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Narrative Review

Safety and Effectiveness of Intravascular Mesenchymal Stem Cells to Treat Organ Failure and Possible Application in COVID-19 Complications

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Background: Although only a small percentage of patients with COVID-19 deteriorate to a critical condition, because of the associated high mortality rate and the sheer number of cases, it imposes a tremendous burden on the society and unprecedented strains the health care resources. Albeit lung is the primary organ involved resulting in acute respiratory distress syndrome (ARDS), many patients additionally present with secondary multiorgan failure. Unfortunately, there is no definitive or curative treatment for this condition, and the management has been predominantly confined to supportive care, which necessitates an urgent need for novel therapies. Mesenchymal stem cell (MSC) therapy has a vast array of preclinical data and early, preliminary clinical data that suggests its potential to regenerate and restore the function of damaged tissues and organs. To date, there has been no review of all the clinical trials that have assessed the safety and efficacy of MSC therapy in organ failure commonly seen in seriously complicated COVID-19 patients.

Objectives: To evaluate the effectiveness of MSC therapy in managing multiorgan failure, utilizing currently available literature.

Study Design: A review of human randomized controlled trials (RCTs) and observational studies assessing the role of MSC therapy in managing multiorgan failure.

Methods: PubMed, Cochrane Library, US National Guideline Clearinghouse, Google Scholar, and prior systematic reviews and reference lists were utilized in the literature search from 1990 through May 2020. Studies that included embryonic stem cells, induced pluripotent stem cells, differentiated MSCs into specific lineage cells, and hematopoietic stem cells were excluded. Trials with intraorgan infiltration of MSC were also excluded.

Outcome Measures: The primary outcome evaluated the improvement in clinical assessment scores and indices of organ function. The secondary outcome assessed the safety of MSC therapy in the clinical trials.

Results: Based on search criteria, 12 studies were found for lung, 52 for heart, 23 for liver, 16 for stroke, and 9 for kidney. Among the 6 studies that specifically assessed the effectiveness of MSC therapy in ARDS, 4 showed positive outcomes. Forty-one of the 52 trials that examined ischemic and nonischemic heart failure reported beneficial effects. Twenty of 23 trials for liver failure from different etiologies revealed favorable outcomes. Nine out of the 15 studies evaluating stroke had satisfactory effects. However, only 3 out of the 9 studies for kidney failure showed positive results. Nonexpanded bone marrow mononuclear cells were used in most of the negative studies. The incidence of disease worsening or major complications was extremely rare from MSC therapy.

Limitations: Among the studies evaluated, although there were many RCTs, there were also numerous case series. Additionally, most recruited a small number of patients.

Conclusions: MSC therapy seems to be promising to treat multiorgan failure from COVID-19. More studies are urgently needed to assess both safety and efficacy.

Key words: Mesenchymal stem cell, multiorgan failure, randomized controlled trial

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The coronavirus (COVID-19) disease continues to spread, with over 1.6 million cases and nearly 100,000 deaths in the United States as of May 25, 2020, making it a leader in the world, however, it remains ninth in the world in terms of deaths per population. A survey showed that 80% of Americans were "very concerned" or "somewhat concerned" about COVID-19 in April 2020, as it has had serious social, economic, and health implications. The personal finances of Americans were more severely impacted compared with the Germans and the English (1). Physicians are not immune to this morass. The negative financial effect is a result of having postponed nonemergency care, ranging from office visits to elective surgery. These are the cases from which physicians and hospitals derive most of their profits. Elective care has declined across the country, with reductions in some services of over 80%. If the COVID-19 shutdown lasts for months or the normal business of health care does not resume until the fall, the implications for physicians, in general, and interventional pain management physicians, in particular, are unprecedented (2-4). Interventional pain physicians have been particularly affected as the vast majority of services they provide are deemed "nonemergent" (2).

In New York City, the outcome of 2,634 of 5,700 patients who were admitted in 12 hospitals for COVID-19 from March 1st to April 4th was published (5). The most common comorbidities were hypertension, obesity, and diabetes, with 14.2% being treated in the intensive care unit (ICU), and among them 12.2% received invasive mechanical ventilation. Among all patients, the mortality rate was 21% (5). Postmortem findings in patients diagnosed with COVID include infiltrations with ground-glass opacity predominantly in middle and lower lung fields detected by chest x-ray, disseminated diffuse alveolar damage at different stages (the histopathological correlate of acute respiratory distress syndrome [ARDS]), mild lymphocytic myocarditis and signs of epicarditis along with minimal periportal lymphoplasma cellular infiltration, and signs of fibrosis in the liver (6). According to the World Health Organization (7), 213 countries have registered COVID-19 cases. The largest cohort of > 44,000 persons with COVID-19 from China showed that illness severity can range from mild to critical (8):

- Mild to moderate (mild symptoms up to mild pneumonia): 81%
- Severe (dyspnea, hypoxia, or > 50% lung involvement on imaging): 14%
- Critical (respiratory failure, shock, or multiorgan system dysfunction): 5%.

In this study, all deaths occurred among patients with critical illness, and the overall case fatality rate was 2.3%. The case fatality rate among patients with critical disease was 49% (8). Among U.S. COVID-19 cases, the proportion of persons who were hospitalized was 19%, and patients with COVID-19 admitted to the ICU was 6% (9). Mortality among patients admitted to the ICU ranges from 39% to 72% depending on the study. The median length of hospitalization among survivors was 10 to 13 days (9). Age is a strong risk factor for severe illness, complications, and death (9). Early US epidemiologic data suggests that the case fatality was highest in persons aged ≥ 85 years (range 10%–27%), followed by 3% to 11% for ages 65 to 84 years, 1% to 3% for ages 55 to 64 years, and < 1% for ages 0 to 54 years (9). Patients in China with no reported underlying medical conditions had an overall case fatality of 0.9%, but case fatality was higher for patients with comorbidities: 10.5% for those with cardiovascular disease, 7.3% for diabetes, and approximately 6% each for chronic respiratory disease, hypertension, and cancer (10).

According to the Centers for Disease Control and Prevention (CDC), as of April 25, 2020, there are no drugs or other therapeutics presently approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19. Current clinical management includes infection prevention and control measures and supportive care, including supplemental oxygen

and mechanical ventilatory support when indicated (11). The National Institute of Health treatment guidelines recommend the cautious use of Remdesivir, hydroxychloroquine, convalescent plasma, and interleukin-6 inhibitors, and state that they must be used mostly in the setting of clinical trials. The lack of treatment options leads to a desperate need for novel therapies in patients afflicted with serious complications from COVID-19. Mesenchymal stem cells (MSCs), also known as medicinal signaling cells, mostly through their paracrine activity secrete growth factors, cytokines, and chemokines resulting in tissue regeneration and improved organ function. Here we want to explore the possibility of MSCs in treating severe complications from COVID-19 to decrease morbidity and mortality.

Pathophysiology of Multiorgan Complications with COVID-19

Even though respiratory compromise is the major clinical manifestation of COVID-19, cardiovascular and other organ involvement may be responsible for eventual poor outcome. Autopsy reports have also shown direct myocardial injury due to viral load on cardiomyocytes, with systemic surge of inflammation appearing to be contributing to cardiovascular and other multiorgan injury. Even though the most dominant clinical manifestation of COVID-19 starts with respiratory symptomatology with a mild flu-like illness, in some cases it progresses to potentially lethal ARDS or life-threatening pneumonia, and preexisting cardiovascular disease risk factors enhance vulnerability to COVID-19, leading to deadly outcome.

Respiratory Complications of COVID-19

The pulmonary complication pneumonia, characterized by cough, fever, and dyspnea, and bilateral infiltrates seen on imaging studies, is the most frequent and serious manifestation of COVID-19 infection. Fortunately, most patients will only experience mild symptoms of the disease, and some patients may experience rapid progression of their symptoms in a few days. The study by Chen et al (12) found that in those patients who developed ARDS, 65% rapidly worsened and died from multiple organ failure. Wu et al (13) reported that ARDS was frequently associated with older age (> 65 years), diabetes mellitus, and hypertension. Imaging studies of these patients showed bilateral lower zone consolidation in 10 to 12 days from the onset of symptoms. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infects type II alveolar epithelial cells and causes COVID-19. After infection, COVID-19 progresses to a viral replicative phase of this disease that clinically may present as mild flu-like symptoms. This phase is followed by a massive release of proinflammatory cytokines causing heightened inflammatory reaction and increased activity of immune cells. This causes recruitment of inflammatory cells, such as macrophages, to the lungs and disrupts the junctions between alveolar epithelial cells and capillary endothelial cells. Eventually an alveolar-capillary barrier is formed causing influx of proteinaceous fluid into the alveoli. Injury to the alveolar epithelial cells causes accumulation of fluid in the alveoli that interferes with normal gas exchange, subsequently causing impaired oxygenation leading to hypoxemia. Widespread pulmonary inflammation also induces the hypoxic state and produces excessive extracellular calcium levels leading to myocyte apoptosis contributing to extensive pulmonary injury .

Cardiovascular Complications in Patients with COVID-19

The most common cardiovascular complication in COVID-19 is acute myocardial injury marked by elevated cardiac enzymes, specifically elevated cardiac troponin I (cTnI). The overall incidence of acute cardiac injury with elevated troponin (cTnI) varies between 8% and 12% (14). The incidence of acute cardiac injury has consistently shown to be a negative prognostic marker in patients with COVID-19 . A study by Wang et al (15) in 138 patients with COVID-19 reported 16.7% incidence of arrhythmia. The incidence was much higher (44.4%) in those requiring ICU admission as compared with those not requiring ICU admission (8.9%).

