctions can form the basis of certain specific cells and tissues with codes from deoxyribonucleic acid (DNA). It has the capacity to transform into various specialized cell lines, allowing it to contribute to the development and maintenance of different tissues and organs in the body. Even when they differentiate, they have the ability to form their cells by carrying the characteristics of the underlying cells. They are diversified according to their potential to differentiate in the root structure.[3]

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The structure that has the ability to differentiate all cell types for the development of cells defined as blastomeres in the embryonic period are called a totipotent stem cell. It is in the root structure, which has the authority to revert to 200 cell types but cannot form a placental structure. This structure is called pluripotent stem cells.[4] It is the root establishment derived from the inner cell mass of this structure. With the continuation of the embryonic process of the zygote baby, they begin to transform into adult stem cells. The structure, which has the ability to differentiate into organs, is referred to as a very strong root structure. Root accumulation can be extended not only according to their differentiation potential but also according to the tissues or organs obtained. It can also be classified as Embryonic root formation, which is shown as the source of embryonic periods, and non-embryonic root formation, which we can call adult root structure.[5]

Cellular therapies are used in regenerative medicine applications, both embryonic and adult root corpuscles. However, embryonic stem cells are less used due to their differentiation productivity, high probability of tumorigenesis, and ethical debates. Adult stem cell devices are preferred in clinical requirements for many needs such as the genes they have, the low risk of tumorigenesis, and the low presence of ethical discussions.[6] Adult vessels can be isolated from different tissues and multipotent entities as differentiation treasures. It is used in (leukemia, anemia, organ-derived cancers, deadly diseases due to immunodeficiency, and hereditary metabolic diseases. Apart from clinical practices, most of the root obtained from bone marrow today is used in services.[7-9] The emergence of various animals is promising for root recovery in tissue damage or organ failure.[9]

STEM CELLS IN THE MANAGEMENT OF SEPSIS IN COVID-19

Mesenchymal Stem Cell Treatment for Patients with COVID-19

A popular choice for coronavirus disease 2019 (COVID-19) is mesenchymal stem cells (MSCs), which have anti-inflammatory and healing qualities. When "mesenchymal stem cells with COVID-19" was searched, it was discovered that as of January 16, 2022, more than 80 clinical trials had been filed according to Xu et al.[10] MSCs have endocrine, paracrine, and autocrine immunomodulatory effects. They have the ability to regulate the host's innate and adaptive immune responses, thereby lowering the production of pro-inflammatory cytokines.[11]

Mesenchymal stem cells uphold immune tolerance, transform mature dendritic cells (DCs) into tolerogenic DCs, and negatively regulate the immune response.[12] Additionally, MSCs can lower pulmonary inflammation by controlling various T cell subsets. For instance, MSCs can prevent T cells from proliferating and becoming activated.[13] In an *ex vivo* lung injury model, MSC-derived extracellular vesicles may also contribute to immunoregulation by lowering absolute neutrophil count and tumor necrosis factor-alpha (TNF-α) levels and transferring functional mitochondria to macrophages to decrease the production of pro-inflammatory cytokines and increase their phagocytic capacity.[14,15] By secreting paracrine factors that control membrane transport, repairing the alveolar epithelial and pulmonary microvascular endothelial lining, reducing pulmonary edema, and ultimately encouraging the restoration of lung structure, MSCs have been shown to enhance alveolar fluid clearance and lung function. Several cytokines, such as keratinocyte growth factor (KGF), angiopoietin-1 (Ang-1), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF), are released through paracrine pathways.[16-18]

Alveolar epithelial type II cells' (AEC2) proliferation and differentiation can be quickly and specifically impacted by KGF, which is produced by MSCs.[16] Additionally, KGF is directly linked to the synthesis of surfactant, relaxation of apoptosis in alveolar epithelial cells, and restoration of sodium-induced alveolar fluid transport.[17-20] Furthermore, endothelial intercellular connections may be restored, caveolin-1 protein expression may be decreased, and endothelial apoptosis may be inhibited by the combination of HGF and VEGF By directly influencing cytoskeletal remodeling, Ang-1 generated by MSCs has the power to boost endothelial cell proliferation during vascular remodeling, encourage vascular stability during inflammation, and enhance human AEC cell permeability.[18-22]