Pathophysiology of Cardiac Complications

The respiratory tract is the prime target for SARS-CoV-2; however, the cardiovascular system is involved in many different ways . The hyperinflammatory response due to cytokine surge, hemophagocytic lymphohistiocytosis, and increased myocardial demand in the setting of acute infection can lead to rupture of the atherosclerotic plaque leading to acute myocardial infarction. The blood pressure abnormalities and cardiac arrhythmia of multifactorial etiology, myocarditis, and hypoxic state due to ARDS, may lead to reduced ejection fraction and heart en-

largement (16).The exact mechanism of cardiovascular complications is not clearly understood, however, there are some possible mechanisms, either single or in combination, that seem to be responsible for the poor outcome. Some observed mechanisms are supported by the postmortem study of patients who had died due to SARS during the Toronto SARS outbreak. This study reported that the viral ribonucleic acid (RNA) was detected in 35% of the human heart samples, providing evidence for direct myocardial injury by the virus (17). Regardless of the relative role of the different mechanisms described, the direct (noncoronary) myocardial injury due to viral myocarditis, and the direct effect of widespread inflammation appear to be the most likely mechanisms. Following are the likely mechanisms. Xiong et al (18) reported that SARS-CoV-2 enters human cells by binding to angiotensin-converting enzyme 2 (ACE2), an aminopeptidase highly expressed in myocardial and pulmonary cell membranes. ACE2 is important for neurohumoral regulation of the cardiovascular system in various disease conditions. The binding of SARS-CoV-2 to ACE2 can result in alteration of ACE2, leading to acute myocardial and lung injury. The severe forms of COVID-19 are characterized by acute systemic hyperinflammatory response and cytokine storm resulting in injury to multiple organ involvement, including myocardium, and ultimately leading to multiorgan failure. The studies have reported high levels of proinflammatory cytokines in patients with severe COVID-19 (14). The systemic inflammation due to cytokine surge causes hyperdynamic state, which subsequently increases shear stress secondary to increased coronary blood flow causing rupture of coronary plaque, creating ideal setup for coronary thrombosis and precipitating acute myocardial infarction. The type of arrhythmia is variable, and etiology can be multifactorial, ranging from hypoxic state due to ARDS to myocarditis. The patients with severe COVID-19 are at the risk of developing hypokalemia owing to interaction of SARS-CoV-2 with the renin-angiotensin-aldosterone system. Hypokalemia increases susceptibility to various tachyarrhythmia. Electrolyte imbalance is not uncommon in critically ill patients, especially in patients with underlying cardiac disorder (19). Increased basal metabolic rate because of the systemic infection coupled with hypoxia caused by acute respiratory illness, further compromising myocardial oxygen supply, and eventually altering myocardial demand-supply ratio .

Renal Complications of COVID-19

Cheng et al (20) reported that most patients develop kidney injury within 7 days of admission. The exact pathogenesis of kidney involvement in COVID-19 infection is unclear, however, it is reported to be due to a component of multiorgan failure secondary to systemic sepsis and shock, leading to acute tubular necrosis (ATN). A study by Naicker et al (21) reported ATN to be based on single-cell transcriptome analysis of ACE2 receptor expression in kidney cells, suggesting the possibility of direct renal cellular damage from SARS-CoV-2. This report was supported by the detection of the virus in a urine sample of an infected patient (21).

Liver and Other Gastrointestinal Complications of COVID-19

The injury to the gastrointestinal tract is not well understood. However, a significant number of patients reported diarrhea, nausea, vomiting, and abdominal pain. In some patients these symptoms were the only clinical presentation. This is supported by detection of SARS-CoV-2 RNA in stool samples of infected patients. It was postulated that ACE2 receptors expressed in the gastrointestinal tract are also affected by COVID-19 (22). Liver injury has been reported in the study by Wong et al (22) starting from mild liver injury to severe liver damage in COVID-19 patients. The blood chemistry had shown abnormal liver function tests (LFTs), including increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin, during the course of the COVID-19 disease.

Coagulopathy and Neurologic Complications of COVID-19

Li et al (23) suggested that viral invasion of the central nervous system by SARS-CoV-2 is possible and can lead to several neurologic complications, including seizures, unconsciousness, acute cerebrovascular disease, and encephalopathy. Early reports from Wuhan, China, described COVID-19 as a proinflammatory and prothrombotic disease, with an increased risk of pulmonary embolism, deep vein thrombosis, and ischemic stroke (15). Massive systemic inflammatory process is responsible for disseminated intravascular coagulation (DIC) as another common complication of COVID-19. The study by Tang et al (24) reported a 71.4% incidence of DIC in nonsurvivors compared with only 0.6% in survivors. This study also reported

that use of anticoagulation with low-molecular-weight heparin or unfractionated heparin improved outcomes in severe cases with coagulopathy.

Stem Cell Therapy in Organ Failure: Mechanism of Action

There are many types of stem cells and can be broadly classified as totipotent, pluripotent, and multipotent cells. Totipotent stem cells cannot only differentiate into all the 3 primary germ layers but also the extraembryonic tissue, such as the placenta. The fertilized egg is the only example. Pluripotent stem cells develop into all 3 germ layers. Embryonic stem cells and induced pluripotent stem cells (iPSCs) are classified as pluripotent. Although multipotent stem cells can differentiate into all 3 germ layers, they usually develop into 1 or 2 cell lines only. In each cell line they can transform into different types of cells. The adult MSCs that are most commonly used in regenerative medicine belong to the multipotent stem cell category. MSCs likely originate from the mesoderm and have the capacity to differentiate into a variety of mesenchymal tissue lineages, such as osteoblasts, chondrocytes, and adipocytes . A dividing MSC produces 2 daughter cells. One is another stem cell, quiescent until it is needed, whereas the other divides further and specializes into one or a few types of cells. Such "self-renewal" is essential to growth and healing.

The International Society of Cell and Gene Therapy requires a cell to meet all the 3 criteria to be defined as an MSC (25):

1. The cell must be plastic-adherent when maintained in standard culture conditions.
2. The cell must express CD105, CD73, and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79α or CD19, and HLA-DR surface molecules.
3. The cell must differentiate to osteoblasts, adipocytes, and chondroblasts in vitro.

MSCs can also be classified as embryonic, fetal, adult, and iPSCs. Embryonic stem cells are derived from the inner cell mass of the blastocyst. They are immortal and highly proliferative. Ethical issues and their propensity to cause tumors precludes clinical utility. Fetal stem cells are mostly obtained from the umbilical cord and placenta. Adult stem cells are usually sourced from the bone marrow and adipose. IPSCs are derived from skin or blood cells that have been reprogrammed back into an embryonic-like pluripotent state that enables the development of any type of human cell. Clinical applications of iPSCs face several major hurdles, such as low cellular reprogramming efficiency, epigenetic memory, oncogenic risks, low efficiency of cardiomyogenesis, and cell line-to-line variations.

MSCs are found in all the tissues in which they replace diseased or aged cells. MSCs can be obtained from multiple sources and are most easily accessible from bone marrow, fat, dental pulp, umbilical cord, amniotic tissue, synovium, and placenta. However, to treat organ failure large doses of MSCs are required for clinical efficacy and the most common route of administration is intravenous (IV) followed by intra-arterial (IA). Hence culture expansion to significantly increase the number of MSCs remains a prerequisite. Autologous MSCs (adipose and bone marrow) or allogeneic MSCs (umbilical cord, placental, endometrial, and amniotic tissue) can be used for culture expansion. For autologous purposes, adipose MSCs seem to be more desirable than bone marrow MSCs primarily because of the significantly higher number of MSCs found in the adipose tissue when compared with the bone marrow. Because the use of autologous MSCs usually requires an invasive procedure, allogeneic sources seem attractive. Moreover, in patients with organ failure, the harvest procedure has inherent risks in lieu of suboptimal health. Additionally, the MSCs from older patients have aging stem cells, which are inferior to younger stem cells, such as umbilical cord MSCs in terms of proliferative, secretory, and differentiation capabilities. This renders older autologous MSCs less potent compared with fetal stem cells, such as umbilical MSCs. Additionally, allogeneic cells are not functionally impaired by the patient's comorbid conditions.

Additionally, allogeneic MSCs are immunoprivileged and rarely evoke immune responses in the host they express low level surface markers of major histocompatibility (MHC) I and hardly express the surface markers MHC II. Also, MSCs do not express the costimulatory molecules, such as CD40, CD80, or CD8. Despite the low expression of MHC I, MSCs cannot activate secondary signals of the immune response, which will result in the absent response status of T cells because of the lack of costimulatory factors . MSCs also have inherent immunosuppressive activity that can prevent an immune response from the host. Patients usually do not develop persistent do-

nor specific anti-HLA antibodies to MSCs. However, it should be emphasized that Unlike umbilical cord blood, which has very few MSCs, the Wharton jelly presents a rich source. Because the umbilical cord is considered a medical waste, it can be easily obtainable and is a plentiful source of MSCs. Even though umbilical MSCs share many surface markers and the superior proliferative/differentiation capabilities of embryonic MSC, unlike embryonic MSCs, they are not known to be tumorigenic. Hence umbilical MSCs may be well positioned for culture expansion to create an "off-the-shelf" product.

To treat organ failure, intravenous infusion of MSCs seems to be the most commonly used route due to its easy accessibility and straightforward approach. Intraarterial administration has been attempted to increase engrafting of the cells in the organ. Direct injection into the organ has also been utilized, however, it has the disadvantage of being an invasive procedure and leading to poor cell distribution through the lesion. Furthermore, a growing body of evidence indicates that cells do not need to enter the organ to produce a therapeutic effect, and very few cells remain in the organ in studies that use IV or IA administration. Instead of direct cell replacement, the functional effects of MSC therapies seem to be mainly due to antiinflammatory and immunomodulatory properties and the release of trophic factors (26). Although the mechanism of action of cell therapy remains elusive, there is compelling in vitro evidence that transplanted cells modulate the function of various immune cell types via release of host paracrine factors directly or through vehicles, such as extracellular vesicles (27).

The fate of injected MSCs have been tracked in animal and human studies (27). When injected intravenously, after 2 hours, the MSCs are mostly seen in the lungs (20.9%), liver (13.5%), kidneys (3.2%), and spleen (2%). After 24 hours, the MSCs concentration decreased in the lungs (7.8%), but increased in the liver (18.5%), kidney (7%), and spleen (3.2%). Very few cells are seen in other organs. In the same study, MSCs were injected into the middle cerebral artery. After 2 hours, most of the cells were found in the liver (40.6%), followed by the lung (7.1%), spleen (5.8%), and kidney (4.2%). After 24 hours, the cell numbers increased slightly in the liver (46.9%), spleen (6.5%), and kidney (7.6%), but decreased in the lung (4.3%). Interestingly, very few cells were noted in the brain 2 hours or 24 hours later, irrespective of IV (0.8% and 0.9%) or IA (0.8% and 0.6%) injection. Very few cells were seen in organs despite IA administration. In another study, after IV infusion of MSCs, scintigraphic images revealed an uptake of 5.4%, 4.3%, and 2.3% of the total infused radioactivity in the heart after 1, 3, and 24 hours, respectively (28). The remaining activity was distributed mainly to the liver, spleen, kidneys, and bladder at all time points. Intraorgan injections, especially highly vascularized, do not seem to enhance engraftment. Akker et al (29) have shown that during direct intramyocardial administration, substantial numbers of MSCs were immediately flushed out of the heart via the venous system within a few heart beats after the start of injection. In another study, after IV infusion, MSCs were detected in the lung within 30 minutes and remained detectable after 24 hours, after which uptake was detected in the liver, spleen, and bone marrow up to 7 days postinfusion (30). However, when MSCs were injected into the avascular lumbar disc, they not only survived for 8 months, but also duplicated, differentiated into chondrocytes, and produced collagen and extracellular matrix (ECM) (31). Using the IA approach, although very few cells remain in the targeted organ, their number is higher than IV administration, albeit transiently. Whether this translates to better clinical outcomes is unknown. IA transplantation decreased the "first bypass" effect of bone marrow MSCs in the lungs and increased uptake in other organs, especially in the liver, spleen, and kidneys (32). Most of the IV-infused cells are cleared from the circulation within 5 minutes, and almost all of them are entrapped in the lungs primarily because MSCs are relatively large cells and express various adhesion molecules (33). A small number reappear in the circulation after a lag period of approximately 10 minutes, probably after release from the lung. Only a miniscule number reaches the target organ and disappears by day 3 (27). In another study, the number of accumulated cells in the lung decreased significantly from 6 hours after transplantation and continued to diminish to 2% or less by day 10 (32). However, although there were fewer cells in the liver and spleen, 2 hours after the infusion, the levels gradually increased with time and had the highest signals by day 10. In one study, the MSCs fell exponentially, with a half-life of approximately 24 hours and practically completely disappeared after 4 days (32). An overwhelming majority of cells die soon after transplantation . More

than 90% of injected cells disappear in the first few days, and < 2% can still be found 4 weeks after transplantation (34). Immediately after delivery, there is significant loss owing to failure of cells to extravasate (34). Then, during the first weeks after transplantation, most of the cells that were initially retained die because of ischemia caused by poor vascularization of the injected region, inflammation with attendant oxidative stress and release of cytotoxic cytokines, immune destruction of allogeneic cells, and apoptosis following disengagement of anchorage-dependent cells from their ECM (anoikis) (34). MSCs barely or not at all detectable in patients after transplantation demonstrates that systemic pathways to eliminate transplanted MSCs may be operating, leading to barely detectable long-term engraftment (32). In summary, regardless of the route of administration, MSCs that get trapped in the lungs and liver with poor homing to the target organ are minimal with poor engraftment and they disappear rapidly (14 days) after transplantation (35).

However, failure of the MSCs to engraft, survive, and differentiate does not preclude positive clinical outcomes as seen in numerous studies, and this salubrious effect seems to result from a "hit and run" systemic mechanism and their beneficial effects are mediated by the release of various factors that act in a paracrine manner to reduce scar formation, inhibit apoptosis, augment angiogenesis, inhibit inflammation, and immunomodulate by suppressing innate and adaptive immunity (27). After IV MSC infusion, the paracrine factors released into the blood by circulating MSCs or from trapped MSCs may indirectly influence survival signaling and the fate of distal cells previously compromised by injury or disease. Thus, for effect, paracrine factors produced by MSCs appear to not depend on long-term MSC engraftment, nor do they require the unlikely differentiation of mesodermal progenitors into tissues of ectodermal or endodermal lineages . Trapped MSCs in the lungs secrete growth factors and immunomodulatory proteins and through exosomes reach the target organ to orchestrate repair and improve function (30,35). In one animal study, the captured MSCs in the lung secreted the antiinflammatory protein TSG-6, which was responsible for decreasing the left ventricular infarct size and improving the ejection fraction. In another study, sequestration of CD8 T cells was decreased thereby improving ventricular function (33). IV MSC resulted in decreased circulating natural killer cells and improvement in cardiac function. Immune cells are known to travel via the blood and lymph between the hematopoietic organs (bone marrow and spleen), lymphoid tissues, and various organs. Because IV-injected MSCs can home to the spleen and various lymphoid and nonlymphoid organs, it is conceivable that they can regulate the locally residing host immune cells, which in turn may affect systemic and local organ inflammation (27). Studies strongly indicate the existence of interactions between transplanted MSCs and cells of the immune system (32). This way, MSCs also biodistribute to the immune system through contact with different types of leukocytes in the circulation or various tissues, such as skin, spleen, and lymph nodes.

MSCs are known to be antiapoptotic, antiinflammatory, immunomodulatory, angiogenic, and antifibrotic. Their antiapoptotic properties are through 3 mechanisms. First, they salvage dying host cells by transferring their mitochondria (cell batteries) through nanotubes thereby "reenergizing" the cells. Second, they fuse with the sick cell and revitalize it. This process is called cell fusion . Third, by transferring mRNA through exosomes, and by secreting growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, hepatocyte growth factor (HGF), insulin-like growth factor (IGF), and others, they reinvigorate the cells. One of the sentinel effects of infused MSCs is from reactivation of the native stem cells in the organ. Regeneration of native cells and production of ECM is one of the capabilities of MSCs. However, it is still unclear if this regeneration is from the differentiation of MSCs into native cells or from stimulation of native MSCs in the tissue (31). MSCs are known to be antiinflammatory. MSCs are known as "protein factories" because they produce mRNA and transfer them to native cells through exosomes, which then secrete antiinflammatory proteins, such as interleukin (IL) 1 receptor antagonist, IL-10, IL-11, transforming growth factor, TSG-6, and others, to neutralize proinflammatory proteins, such as IL-1, IL-6, IL-12, metalloproteinases, tumor necrosis factor, and others. This transforms the microenvironment from a proinflammatory to an antiinflammatory state. Immunomodulation is one of the most attractive characteristics of MSCs. By secreting various chemokines and growth factors, they influence the Treg cells to decrease the production of the proinflammatory Th1 cells and increase

the numbers of the antiinflammatory Th2 cells. This change in the Th1/Th2 ratio reverses the negative consequences of the body's autoimmune attack on its tissues. The paracrine secretion also alters the proinflammatory macrophage (M1) and antiinflammatory (M2) ratio to promote tissue repair. Fibrosis is generally defined as an accelerated accumulation of ECM factors (predominantly collagen type I) that prevents the regeneration of tissue. It can occur in virtually any tissue because of trauma, inflammation, immunological rejection, chemical toxicity, or oxidative stress. Through immunomodulation and inhibition of myofibroblasts, MSCs decrease scar formation and enhance tissue matrix remodeling. MSCs secrete several angiogenesis factors, including IL-8, IGF, HGF, and VEGF compared with mature cell types, such as fibroblasts. These proangiogenic factors form vascular networks.

In summary, MSCs decrease cellular death (cell fusion and mitochondrial transfer and growth factor secretion), decrease fibrosis (decreasing fibroblast activity), modulate tissue remodeling (antiinflammatory activity and immunomodulation), and increase blood supply (neovascularization), thereby enhancing organ function.

MSCs have been used since the early 2000s to treat various conditions refractory to conventional treatments. The first generation of MSCs were mononuclear cells isolated from bone marrow aspiration and are autologous and nonexpanded in all the published studies. Unfortunately, bone marrow is a relatively poor source of MSCs and despite that some studies showed positive outcomes. Adipose tissue has a significantly higher number of MSCs and is currently positioned as the best autologous source. However, treatment of systemic conditions and organ failure does require a large quantity of MSCs, and hence culture expansion may be a requisite. Multiple tissues can serve as a cache of MSCs for expansion with bone marrow, adipose, and perinatal tissues being most frequently used. Because embryonic and iPSCs are tumorigenic, we did not include them in our analysis. Similarly, because differentiated MSC into specific lineage cells may not possess paracrine activity, and because of the concern of poor engraftment along with the possible expression of MHA I and II surface markers, these studies were also excluded. Hematopoietic stem cells were not considered as they do not have secretory functions and differentiation capabilities to nonhematopoietic cells.

Results

MSC Treatment for Organ Failure

Lung Failure

Acute inflammatory and chronic fibrotic lung diseases are a major cause of morbidity and mortality. This includes ARDS, bronchopulmonary dysplasia, pulmonary arterial hypertension, silicosis, sarcoidosis, chronic obstructive pulmonary disease (COPD), and idiopathic pulmonary fibrosis (IPF).

ARDS is a major cause of acute respiratory failure and is often associated with multiple organ failure with a large financial burden due to long hospital and ICU stays, poor survival rate, and increased use of health services after discharge. No pharmacologic agent has shown to reduce mortality in ARDS. Current treatment remains primarily supportive, with lung-protective ventilation and a fluid conservative strategy. Although this has caused a modest decline in mortality, however, it still remains high. Therapy with MSCs is a potential new treatment for lung injury in patients with ARDS.