Mesenchymal stem cells can alter the microenvironment around lung cells by lowering the concentrations of profibrogenic substances. By restoring lung epithelial cell proliferation and lowering collagen deposition in a bleomycin-induced idiopathic pulmonary fibrosis model, MSC infusion aids in the restoration of lung structure.[23,24] The corrective action of incorrect epithelial-mesenchymal transition is also connected to the effectiveness of MSCs.[25]

Stem Cell-Based Therapy to Treat Neurological Disorders Due to COVID-19

Neurological complications have been observed in association with COVID-19. It has been suggested that severe acute respiratory distress syndrome (ARDS) caused by the SARS-CoV-2 virus may be followed by a potential decrease in the function of the central nervous system. Neurological disorders can be brought on by direct invasion, metabolic abnormalities that are caused, and autoimmune reactions to viral infection.[26] These neurological issues include the risk of various neurological difficulties connected to the central nervous system (CNS) and peripheral nervous system, in addition to the danger of neurodegenerative disorders and dementia.[27,28] Loss of CNS neurons and glial cells is a common feature of human neurological disorders, whether they are neurodegenerative disorders like Alzheimer's disease and Parkinson's disease or other sorts like cerebral palsy. In this context, stem cell-based biotechnologies have gained attention as intriguing treatment options for various diseases since they can generate neurons and glial cells in a variety of forms, attenuating some defects in animal models of neurological disorders as well as in actual patients. They can alter inflammatory, trophic, and cell replacement processes to carry out their intended tasks.[29]

A comprehensive grasp of the various facets of the pathophysiology of neurological disorders is necessary for this therapy strategy. It's also important to understand how different stem cell techniques affect different types of cells and their functional characteristics. The histological and functional information collected from animal research can be used to design the best stem cell kind and technique.[30]

Neurodegenerative disorders can be treated with human embryonic stem cells (ESCs) and human induced pluripotent stem cells (iPSCs) as pluripotent stem cells. ESCs have the best cell sources for cell replacement therapy, however, removing contamination risks and fixing current ethical problems remain obstacles.[31,32] With no need for immunosuppressive medications and no ethical concerns, iPSCs can be employed as models for neurodegenerative disorders and for autologous transplantation (due to somatic cell sources). Induced pluripotent stem cells with morphology, differentiation capacity, and gene expression profiles similar to ESCs face the same difficulties as ESCs, including considerable reprogramming variability and increased cancer risks.[29-33] Other multipotent stem cell types that benefit from neovascularization and preserving hemostasis without raising ethical questions include human hematopoietic stem cells (HSCs). However, there are certain potential difficulties, including the necessity for "*ex vivo*" cell multiplication and the consistency of cell quantity and strength.[29] Other multipotential cells with neurogenic potential include neural crest stem cells (NCSCs), human dental pulp stem cells (DPSCs), human epidermal neural crest stem cells (EPI-NCSCs), and olfactory sheath glia (also known as olfactory ensheathing cells).[34]

The best source for cellular grafts remains a challenge despite significant advancements in stem cell-based biotechnologies for treating neurological disorders. This is due to neurons can be recruited from a variety of sources, including ESCs, umbilical cord blood hematopoietic stem cells, bone marrow MSCs (BM-MSCs), and iPSCs. Risks associated with tumorigenicity should be considered while resolving safety issues. Additionally, it has been discovered that certain cell types produced from ESCs may interact unfavorably with host neurons or other glial or neuronal cell types.[35] Additionally, neurological problems can be cited as significant COVID-19 side effects.[36] Although the cause or actual occurrence has not yet been established, COVID-19 infection may be linked to a variety of neurological symptoms. Up to this point, characteristics of alternative treatment modalities and immunoreactive medicines have been reported. New treatment approaches are still required, though.[37]

Treatment of COVID-19 Using Mesenchymal Stromal Cells for Sepsis and Septic Shock

Mesenchymal stem cells increase bacterial clearance, decrease organ failure, boost survival, control cytokine production, and enhance kidney, lung, liver, heart, and muscle function.[38,39] These advantageous effects seem to be directly linked to the strong immunomodulatory abilities of MSCs. By lowering environmental inflammation and encouraging anti-inflammatory cytokines and mediators, they prevent organ damage.[40,41] These results were obtained using small and big sepsis animal models.[42,43] However, certain findings may be inconclusive due to the highly diverse study design (severity of sepsis, length of treatment, MSC tissue source, dosage, etc.). In contrast to earlier research, ours did not find any evidence of MSC effects on inflammatory secreted factors, even though MSCs improved survival, organ failure, and bacterial load in murine and porcine models of septic shock.[42,43]

It has been demonstrated that MSC therapy is linked to dramatically lower mortality rates.[44] The onset of the severe SARS-CoV-2 infection, sepsis, may soon lead to numerous answers regarding the clinical effects of MSCs. The usage of these cells during sepsis has only recently been studied by a small number of teams and clinical trials. However, in the absence of any specific medicines, the pandemic has stimulated considerable research for novel medications and several developments related MSCs. Up to 30 clinical trials were announced within a few weeks. Umbilical cord (UC-MSC) infusions for the COVID-19 indication have so far yielded good outcomes, according to two Chinese papers. The first recorded case of UC-MSCs being used compassionately was on a 65-year-old patient who needed mechanical breathing due to multi-organ failure. The patient left the intensive care unit after three days without experiencing any negative effects according to Liang et al.[45]

COVID-19 Pneumonia Treatment with Mesenchymal Stem Cells

There is a need to treat a sizable number of people who get pneumonia as new vaccinations are created and spread to lower the rate of COVID-19 infection. Excellent new data obtained with MSC shows effective usage of endogenous natural pathways with strong protective qualities. Trunk-associated growth factors decline with aging and are replaced by an increase in inflammatory cytokines, such as interleukin-6 (IL-6), which is linked to COVID-19-related in-hospital death.[46]

It is well established that leukemia inhibitory factor (LIF) is essential for limiting the lung cytokine storm during viral pneumonia.[47,48] Even though MSCs release LIF, this approach does not work since they are cell-based and have a significant cost. "LIFNano" is a form of synthetic stem cells made utilizing nanotechnology that is 1000 times more potent than soluble LIF.[49]

ROLL OF STEM CELL IN SEPSIS-ASSOCIATED ACUTE RESPIRATORY DISTRESS SYNDROME

Treatment of Sepsis and Acute Respiratory Distress Syndrome Using Stem Cells

Severe sepsis is a syndrome in which the body's response to systemic infection is excessive. As a result of the inflammatory response, it can lead to a state of dysfunction in the organs. The organs most affected by sepsis is the lung, due to factors such as tachycardia and the release of pro-inflammatory cytokines.[50,51] One of the causes of ARDS is sepsis. Cell therapies, which are a therapeutic treatment method for ARDS and sepsis, which have mortality and morbidity, have gained potential in recent years.[52]

While mesenchymal stem (or stromal) cells, epithelial progenitor cells (EpPCs), and ESCs are used in the treatment of both syndromes, they are among the cell types that show high efficiency.[53] Although there are research groups using iPSCs, alveolar type II cells for treatments, ESCs, and EpPCs, including multipotent stem cells (veta stromal), MSC in the majority of clinical studies used.[50]

The characteristics of the cells used in cell therapies are important for the permanent success of the treatments.[50] Mesenchymal stem cells are the most commonly used cell type in treatments. It can be easily isolated from adipose tissue or bone marrow and its propagation properties in the culture medium are among its great advantages.[54,55] Due to its isolation from body cells, it shows orthologous properties and reduces the risk of immune rejection.[50-55] Despite these conditions, studies show high tumorigenic potential. It has been observed that it reduces edema in the lungs in ARDS and has an immunomodulatory effect. It is seen that it significantly reduces mortality in sepsis and shows antibacterial activity.[56-58]

Induced pluripotent stem cells have not been tested *in vivo* for ARDS but are known to be easy to distinguish from AEC2 cells. They obtained from animal and differentiated human somatic cells can be easily isolated from a skin biopsy.[50] Due to their autologous characteristics like MSCs, the risk of rejection by immune cells is shallow. While it shows differentiation to all cell types in the human body, it also has high tumorigenic potential properties that have not been studied extensively.[59,60]

Acute respiratory distress syndrome is known for its damage to the endothelium. For this reason, it is predicted that (endothelial progenitor stem cells) EnPCs, which can regenerate endothelial tubes, may have an important role in damage repair.[62]