We found 12 studies assessing the effect of MSCs for treatment in patients with severe lung disease. There are 6 clinical studies (2 randomized controlled trials [RCTs], 3 case series, and 1 prospective controlled trial) on cell therapy in patients with ARDS (30,36-40), which are described in Table 1. Two studies focused on COPD (41,42) and IPF (43,44), and 1 each on acute lung injury (45) and bronchiolitis obliterans syndrome (BOS) (46) (Table 1). Most of the studies used bone marrow MSCs, whereas 2 studies used human umbilical cord MSCs, 1 study used adipose-derived MSCs, and the other used MSCs from menstrual blood. Mesenchymal stromal cells were administered intravenously in all trials. Among the 6 studies for ARDS, 4 showed positive outcomes ranging from improved lung function, Sequential Organ Failure Assessment (SOFA)/Lung Injury Scores (LSIs) to survival rates, and discharge rates from the hospital. No complications were reported in any of these studies, however, Matthay et al (30) showed a nonsignificant increase in mortality in the MSC group than in the placebo group. They opined that this was a result of increased severity of illness, represented by SOFA and APACHE III scores, at baseline in the MSC group. Out of the 2 studies on COPD, one was not favorable as it did not show any decrease in the frequency of COPD exacerbations, pulmonary function tests, or the

Table 1. *MSC therapy studies treating pulmonary failure.*

Author	Year	Type of Study	Number of Patients in the Treatment Group	BMA (mL)	Number of MSC	Type of Stem Cell	Delivery Method	Outcome	Condition	Follow-Up	Findings
Liu et al, *Chin J Ind Hyg Occup Dis* 2012; 30:811-815	2012	PCT	5	NA	1 million	UCB	IV	Yes	Acute lung injury	15 days	Decreases SOFA score. All patients in the treatment group survived and 1 out of 7 in the control survived. LSI score improved in the treatment group.
Weiss et al, *Chest* 2013; 143:1590-1598	2013	RCT	62	NA	100 million x 4 doses	Allo BM MSC	IV	No	COPD	2 years	No differences in frequency of COPD exacerbations, PFTs, or QOL indicators.
Zheng et al, *Respir Res* 2014; 15:39	2014	RCT	12	NA	1 million	Allo Adipose	IV	No	ARDS	28 days	Length of hospital stay, ventilator-free days, and ICU-free days at day 28 after treatment were similar. PaO2/FiO2 did not improve.
Simonson et al, *Stem Cells Transl Med* 2015; 4:1199-213	2015	Case series	2	28	2 million	BM MSC	IV	Yes	ARDS	NA	Improved lung function, tidal volumes, and compliance. Resolution of multiorgan failure and discharge from the hospital.
Wilson et al, *Lancet Respir Med* 2015; 3:24-32	2015	Case series	9	NA	1, 5, 10 million	Allo BM MSC	IV	Yes	ARDS	60 days	Mean LSI and SOFA scores declined with all doses with the highest decline in the high-dose group. Mortality rate (22%) lower than the expected mortality (32%) in patients with moderate ARDS.
Matthay et al, *Lancet Respir Med* 2019; 7:154-162	2018	RCT	40	100	1, 5, 10 million	Allo BM MSC	IV	No	ARDS	12 months	Higher mortality in the MSC group, however, not statistically significant. The MSC group had sicker patients represented by SOFA and APACHE III scores at baseline. SOFA scores not reported in the study.
Armitage et al, *Eur Respir J* 2018; 51:1702369	2018	Case series	9	NA	2 million x 2 doses	Allo BM MSC [Pas 3]	IV	Yes	COPD	12 months	Reduction in hospital admissions postinfusion (from 11–6). No statistically significant change in FEV-1 and FVC at 3 weeks.

Table 1 con't. *MSC therapy studies treating pulmonary failure.*

Author	Year	Type of Study	Number of Patients in the Treatment Group	BMA (mL)	Number of MSC	Type of Stem Cell	Delivery Method	Outcome	Condition	Follow-Up	Findings
Averyanov et al, *Stem Cells Transl Med* 2020; 9:6-16	2019	PCT	10	100-150	1.6 trillion in divided doses	Allo BM MSC [Pas 3-5]	IV	Yes	IPF	12 months	Improvement in FVC, DLCO, and 6-minute walk test. HRCT fibrosis score did not differ significantly from baseline.
Chen S et al, *EBioMedicine* 2019; 49:213-222	2019	PCT	81	NA	1 million/kg x 6 doses	Allo BM MSC	IV	Yes	BOS	3 months	Improvement in FEV1 and steroid-sparing effect. No improvement in mortality.
Chen J et al, *Engineering (Beijing)* 2020 Feb 28. [Epub ahead of print]	2020	PCT	17	100	1 million	Allo MSC from menstrual blood	IV	Yes	ARDS	12 months	Improve lung function. Increased incidence of shock in MSC group. Higher survival rate. Death rate in treatment group 16.7% compared with 54.5% in control.
Leng et al, *Aging Dis* 2020; 11:216-228	2020	Case series	10	NA	1 million	UC MSC	IV	Yes	ARDS	14 days	Improvement of ARDS, multiorgan failure, and survival.

PCT, prospective controlled trial; UCB, umbilical cord blood; LSI, lung injury score; PFT, pulmonary function test; QOL, quality of life; FEV, forced expiratory volume;; FVC, forced vital capacity; APACHE III, Acute Physiology and Chronic Health Evaluation III; DLCO, diffusing capacity of the lung for carbon monoxide; HRCT, high-resolution computed tomography; NA, not available; BMA, Bone marrow aspirate; Allo, allogeneic; BM, bone marrow; Pas, passage number; ..

quality of life indicators. Conversely, Armitage et al (42) did find reduction in hospital stay among patients who received MSC therapy. Chambers et al (43) used placenta-derived MSCs in patients with IPF, which showed no change in the outcome after 6 months with respect to lung function (forced vital capacity [FVC], diffusing capacity of carbon monoxide [DLCO]), 6-minute walking distance test, and lung fibrosis score. Averyanov et al (44) used a very high concentration of MSCs in patients with IPF. They were able to show improvement in FCV, DLCO, and the 6-minute walking distance test. One study on acute lung injury showed a decrease in SOFA and LSI scores along with a higher survival rate in the treatment group. The single study on BOS patients showed that although there was no reduction in mortality, improvement in the FEV1 was noted along with a steroid-sparing effect. Table 1 summarizes MSC therapy studies in pulmonary failure.

Cardiac Failure

Heart failure is a chronic disease and the end stage of various heart conditions. It is a progressive syndrome that results in a poor quality of life for the patient and places an economic burden on the health care system. Once heart failure occurs, it continues to develop even in the absence of new pathogenic factors and causes serious harm to the patient. The hospitalization and mortality rates related to heart failure are high (47). Despite improved pharmacologic therapy, congestive heart failure remains the leading cause of cardiovascular mortality in the industrialized world. The use of stem cell–based therapy is becoming increasingly recognized as having the potential to salvage damaged myocardium and to promote endogenous repair of cardiac tissue, thus having the potential for the treatment of heart failure (47).

Table 2. *MSC therapy studies treating cardiac failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SCs	Type of Stem Cell	Delivery Method	Condition	Outcome	LVEF Impact	Follow-Up	Findings
Strauer et al, *Circulation* 2002; 106:1913-1918	2002	PCT	10	40	28 million	BM MNC	IC	IHD	Yes	Not assessed	3	Improvement in infarct region and wall motion, decrease in perfusion defect, increase in systolic pressure/end-systolic volume, but no change in velocity of circumferential fiber shortening.
Chen et al, *Chin Med J (Engl)* 2004; 117:1443-1448	2004	RCT with placebo	34	UNK	UNK	BM MNC	IC	IHD	Yes	Yes - improvement	3	Decrease in functional defect, increase in wall movement velocity, perfusion defect improved, increase in systolic pressure/end-systolic volume.
Wollert et al, *Circulation* 2004; 364:141-148	2004	RCT	30	128	2.4 billion	BM MNC	IC	IHD	Yes	Yes - improvement	6	Improvement in overall LVEF. Increased regional LVEF and systolic wall motion in the border zone but not infarcted zone. No change in LVEDV.
Katritsis et al, *Catheter Cardiovasc Interv* 2005; 65:321-329	2005	PCT	11	15	1–2 million	BM MSC [Pas 0]	IC	IHD	Yes	Not assessed	4	Decrease in wall motion score index, improvement in myocardial contractility, reversible ischemia, and viability.
Ruan et al, *Chinese Med J* 2005; 118:1906	2005	PCT	9	UNK	UNK	BM MNC	IC	IHD	Yes	Yes - improvement	6	Improvement in perfusion and LVEF, EDV, and ESV for 6 months.
Chen et al, *J Invasive Cardiol* 2006; 18:552-556	2006	PCT	22	UNK	UNK	BM MNC	IC	IHD	Yes	Yes - improvement	12	Decrease in reversible defect, improvement in level of exercise tolerance (3 months), and NYHA.
Ge et al, *Heart* 2006; 92:1764-1767	2006	RCT	12	40	40 million	BM MNC	IC	IHD	Yes	Yes - improvement	6	Increase in LVEF, decrease in perfusion defect, increase in LVEDD in control patients. MSCs injected immediately after PCI.
Wang et al, *Zhonghua xin xue guan bing za zhi* 2006; 34:107-110	2006	RCT	12	UNK	UNK	BM MSC	IC	DCM	Yes	No	3 and 6	Increase in plasma BNP levels and in 6-minute walking distance. No changes in LVEF, LVEDV, IL-6, TNF-α, and CRP.

Table 2 con't. *MSC therapy studies treating cardiac failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SCs	Type of Stem Cell	Delivery Method	Condition	Outcome	LVEF Impact	Follow-Up	Findings
Janssens et al, *Lancet* 2006; 367:113-121	2006	RCT	33	304 billion cells	172 billion	BM MNC	IC	IHD	Yes	No	4	Reduction in myocardial infarct size and recovery of regional systolic function, no increase in LVEF or myocardial perfusion and metabolism.
Huang et al, *Zhonghua Xin Xue Guan Bing Za Zhi* 2006; 34:111-113	2006	PCT	10	UNK	UNK	BM MNC	IC	IHD	Yes	No	24	Improvement of 6-minute walking distance (6 months) and decreased hospitalization (2 years). No change in LVEF, LVEDD, or myocardium lesion area.
Schächinger et al, *Eur Heart J* 2006; 27:2775-2783	2006	RCT	101	50	198 billion	BM MNC	IC	IHD	Yes	Not assessed	12	Reduction in death, MI, need for revascularization. Also reduction of recurrence of MI, and/or rehospitalization for health failure.
Seth et al, *J Am Coll Cardiol* 2006; 48:2350-2351	2006	RCT	24	50–60	28 million	BM MNC	IC with CS occlusion	DCM	Yes	Yes - improvement	6	Improvement in NYHA functional class. Reduction in end-systolic volumes.
Chen et al, *Saudi Med J* 2008; 36:1087-1091	2008	PCT	71	UNK	UNK	BM MNC	IC	DCM	Yes	Yes – improvement	24	Improvement in 6-minute walking distance (24 month) and LVEF (1 month only), LVEF was the same (2 years), decrease in ischemic segments (3 months) and no change in necrotic segments. No change in survival but decrease in annual hospitalization days.
Hare et al, *J Am Coll Cardiol* 2009; 54:2277-2286	2009	RCT	34	NA	0.5 or 1.6 or 2.5 million/ kg	Allo BM MSC	IV	IHD	Yes	Yes - improvement	6	Improvement in V-TACH episodes, LVEF, EF, reverse remodeling, FEV1, and "Global Assessment of Personal Health." No difference in 6-minute walk duration.
Dill et al, *Am Heart J* 2009; 157:541-547	2009	RCT	27	Not disclosed	Not disclosed	BM MNC	IC	IHD	Yes	Yes - improvement	12	Improvement of LVEF, reduced EDV and ESV, increase only in patients with EF <49%.
Miettinen et al, *Heart* 2010; 96:362-367	2009	RCT	39	80	400 million	BM MNC	IC	IHD	Yes	Yes - improvement	6	Elevated LVEF seen in patients with EF <65 with increases in N-terminal probrain natriuretic peptide but not N-terminal proatrial natriuretic peptide.

Table 2 con't. *MSC therapy studies treating cardiac failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SCs	Type of Stem Cell	Delivery Method	Condition	Outcome	LVEF Impact	Follow-Up	Findings
Lasala et al (72)	2009	Case series	10	30–50	7.5 million MSC [Pas 1–2] and MNC each	BM MSC + BM MNC	IC	IHD	Yes	Yes - improvement	6	Improvement in MI episodes and QOL in patients with angina.
Herbots et al, *Eur Heart J* 2009; 30:662-670	2009	RCT	33	Not disclosed	304 million	BM MNC	IC	IHD	Yes	Not assessed	4	Improvement in end-systolic strain in the segments with a transmural infarct along with peak-systolic strain rate along with systolic BP.
Beitnes et al, *Heart* 2009; 95:1983-1989	2009	RCT	50	50	68 million	BM MNC	IC	IHD	No	No	36	No change in LVEF or improvement in exercise time or peak oxygen consumption (2–3 weeks to 3 years).
Assmus et al, *Circulation: Heart Failure* 2010; 3:89-96	2009	RCT	100	Not disclosed	Not disclosed	BM MNC	IC	IHD	Yes	Not assessed	24	Reduction in death, MI, need for revascularization, recurrence of MI, and/or rehospitalization for health failure. Increase in left ventricular contractility of infarcted segments.
Yang et al, *Cardiovascular therapeutics* 2010; 28:380-385	2010	RCT	16	20–40	12–13 million [Pas 0]	BM MSC	IC	IHD	Yes	Yes	6	Improvement in NYHA score, myocardial viability in the infarct area, LVEF but not LVEDV. No difference if injected in infarcted or noninfarcted coronary.
Piepoli et al, *European Journal of Heart Failure* 2010; 12:172-180	2010	RCT	19	100	248 million	BM MNC	IC	IHD	Yes	Yes - improvement	12	Improvement in LVEF, LVEDV and LVESV, SV, CO, indices of autonomic control, exercise tolerance, and ventilatory response to exercise.
Traverse et al, *Am Heart J* 2010; 160:428-434	2010	RCT	30	80–100	100 million	BM MNC	IC	IHD	Yes	No	6	Improvement in LV remodeling and decrease in LVEDV. No change in LVEF, however, patients with preinfarction angina had a 4-fold increase in LVEF compared with those without preinfarction angina.
Beitnes et al, *Eur J Echocardiogr* 2011; 12:98-106	2010	RCT	50	50	68 million	BM MNC	IC	IHD	No	No	36	No difference between control and study. Both groups experienced improvement of global, regional, and diastolic LV function after 3–6 months.

Table 2 con't. *MSC therapy studies treating cardiac failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SCs	Type of Stem Cell	Delivery Method	Condition	Outcome	LVEF Impact	Follow-Up	Findings
Hu et al, *J Am Coll Cardiol* 2011; 57:2409-2415	2011	RCT	31	60	100 million	BM MNC	CABG	IHD	Yes	Yes - improvement	6	Improvement in LV end-systolic volume index, wall motion index, B-type natriuretic peptide, and 6-minute walking distance. MSC infused during CABG.
Diederichsen et al, *Scand Cardiovasc J* 2010; 44:139-145	2011	Case series	32	150	647 + 889 million	BM MNC	IC	HF	Yes	Not assessed	12	Decrease in E/e ratio and left atrial volume.
Turan et al, *Stem Cell Rev Rep* 2011; 7:646-656	2011	RCT	38	120	Not disclosed	BMC	IC	IHD	Yes	Yes	12	Increase in global EF, infarct wall movement velocity SVI, and NYHA classification. Decrease of infarct size and LVESV (3 and 12 months). MSC infusion 28 months after MI.
Tuma et al, *J Transl Med* 2011; 9:183	2011	Case series	14	300	800 million	BM MNC	IC	IHD	Yes	Yes - improvement	24	Improvement in ischemic myocardium, systolic LV function in patients with low ejection at baseline in patients with angina. MSC infusion in the coronary sinus.
Hopp et al, *J Transl Med* 2011; 13:22	2011	RCT	15	300	800 million	BM MNC	IC	IHD	No	No	6	No change in LVEF, LV mass, and infarct size.
Houtgraaf et al, J Am Coll Cardiol 2012; 59:539-540	2012	RCT	10	200	17 million	Adipose SVF	IC	IHD	Yes	No	6	No change in LVEF but significant decrease in LV infarct percentage by 52% and improvement in perfusion defect.
Plewka et al, J Am Coll Cardiol 2011; 69:1234-1240	2011	RCT	40	UNK	UNK	BM MNC	IC	IHD	Yes	Yes – improvement	144	Increase in LVEF at 2 years.
Wohrle et al, *Clin Res Cardiol* 2013; 102:765-770	2013	RCT	29	15	324 million	BM MNC	IC	IHD	Yes	Yes - improvement	6	Improvement of LVEF maintained during long-term follow-up at 12, 24, and 36 months in patient who received >324 million cells (dose-dependent) and w/o microobstruction.

Table 2 con't. *MSC therapy studies treating cardiac failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SCs	Type of Stem Cell	Delivery Method	Condition	Outcome	LVEF Impact	Follow-Up	Findings
Lu et al, *Int J Cardiology* 2013; 168:2221-2227	2013	RCT	31	60	133 million	BM MNC	CABG	IHD	Yes	Not assessed	12	Improvement in LVEDV, LVESV, systolic wall thickening in the infarct zone, and border zone. No change in SV, CO, CI, ventricular mass index and late contrast enhancement. MSC infusion during CABG.
Gao et al, *Int J Cardiol* 2013; 168:3191-3199	2013	RCT	21	80	3 million [Pas 2]	BM MSC	IC	IHD	No	No	24	No change in myocardial viability and perfusion, LVEF, LVEDV, LVESV, death, recurrent MI, and rehospitalization. One patient report of coronary occlusion during MSC infusion treated with tirofiban and balloon inflation.
Lee et al, *J Korean Med Sci* 2014; 29:23-31	2014	RCT	33	20–25	72 million [Pas 4–5]	BM MSC	IC	IHD	Yes	Yes - improvement	6	Improvement in LVEF. No significant differences in LVEDV, LVESV, WMSI, and changes in WMSI. MSC infusion 1 month after MI.
Zhao et al, *Genet Mol Res* 2015; 14:3010-3017	2015	RCT	30	Not disclosed	Not disclosed	UC MSC	IC	HF	Yes	Yes - improvement	6	Improvement in LVEF, LVEDD, BNP, 6-minute walking distance, and mortality rate. One patient had transient ST elevation and chest pain, which resolved after saline solution flush.
Gao et al, *BMC Medicine* 2015; 13:162	2015	RCT	58	NA	6 million [Pas 3]	UC MSC	IC	HF	Yes	Yes - improvement	18	Improvement in infarct size, myocardial perfusion and viability, and LVESV and LVEDV. UC MSC transplantation prevented postinfarct LV adverse remodeling. No change in death, recurrent MI, or rehospitalization.
Li et al, *Curr Pharm Des* 2015; 21:1426-1432	2015	Case series	15	NA	3, 4, 5 million	UC MSC	IC	IHD	Yes	Yes - improvement	24	Decrease in infarct size and improvement in LVEF.
Nair et al, *Indian J Med Res* 2015; 142:165-174	2015	Controlled trial	109	100–150	200–500 million	BM MNC	IC	IHD	No	No	6	No change in LVEF.

Table 2 con't. *MSC therapy studies treating cardiac failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SCs	Type of Stem Cell	Delivery Method	Condition	Outcome	LVEF Impact	Follow-Up	Findings
Patel et al, *Stem Cells Transl Med* 2015; 4:1021-1027	2015	RCT	24	240	3.7 billion	BMC	CS	HF	Yes	Yes - improvement	6	Improvement of LVEF in ICF and NICF. Decrease of LVESD and B natriuretic peptide only in NICF.
Martino et al, *Eur Heart J* 2015; 36:2898-2904	2015	RCT	57	100	2.36 billion	BM MNC	IC	DCM	No	No	12	No change in LVEF, EF, LVEDV, and LVESV.
Huang et al, *Stem Cell Res Ther* 2015; 6:112	2015	Controlled trial	79	Not disclosed	490 million	BM MNC	IC	IHD	Yes	Yes	12	BMC transplantation within 24 hours or at 3–7 days after PCI further improved cardiac function, whereas BMC infusion performed later (7–30 days after PCI) offered no additional benefits.
Choudry et al, *European Heart Journal* 2016; 37:256-263	2016	RCT	55	100	59.8 million	BM MNC	IC	IHD	Yes	No	12	Increase in myocardial salvage index (3 days).
Sürder et al, *Circ Res* 2016; 119:481-490	2016	PCT	95	65–70	139–159 million	BM MNC	IC	IHD	No	No	12	No change if given 5–7 days or 3–4 weeks after MI.
Srimahachota et al, *J Med Assoc Thai* 2011; 94:657-663	2011	RCT	11	100	420 million	BM MNC	IC	IHD	No	No	6	No change in LVEF, scar volume, wall motion score index.
Bartolucci et al, *J Med Assoc Thailand* 2017; 121:1192-1204	2017	RCT	15	NA	1 million/kg [Pas 3]	UC MSC	IV	HF	Yes	Yes - improvement	12	Improvement in LVEF, NYHA class, and MLHFQ. No change in mortality, heart failure admissions, arrhythmias.
Xiao et al, *Int Heart J* 2017; 58:238-244	2017	RCT	16, 17	80–100	510 million MNC, 490 million [Pas 3] MSC	BM MNC, BM MSC	IC	DCM	Yes	Yes - improvement	12	Improvement in LVEF and NYHA and perfusion at 3 months but maintained only in MSC group at 12 months. LVEDV decreased only in the MSC group at 12 months.
Mostafavian et al, *J Med Life* 2018; 11:359-364	2018	PCT	30	100	6–8 million	BM MNC	IC	HF	No	No	3	No change in QOL, NYHA, and LVEF.