EnPcs, which are known to have no tumorigenic feature, are difficult to isolate from blood. It has been observed that the treatment of sepsis reduces the damage by renewing the micro and macro circulation. In ARDS, it has been seen to improve lung function and contribute to ensuring integrity. It should be noted that there are not enough clinical studies for its use in treatments.[62]

The tumorigenic risk of EpPCs, which is expressed in development in every tissue and located in some parts of the lung alveolar, is very low. They can be difficult to isolate from donor tissue and in small quantities. Test results are showing that it reduces lung inflammation.[63,34]

Embryonic stem cells are cells that can differentiate into potentially any cell. While totipotent properties provide advantages for ESCs obtained from blasticides in the embryonic period, they also have disadvantages such as high tumorigenic properties and ethical problems.[65] It has not been tested *in vivo* in ARDS yet. It is known to be easy to distinguish from AEC2. It has been reported to reduce lung inflammation by reducing mortality in sepsis.[66]

Treatment of Acute Respiratory Distress Syndrome with Allogeneic Mesenchymal Stem Cells Generated from Adipose Tissue

Among cell types for the treatment of lung injury and ARDS, MSCs are less controversial due to their properties.[67] MSCs have many mechanisms against adverse immune responses. Allogeneic MSCs are cells used in clinical research to treat myocardial infarction and inflammatory bowel diseases.[68] Among the MSCs, they also consider those of adipose origin to be of interest.There are research groups that study allogeneic adipose-derived MSCs in the treatment of ARDS. Mesenchymal stem cells from bone marrow and adipose tissue were used for treatment. As a result of the studies conducted on a group of six people, it was observed that the lung damage caused by bleomycin and lipopolysaccharide could be healed with the applied treatment.[67,68] As a result of the research, the rate of MSCs derived from bone marrow is considerably lower than MSCs produced from adipose. It gave better results than BM-MSCs in inhibiting the expression of CD83, CD80, and CD86 by adipose-derived MSCs (ASCs). The results of the study revealed that the infusion of MSCs derived from allogeneic adipose is safe. However, it is stated that more research is needed to apply treatments with drugs and dosages.[69-71]

Why Radiation-Activated Mesenchymal Stromal/Stem Cells Should Be Used in Acute Respiratory Distress Syndrome?

Mesenchymal stem cells have also been used in various tumor studies. They derived from the human umbilical cord have been used in radiotherapy in clinical research to reduce side effects.[72] There is a variety of bioactivation of MSCs. It has been suggested that there are intratumoral actions secreted from radio-activated MSCs when used in combination with radiotherapy.[73,74] It has been observed that MSCs have therapeutic effects and treat tissue damage thanks to their tissue-recovery properties. As a result of the research, it was observed that when human melanoma tumor colonies are exposed to radiation-conditioned environments, there is a decrease in tumor cells.[72-75]

RELATIONSHIP BETWEEN SEPSIS AND OTHER FACTORS

Using Preclinical Meta-Analysis to Assess Mesenchymal Stem Cell Treatment for Sepsis Before Beginning a First-in-Human Trial

Before beginning early-phase clinical investigations, preclinical evidence has traditionally been evaluated by choosing individual studies in a non-systematic method that may create bias. Mesenchymal stromal cells for septic shock will thus be tested for the first time in humans, therefore scientists used systematic review methods to assess all available preclinical data. *In vivo,* sepsis models from 20 controlled comparative trials (980 animals from 18 publications) were found.[76] The latest time point provided for each trial was included in the meta-analysis to show that MSC therapy of preclinical sepsis significantly decreased mortality under a variety of experimental circumstances (odds ratio 0.27, 95% confidence interval 0.18-0.40). Few research mentioned components like randomization, and none of the studies provided an accurately estimated sample size, thus the possibility of bias was unknown.[77] In addition, publication bias led to a 30% overestimation of impact, and challenges to validity reduced the validity of our findings. Before beginning first-in-human clinical investigations, this innovative future approach of systematic review technique may be used as a framework to assess preclinical evidence.[77]