Table 2 con't. *MSC therapy studies treating cardiac failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SCs	Type of Stem Cell	Delivery Method	Condition	Outcome	LVEF Impact	Follow-Up	Findings
Traverse et al, *Circ Res* 2018; 122:479-488	2018	RCT	79	100	150 million	BM MNC	IC	IHD	No	No	24	No change.
Kim et al, *Cardiovasc Drugs Ther* 2018; 32:329-338	2018	Controlled trial	14	20–25	70 million	BM MSC [?Pas#]	IC	IHD	Yes	Yes - improvement	12	Improvement in LVEF at 4 and 12 months.
Qi et al, *J Clin Ultrasound* 2018; 46:512-518	2018	RCT	24	60	130 million	BM MNC	CABG	IHD	Yes	Not assessed	12	Improvement in ventricular function. MSC infusion during CABG.
Nicalau et al, J Cardiothoracic Vasc Anesth 2018; 41:392-399	2018	RCT	66	100	100 million	BM MNC	IC	IHD	No	No	6	No change in LVEF, systolic and diastolic volumes, as well as infarct size.

PCT, prospective controlled trial; BM MNC, bone marrow mononuclear cells; BM MSC, bone marrow mesenchymal stem cells; UC MSC, umbilical cord mesenchymal stem cells; PAS, passage; SVF, stromal vascular fraction; UNK, unknown; IC, intracardiac injection; CS, coronary sinus; CABG, coronary artery bypass grafting; IV, intravenous injection; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; HF, heart failure; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; EDV, end-diastolic volume; ESV, end-systolic volume; NYHA, New York Heart Association Functional Classification; LVEDD, left ventricular end-diastolic diameter; PCI, percutaneous coronary intervention; BNP, B-type natriuretic peptide; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; CRP, C-reactive protein; V-TACH, ventricular tachycardia; EF, ejection fraction; FEV1, forced expiratory volume in 1s; MI, myocardial infarction; QOL, quality of life; BP, blood pressure; LVESV, left ventricular end-systolic volume; SV, stroke volume; CO, cardiac output; LV, left ventricular; SVI, stroke volume index; CI, cardiac index; WMSI, Wall Motion Score Index; ST, sinus tachycardia; ICF, ischemic cardiac failure; NICF, nonischemic cardiac failure; MLHFQ, Minnesota Living with Heart Failure Questionnaire; BMA, bone marrow aspirate; SC, stem cells; NA, not available; Allo, allogeneic; BMC, bone marrow concentrate; E/e, heart failure ratio.

At least 52 studies, many of which are RCTs, have assessed the ability of intravascular stem cells to treat heart failure of ischemic and nonischemic etiology . These studies have been summarized in Table 2. Studies that injected stem cells into the cardiac muscle were excluded. Ischemic heart disease was addressed in most studies; however, heart failure and dilated cardiomyopathy was treated in 6 and 5 studies, respectively. Carotid sinus infusion was used in one study and IV infusion in 2 studies with intracoronary in the rest. In 3 trials, MSC infusion was performed into the grafts during coronary artery bypass grafting (CABG) surgery (48-52). Thirty-nine of the 52 trials used autologous bone marrow mononuclear cells. Twenty-nine of these 39 studies showed beneficial effects. Seven studies utilized expanded bone marrow MSCs and only one of these trials used allogeneic expanded bone marrow MSCs and the rest were autologous. Positive outcomes were noted in all but 1 of these 7 trials. Umbilical cord MSCs were used in 4 studies, bone marrow concentrate using bedside devices were used in 2 studies, both bone marrow MNC and expanded bone marrow stem cells were used in 2 studies, and all these trials reported statistically significant favorable outcomes in various measured indices in the treatment cohort when compared with controls. Most studies enhanced left ventricular ejection fraction (LVEF) and a few also improved ventricular remodeling parameters, such as left ventricular end diastolic and systolic volumes. Although not observed in all studies, many studies showed improved death/hospitalization/myocardial reinfarction rates and New York Heart Association scores (Table 2). In 3 trials, MSC infusion into the grafts

during CABG improved LVEF, ventricular remodeling, and desynchrony (50-52). Two trials evaluating the effect of treating angina with MSCs revealed clinical and functional improvement (47,53). All trials that did not have a favorable outcome had bone marrow mononuclear cells except one study, which used expanded bone marrow stem cells. Among all these studies only 2 serious complications were noted. In one patient, during expanded bone marrow MSC infusion, coronary occlusion was diagnosed by electrocardiogram changes and was successfully treated with tirofiban and balloon inflation at the site of occlusion (54). In another study, one patient experienced chest discomfort and showed ST-T wave changes, but spontaneous remission was achieved 15 minutes after physiological saline solution flushing (55). Both patients had an uneventful recovery.

Liver Failure

Liver disease, one of the major causes of human mortality and morbidity worldwide, is a serious clinical syndrome. Generally, acute, or chronic liver damages could be caused by alcohol consumption, hepatotoxic drugs, and virus infections, such as hepatitis B virus and hepatitis C virus. Liver transplantation offers an effective cure and is the criterion standard for treatment of end-stage liver disease. However, several limitations regarding transplantation currently restrict its application, such as limited number of donor organs, long waiting lists, high cost, potential serious complications, and lifelong immunosuppression. Therefore it is an urgent task to explore new treatment options for liver disease (56).

We identified 23 clinical studies that assessed the ability of MSCs to treat chronic/acute liver failure, including end-stage liver disease, from different etiologies ranging from alcoholic cirrhosis/primary biliary cirrhosis to hepatitis B. The studies are described in Table 3. Most studies were prospective controlled trials and case series along with 4 RCTs. In 10 studies, hepatic artery infusion was performed, and in one trial the MSCs were administered into the portal vein, and the rest were IV. Eight studies utilized cultured bone marrow MSCs, mostly autologous; 6 used allogeneic umbilical cord MSCs; and in the remaining, nonexpanded bone marrow mononuclear cells were given. All trials except 3 reported positive outcomes. Expanded bone marrow MSCs were used in 2 trials, and nonexpanded bone marrow MNCs were used in the third. Improvements in LFTs, prothrombin time (PT), model for end stage live disease (MELD) scores, Child Pugh scores, and ascites were noted in various studies. In 2 studies, when bone marrow MSCs were infused in the hepatic artery in patients with cirrhosis, histological improvement along with decreased fibrosis markers was seen (57,58). Another trial showed that by injecting bone marrow mononuclear cells into the hepatic artery, there was decreased incidence of hepatic encephalopathy and bacterial peritonitis (59). Xue et al (56) found that when umbilical cord MSCs were administered through the hepatic artery in patients with end-stage liver dysfunction, there was a decrease in hospitalization and increase in the quality of life. Increases in liver volumes were reported in 2 studies when bone marrow mononuclear cells were used either IV or through the portal vein (60,61). Importantly, 2 studies revealed increased survival rates. One utilized umbilical cord MSCs in the hepatic artery and the other used bone marrow MSCs intravenously (62,63). It is significant to note that no serious complications were noted in any of these studies. Although in one trial, when umbilical cord MSCs were administered through the hepatic artery, elevations were seen in bilirubin and ALT levels but interestingly, clinical improvement in terms of MELD scores, ascites, and decreased hospitalizations were noted (56).

Stroke

Ischemic stroke is a leading cause of death and a leading cause of disability in the Western world. IV thrombolysis remains the only proven therapy for acute ischemic stroke. However, even in developed countries, only a small minority of stroke patients currently receive this therapy due to difficulty in access and also timing. In addition, several neuroprotective strategies have failed to show any definite benefit after stroke. Acute ischemia causes irreversible damage to neurons and glial cells, leading to severe functional deficits and chronic sequelae. Cell therapy with bone marrow–derived stem cells has shown to have beneficial effects in animal models of stroke. Although the mechanisms involved are still subject to debate, it has been suggested that the injected cells release cytokines and trophic factors and modulate neuronal death and inflammation in the penumbra area. There are no treatment options for the patients during the poststroke period when they have difficulties in performing activities of daily living, ambulation, and self-care. Use of stem cell–based therapy is becoming recognized as having the potential to improve the neurologic function in poststroke patients.