Treatment for Sepsis Using Mesenchymal Stem Cells

In decreasing order, the most prevalent causes of sepsis are pneumonia, intra-abdominal-, urinary tract, and soft tissue infections.[53] Only one-third of blood cultures are positive, while up to one-third of all body locations are culture negative. Sepsis happens when the host's tissues and organs are damaged as a result of the body's reaction to infection. During sepsis, the host response is dysregulated, with both excessive pro-inflammatory and immunological suppressive anti-inflammatory components.[78] Sepsis is the

biggest cause of mortality and the most common cause of death in non-coronary, and despite advances in treatment, the mortality rate of severe sepsis and septic shock remains extremely high, demonstrating that current treatments are insufficient to combat this syndrome. The application of MSCs in animal studies of sepsis has revealed compelling evidence of MSC therapy's therapeutic promise in this context. These studies have mostly focused on the impact of MSCs on the pro-inflammatory phase of sepsis, whereas the effects of MSCs on the later anti-inflammatory/ immune exhaustion phase of the illness have yet to be determined and will require additional research.[78] MSCs increase survival in sepsis models through the combined impact of their immunomodulatory and anti-microbial features: MSCs treatment reduces inflammation in septic mice via a mechanism that requires macrophage reprogramming onto a more anti-inflammatory phenotype (release of anti-inflammatory IL-10), affecting the level of pro-inflammatory cytokines in blood and organs and reduced immune cell infiltration in infected tissues (monocytes and neutrophils).[79] Furthermore, MSCs have antimicrobial actions that are both direct (the production of the LL-37 peptide) and through (an increase in the phagocytic characteristics of monocytes/macrophages and neutrophils). The combined impact of lowering both the immune reaction and the bacterial load improves organ function and increases survival rates.

The excellent results observed in these small animal preclinical effectiveness trials imply that MSCs may be a therapeutic alternative for treating sepsis in people.[80] Importantly, the effectiveness of MSCs in large animal models that better mimic the inflammatory response, organ failure, and illness in people (e.g., sheep models) will be significant to testing and validation of the therapeutic benefits of allogeneic MSC therapy in humans. To ensure a clear outcome of the MSC therapy effect, these medical studies should be open, controlled, and randomized. Furthermore, given the complexity and heterogeneity of sepsis, as well as the dismal results of previous sepsis clinical trials, we feel that such trials should begin with well-defined and homogenous sepsis patients.[81]

Menstrual Blood-derived Mesenchymal Stem Cells Applications in Sepsis

In the present study scientists investigated the therapeutic impact of menstrual blood-derived mesenchymal stem cell (MenSC) treatment in an animal model of severe sepsis generated by cecal ligation and puncture (CLP), which is the major model for polymicrobial human sepsis.[81] MenSC was tested for antimicrobial activity *in vitro*, as well as the expression of several antimicrobial peptides that might be implicated in the antibacterial impact. Furthermore, scientists investigated MenSCs' ability to diminish systemic inflammation and organ dysfunction via immune response regulation and the production of tissue-protective/regenerative proteins. Furthermore, they examined MenSCs' therapeutic impact and synergy with antibiotic (AB) treatment, which is regarded as the first-line therapy for sepsis. MenSCs are a well-characterized multipotent stromal cell type that has demonstrated a variety of regeneration characteristics in preclinical animal models.[82-84] In sepsis, the use of MSCs to battle systemic infection or alter the host immune system's response to the disease [40,85] has previously been explored, indicating that MSCs may be effective in sepsis therapy when infused at disease start. Since clients with sepsis have a rapid worsening of their state in the initial few hours of commencement, an MSCs therapy might be delivered with the same zeal.[86] In an *in vivo* animal model study, MenSCs reduced animal mortality by regulating different aspects of sepsis, such as organ failure, modulation of the immune response without serious immunosuppression, and promotion of bacterial clearance, to a degree comparable to standard clinical sepsis treatment (antibiotic therapy). Notably, the synergism between MenSCs+AB resulted in the greatest improvement in the surviving animal proportion, indicating that the introduction of MenSCs in the clinic should be in conjunction with existing sepsis therapy. In lung damage and inflammation.[87]