Table 3. *MSC therapy studies treating liver failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SC	Type of Stem Cell	Delivery Method	Result	Follow-Up (months)	Condition	Findings
Esch et al, *Stem Cells* 2005; 23:463-470	2005	PCT	3	60–220	2.4–12.3 million	BM MNC	PVI	Yes	26 days	Post liver resection	Mean daily hepatic growth rates were 2.5-fold higher when contrasted with a comparable group.
Terai et al, *Stem Cells* 2006; 24:2292-2298	2006	Case series	9	400	5.2 billion	BM MNC	IV	Yes	6	Cirrhosis	SS improvement in albumin and total proteins and Child Pugh scores along with decrease in ascites and improvement in AFP and PCNA expression based on liver bx reflecting liver regeneration. Decreased P111P levels implying decrease in liver fibrosis when followed for 6 months.
Mohamadnejad et al, *Arch Iran Med* 2007; 10:459-466	2007	Case series	4	80–100	31 million	BM MSC (Pas 2–4)	IV	Yes	12	Cirrhosis	Improvement in LFTs and MELD score and the SF-36 mean physical and mental component scores.
Lyra et al, *World J Gastroenterol* 2007; 13:1067-1073	2007	Case series	10	50	100 million	BM MNC	HAI	Yes	4	CLD	Mild improvement in bilirubin, albumin, and INR levels.
Lyra et al, *Eur J Gastroenterol Hepatol* 2010; 22:33-42	2010	RCT	15	50	378 million	BM MNC	HAI	Yes	12	Cirrhosis	Child Pugh score/albumin decreased max at 3 months but no change by 12 months and no change in the MELD. No change in bilirubin levels.
Peng et al, *Hepatology* 2011; 54:820-828	2011	PCT	53	100–120	340 million	BM MSC [Pas 3]	HAI	Yes	6	Hepatitis B liver failure	ALB levels increased up to 6 months. TBIL and PT were better for 4–12 weeks. MELD improved for 3–36 weeks.
Saito et al, *Stem Cells Dev* 2011; 20:1503-1510	2011	PCT	5	400	8 billion	BM MNC	IV	Yes	6	Cirrhosis	ALB and total protein and prothrombin time improved. Three out of 5 study patients showed improvement in the CP score. No change in liver fibrosis markers.
Zhang et al, J Gastroenterol Hepatol 2012; 27(suppl 2):112-120	2012	PCT	30	NA	0.5 million/kg	WJ MSC (Pas 3–4)	IV	Yes	12	Cirrhosis	ALB increased for 48 weeks and CHE increased for 4 weeks. TBIL decreased for 48 weeks. MELD decreased, PLTS increased and ascites decreased for 48 weeks. Serum laminin, hyaluronic acid, PIIINP, and type IV collagen, which are markers for disease severity of liver fibrosis were significantly decreased at weeks 24 and 48.

Table 3 con't. *MSC therapy studies treating liver failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SC	Type of Stem Cell	Delivery Method	Result	Follow-Up (months)	Condition	Findings
Wang et al, *J Gastroenterol Hepatol* 2013; 28(suppl 1):85-92	2012	Case series	7	NA	0.5 million/ kg x 3 doses	WJ MSC (Pas 4)	IV	Yes	48 weeks	PBC	Fatigue, pruritus, and ascites improved but no major change in other parameters. Serum ALP levels and MRS are 2; data indicate that UC MSC transfusion can significantly reduce the serum ALP levels and stabilize MRS (2 key parameters for the definition of response to treatment in patients with PBC) during a 48-week follow-up period.
Shi et al, *Stem Cells Transl Med* 2012; 1:725-731	2012	PCT	43	NA	0.5 million/ kg x 3 doses	WJ MSC (Pas 3–4)	IV	Yes	12 or 18	Acute on chronic liver failure	MELD improved. Albumin, CHE, and PTA increased showing improved liver functioning. ALT and TBIL levels decreased. AFP levels increased showing liver proliferation. Improvement in survival seen.
Jang et al, *Liver Int* 2014; 34:33-41	2013	Case series	12	10–20	50 million x 2 doses	BM MSC (Pas 4–5)	HAI	Yes	3	Cirrhosis	Histological improvements were observed in 6 of the 11 patients (54.5%). The Child Pugh score improved in 10 patients, and the expressions of TGF-b1, collagen-1 and, a-SMA were significantly decreased.
Spahr et al, *PLoS One* 2013; 8:e53719	2013	RCT	28	103	5 million	BM MNC	HAI	No	3	Alcoholic liver disease	No change.
Mohamadnejad et al, *Liver Int* 2013; 33:1490-1496	2013	RCT	14	250	195 million	BM MSC (Pas 3–4)	IV	No	12	Cirrhosis	No change.
Xu et al, *J Gastroenterol Hepatol* 2014; 29:1620-1628	2014	PCT	20	130–150	800 million	BM MNC	HAI	Yes	6	Hepatitis B Cirrhosis	No change in ALB and TB levels but MELD was lower. MSC transplantation markedly increased Treg cells population at weeks 2, 4, and 12. Importantly, the ratio of Treg/Th17 was increased. The reduction in IL-6, IL17, and TNF- levels was more pronounced in the transplantation group, indicating an antiinflammatory effect of ABMSC transplantation.

Table 3 con't. *MSC therapy studies treating liver failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SC	Type of Stem Cell	Delivery Method	Result	Follow-Up (months)	Condition	Findings
Bai et al, *World J Gastroenterol* 2014; 20:8660-8666	2014	PCT	32	80–100	Not reported	BM MNC	HAI	Yes	24	Cirrhosis	Decrease in hepatic encephalopathy and bacterial peritonitis. No change in esophageal bleeding. Improvement in ALB, preALB, and TB after 1 year but not 2 years. PT and PT activity improved up to 6 months and fibrinogen levels improved for 1 year. HGB improved for 6 months and PLT improved for 1 year.
Wang et al, *Stem Cells and Dev* 2014; 23:2482-2489	2014	Case series	10	20	0.3–0.5 million	BM MSC (Pas 3–5)	IV	Yes	12	PBC	Improvements in the PBS 40 score, AST, serum IgM at 12 months. ALT, GGT, DBIL improvement at 6 months . No change in TBIL or ALP. CD4 T cells increased and CD8 decreased up to 6 months. IL-10 decreased for 3 months.
Xue et al, *Transplant Proc* 2015; 47:412-418	2015	Case series	50	NA	30 million	WJ MSC (Pas 3)	HAI	Yes	6	ESLD	The frequency of hospitalization decreased because of improved ascites, hypoproteinemia, and quality of life. Bilirubin and ALT interestingly were increased for 24 weeks. PTT was decreased up to 24 weeks but no change in PT. MELD decreased at 24 weeks.
Kantarcıoğlu et al, *Turk J Gastroenterol* 2015; 26:244-250	2015	Case series	12	20–40	1 million/ kg	BM MSC (Pas 2)	IV	No	6	Cirrhosis	No change in MELD scores were observed. Serum albumin levels markedly increased in the third month. In patients with nonresponder hepatitis C, HCV RNA levels both became negative in 2 patients. Histopathological examinations of liver tissues before and at 6 months after transplantation revealed no change in liver tissue regeneration or fibrosis.
Li et al, *Stem Cell Rev Rep* 2016; 12:645-	2016	PCT	11	NA	100 million (Pas 3–4)	WJ MSC (Pas 3–4)	HAI	Yes	24	Acute on chronic liver failure	Increased survival. Improved MELD at 4 weeks. At 2 years, there was improvement in AST, albumin, PT, and INR, however, there was no change in ALT, TBIL, DBIL, Cr, WBC, HGB, PLT, and ascites.
Suk et al, *Hepatology* 2016; 64:2185-2197	2016	RCT	18, 19	10–20	50 million	BM MSC (Pas 4–5)	HAI	Yes	12	Cirrhosis	CP score improved in both active groups but not control. ALP decreased in study groups. No change in MELD. AST, ALT, albumin, bilirubin, GGT, fibrosis, and INR.

Table 3 con't. *MSC therapy studies treating liver failure.*

Author	Year	Type of Study	No. of Patients in Treatment Group	BMA (mL)	Number of SC	Type of Stem Cell	Delivery Method	Result	Follow-Up (months)	Condition	Findings
Lin et al, *Hepatology* 2017; 66:209-219	2017	RCT	54	Not reported	0.1–1 million/kg x 4	BM MSC (Pas 5–6)	IV	Yes	6	Acute on chronic liver failure	Decrease in bilirubin and MELD and decreased incidence of infection with higher survival rates.
Liang et al, *Int J Rheum Dis* 2017; 20:1219-1226	2017	Case series	26	NA	1 million/ kg	Mostly UC MSC (Pas 2–5)	IV	Yes	24	Cirrhosis	Bilirubin decreased up to 1 year. ALB increased for 2 years. PT lowered for 6 months. PLT CT increased for 4 years. No change in MELD.
Kim et al, *Cell Transplant* 2017; 26:1059-1066	2017	Case series	19	500–750	92 million/ kg	BM MNC	IV	Yes	60	Cirrhosis	ALB increased for 1 year. TB no change. PT improved for 9 months. HGB and Child Pugh score improved for 12 months. Increase in liver volume at 6 months along with decreased portal/septal/fibrillar tissue collagen.

PCT, prospective controlled trial; NA, not applicable; BM MNC, bone marrow mononuclear cells; BM MSC, bone marrow mesenchymal stem cells; WJ MSC, Wharton's jelly mesenchymal stem cells; UC MSC, umbilical cord mesenchymal stem cells; PVI, portal vein injection; IV, intravenous injection; HAI, hepatic artery injection; CLD, chronic liver disease; PBC, primary biliary cholangitis; ESLD, end-stage liver disease; AFP, alpha-fetoprotein; PCNA, proliferating cell nuclear antigen; P111P, procollagen-III peptide; LFT, liver function test; MELD, Model for End-Stage Liver Disease; INR, international normalized ratio; TBIL, bilirubin; PT, prothrombin time; ALB, albumin blood test; CP, ceruloplasmin test; CHE, serum cholinesterase; PLTS, platelets; ALP, alkaline phosphatase; MRS, Mayo risk score; PTA, percutaneous transluminal angioplasty; ALT, alanine transaminase; TGF-b1, transforming growth factor-beta; a-SMA, alpha-smooth muscle antibodies; TB, mycobacterium tuberculosis; ABMSC, autologous bone marrow stem cells; Treg/Th17, T regulatory cell/ T helper 17 cell; IL6, interleukin 6; IL 17, interleukin 17; TNF-α, tumor necrosis factor-alpha; pre-ALB, pre-albumin blood test; HGB, hemoglobin; PBS, (L17); AST, aspartate aminotransferase; IgM, serum immunoglobulins; DBIL, (L17); IL10, interleukin 10; PTT, partial thromboplastin time; Cr, creatinine; WBC, white blood cells; GGT, gamma-glutamyl transferase, BMA, Bone marrow aspirate; SC, stem cells; Pas, passage number; HCV, hepatitis C virus; PLT, platelets; CT, computed tomography.