Acute myocardial infarction and sepsis paracrine factors have been proposed as a mechanism in tissue regeneration/protection.[87-99] In this regard, we studied the effect of MenSCs' soluble antibacterial and other tissue-protecting components by treating mice with its conditioned medium (CM). Although the trial results demonstrated that mice injected with MenSCs CM lived longer than untreated mice, the improvement did not meet the degree of survival shown in the MenSCs treated groups.[88] This implies that, while the CM was helpful, the persistence of cells in the inflammatory and infection setting was required to generate the significant therapeutic impact achieved. Indeed, it is widely known that several MSC-expressed components, such as hepcidin expression after microbial stimulation, can be triggered in response to stress or particular stimulation. Although testing the impact of pre-activated cells or stimulated CM

in future experimental designs is fascinating, the dosage (low, medium, or high), frequency (one or many), and time of administration (early or late) of the infusion should also be established.[88]

While the current findings provide a new source and proof for the therapeutic benefit of allogeneic MSCs in sepsis, substantial progress is needed to fully comprehend the cell-based therapy's numerous modes of action. Furthermore, there are important restrictions that must be addressed, taking into account the limited time period for the treatment of sepsis, where ready-to-inject doses of cells must be accessible.[89]

Mesenchymal Stem Cells Applications in Bacterial Infection-based Sepsis

Scientists showed that BM-MSCs reduce mortality and attenuate multiple organ failure in a clinically relevant model of polymicrobial sepsis caused by CLP, which leads to a mixed infection of gram-negative and gram-positive organisms. This reduction in sepsis-induced death and morbidity was related to a reduction in total inflammatory response but considerably improved bacterial clearance. MSC treatment began six hours after surgery to imitate the inherent time lag in the clinical detection of sepsis in people.[90,91] As a result, MSC management in CLP-injured mice contributed to a coordinated modulation of the host transcriptional response characterized by an overall down-regulation of inflammation and inflammation-related genes and an increase in the expression of genes involved in antigen presentation, phagocytosis, and bacterial killing. A balanced "reprogramming" of the inflammatory response in sepsis can only be accomplished by coordinated regulation of critical pathways involved in the innate immune response to microbial infections. Findings support the feasibility and efficacy of MSC-based cell therapy in experimental sepsis, and they may serve as the foundation for the progress of an adjunctive therapeutic approach for the management of overwhelming inflammation in clinical sepsis, which remains a major cause of morbidity and mortality in critically ill patients.[39]

In COVID-19, there have been instances of re-infection and post-vaccination breakthroughs. The majority of infected people exhibit mild to moderate symptoms if any at all. For people who are severely immunocompromised, MSCs can be an alternate immunotherapeutic option and help to improve COVID-19[92] results. To enhance their therapeutic effects, it will be necessary to use optimum standard procedures for MSC clinical application methods, which are different. Although the safety and efficacy of MSC therapy for COVID-19 patients have been demonstrated by available data from preliminary clinical studies, there are significant discrepancies due to inconsistent inclusion and exclusion criteria. Therefore, more multicenter, randomized, controlled trials and long-term follow-up studies will be needed to identify patients who may benefit clinically more from MSC therapy.

In conclusion, MSCs have been proven to be more effective and useful in the treatment of sepsis. It has been shown to exhibit anti-inflammatory and immunomodulatory effects. Despite the risk of setting aside their very promising use in bacterial sepsis, especially due to their significant antibacterial capacity, it will be necessary to remember that COVID-19 is not the main etiology of sepsis. MSCs have less danger, according to numerous research using ESC, MSC, EpPC, EnPC, and iPSCs for cell treatments using diverse cell types against harm brought on by sepsis and ARDS as a result of an inflammatory immune response. One of the difficulties with stem cell treatments appears to be the possibility of cell tumorigenesis. There are *in vivo* therapeutic modalities that have not been studied, it should be highlighted. MSCs can be separated into adipose-derived and bone marrow-derived. Adipose-derived MSCs are superior, according to studies, as a greater quantity is collected after isolation. Radiation may be present at the time of MSC activation, it has been reported. By paracrine mechanisms, MSCs have positive effects on experimental sepsis, and immunomodulatory cell therapy has become a successful adjunctive treatment to lower sepsis-related morbidity and mortality. MenSCs also provide a workable strategy for sepsis clinical treatment in the future. Cell-based therapies used now are seen to be a new form of treatment. Future treatments using smart cells should therefore be usefully customizable.

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