A total of 16 studies , many of which are RCTs, have assessed the ability of intravascular stem cells to treat cerebral strokes of ischemic and nonischemic etiology. These are tabulated in Table 4. In 10 trials, MSCs were infused intravenously and in 5 IA. All studies evaluated the efficacy of MSCs in ischemic stroke, except one that was in hemorrhagic stroke. Cultured bone marrow MSCs and nonexpanded bone marrow mononuclear cells were used in 6 studies each; one study used both. One study utilized umbilical cord MSCs. Ten of the 15 studies showed improved neurologic functions, many measured by neurofunctional tests. Five of the 15 trials showed improvement in National Institutes of Health Stroke Scale, 4 out of the 15 trials showed improvement in Barthel index and modified Rankin score. Some trials have shown measurable increase in modulatory cells or trophic factors in the treated patients. No clinical response was seen in 6 studies, and nonexpanded bone marrow mononuclear cells were used in most of these trials. There were no serious adverse effects that were noticed during the postprocedural period on these patients. In one study (64), there was a higher number of safety measures in the treatment group, including deep vein thrombosis, pulmonary embolism, seizures, and rehospitalizations. Although these adverse events were not adjudicated as study-related, their increased frequency raises the possibility that they could have been associated with the intervention. There were no long-term teratogenic effects, and radiologic imaging has not shown any change in existing lesions or development of any new procedural-related lesions in any of these trials.

Table 4. *MSC therapy studies treating stroke.*

Author	Year	Type of study	Number of Patients in Treatment	BMA (mL)	Number of SC	Type of SC	Delivery	Outcome	Follow-Up	Findings
Bang et al, *Ann Neurol* 2005; 57:874-882	2005	RCT	30	5	100 million	Auto BM MSC	IV	Yes	1 year	Improvement of NIHSS, Barthel index, and modified Rankin score.
Lee et al, *Stem Cells* 2010; 28:1099-1106	2010	RCT	52	5	100million	Auto BM MSC	IV	Yes	118 weeks	Improvement in modified Rankin score
Honmou et al, *Brain* 2011; 134:1790-1807	2011	Case series	12	30–73	60–160 million	Auto BM MSC (Pas 3 or less)	IV	Yes	1 year	Improvement of NIHSS scores, correlation of lesion volume and NIHSS score.
Prasad et al, *Indian J Med Res* 2012; 136:221-228	2012	Case series	11	115	85 million	BM MNC	IV	No	1 year	No improvement in NIHSS, Barthel index, and modified Rankin score. No change in infarct volume.
Bashin et al, *Clin Neurol Neurosurg* 2013; 115:1003-1008	2013	PCT	20	40–50	50–60 million	Auto BM MNC or BM MSC (Pas 4)	IV	No	24 weeks	Modified Barthel index improved only at 8 weeks but not at 24 weeks. No change in FM, Ashworth, and MRC scores.
Jiang et al, *Cell Transplant* 2013; 22:2291-2298	2013	Case series	4	NA	20 million	UC MSC	IA (MCA)	Yes	6 months	Improvement in modified Rankin score seen only in ischemic stroke but not in hemorrhagic stroke.
Prasad et al, *Stroke* 2014; 45:3618-3624	2014	RCT	58	108	280 million	BM MNC	IV	No	1 year	No improvement in NIHSS and Barthel index.
Taguchi et al, *Stem Cells Dev* 2015; 24:2207-2218	2015	Case series	12	25 and 50	250 and 340 million	BM MNC	IV	Yes	120 days	Improvement of NIHSS scores in both high- and low-dose groups. No significant difference between the groups.
Hess et al, *Lancet Neurol* 2017; 16:360-368	2017	RCT	126	NA	400 and 1200 million cells	Multipotent progenitor cells	IV	No	1 year	No change in global stroke recovery or NIHSS or modified Barthel index.
Bhatia et al, *Am J Neuroradiol* 2018; 39:899-904	2018	RCT	20	118	930 million	BM MNC	IA MCA	Yes	6 months	Improvement in the modified Barthel index.
Levy et al, *Stroke* 2019; 50:2835-2841	2019	PCT	36	NA	0.5, 1, and 1.5 million/kg	Allo BM MSC (Pas 4)	IV	Yes	6 and 12 months	Improvements in NIHSS, Barthel index, mini mental status exam, and geriatric depression scale scores.
Savitz et al, *Circulation* 2019; 139:192-205	2019	RCT	100	150	3 million	BMSC	Carotid IA	No	1 year	No change in modified Rankin score, NIHSS, and Barthel index.
Tsang et al, *World J Stem Cells* 2017; 9:133-143	2017	RCT	9	29	14–84 million	BM MSC (Pas 4)	IV	Yes	60 weeks	Improvement in Barthel index and functional independence measure.
Moniche et al, *Stroke* 2012; 43:2242-2244	2012	PCT	10	50	159 million	BM MNC	IA	No	6 months	No change in Barthel index or neurologic function.
Friedrich et al, *Cell Transplant* 2012; 21(1 suppl):13-21	2012	Case series	20	50	2.2 million	BM MNC	IA	Yes	6 months	Improvement in NIHSS.

PCT, prospective controlled trial; NA, not applicable; BM MSC, bone marrow mesenchymal stem cell; BM MNC, bone marrow mononuclear cells; UC MSC, umbilical cord mesenchymal stem cell; SC, stem cell; BMSC, bone marrow stem cell; MCA, middle cerebral artery, NIHSS, National Institute of Health Stroke Scale, FM, Fufl-Meyer, MRC, Medical Research Council; BMA, bone marrow aspirate; Pas, passage number; Allo, allogeneic.

Table 5. *MSC therapy studies treating kidney failure.*

Author	Year	Type of Study	Number of Patients in Treatment Group	BMA (mL)	Number of MSC	Type of Stem Cell	Delivery Method	Outcome	Condition	Follow-Up	Findings
Liang et al, *ChinaXiv 2020; 1-13*	2010	Case series	15	NA	1 million	Allo BM MSC	IV	Yes	SLE	18 months	Decrease in proteinuria, 4 patients showed remarkable improvement in SLEDAI score. Stabilization of renal function. Improvement in GFR.
Sengupta et al, *Stem Cells Dev* 2020; 29:747-754	2013	Case series	12	162	85–232 million	BM MNC	IV	No	Idiopathic membranous nephropathy	6 months	Decrease in proteinuria and increase in serum albumin at 1 month and decrease in serum creatine for 6 months.
Gu et al, *Clin Rheumatol* 2014; 33:1611-1619	2014	Case series	81	20	1 million	Allo BM (23) or UC MSC (58)	IV	Yes	Lupus nephritis	12 months	Improved SLEDAI/BILAG scores and GFR, 60.5% achieved partial or complete remission.
Packham et al, *EBioMedicine* 2016; 12:263-269	2016	RCT	20	NA	150 million 10 patients and 300 million in 10 patients	Allo BM MSC	IV	No	Diabetic nephropathy	15 months	GFR stabilized in the MSC group, however, not statistically significant. Response better in patients with eGFR >30.
Deng et al, *Ann Rheum Dis* 2017; 76:1436-1439	2017	RCT	12	NA	2 billion, 2 doses 1 week apart	Allo UC MSC	IV	No	Lupus nephritis	12 months	75% remission in MSC group (9/12) and 83% (5/6) in control. Trial abandoned.
Makhlough et al, *Stem Cell Res Ther* 2017; 8:116	2017	Case series	6	10	2 million	BM MSC	IV	No	ADPKD	12 months	No significant change in eGFR or sCr.
Saad et al, *J Am Soc Nephrol* 2017; 28:2777-2785	2017	PCT	14	NA	100K–250K	Auto adipose MSC	RA	Yes	RVD	3 months	Cortical perfusion and RBF increased in the treatment group and renal hypoxia decreased. No change in renal artery patency. GFR stabilized.
Swaminathan et al, *J Am Soc Nephrol* 2018; 29:260-267	2018	RCT	156	NA	2 million	Allo BM MSC	Intraaortic	No	AKI postcardiac surgery	90 days	Did not reduce the time to recovery of kidney function, provision of dialysis, or mortality compared to placebo. Mortality or need for dialysis higher in MSC group, however, not statistically significant.
Makhlough et al, *Cytotherapy* 2018; 20:660-669	2018	Case series	7	Not disclosed	1–2 million	Auto BM MSC	IV	No	CKD	18 months	No significant change in eGFR or sCr.

PCT, prospective controlled trial; UC MSC, umbilical cord mesenchymal stem cells; BM MSC, bone marrow mesenchymal stem cells; CKD, chronic kidney disease; AKI, acute kidney injury; ADPKD, autosomal dominant polycystic kidney disease; SLE, systemic lupus erythematous; eGFR, estimated glomerular filtration rate; SLEDAI, Systemic Lupus Erythematous Disease Activity Index; BILAG, British Isles Lupus Assessment Group; RVD, atherosclerotic renovascular disease; RA, renal artery; GFR, glomerular filtration rate; BMA, bone marrow aspirate; NA, not available; Allo, allogeneic; MNC, mononuclear cells; sCr, serum creatinine; RBF, renal blood flow.

Kidney Failure

Kidney disease can be either acute or chronic, which can lead to decline in function and ultimately organ failure. Acute kidney injury is characterized by rapid loss of function and can occur from renal ischemia, crush injury, inflammation, or infection, whereas chronic kidney disease (CKD) is characterized by progressive loss of kidney function leading to end-stage renal disease. Many diseases and conditions, such as diabetes, polycystic kidney disease, autoimmune conditions, interstitial nephritis, recurrent infections, and others, can lead to CKD. This is a significant global public health problem causing significant morbidity and mortality.

Numerous studies have investigated the feasibility, safety, and efficacy of MSC-based therapies for kidney disease, which are described in Table 5. We looked at human clinical trials assessing the effect of MSCs in various conditions causing kidney disease. We found a total of 9 studies (5 case series, 3 RCTs, and 1 pragmatic clinical trial). Among these, 3 trials were on lupus nephritis , one on idiopathic membranous nephropathy, one RCT on diabetic nephropathy , one on renal vascular disease , and one RCT on acute kidney injury after cardiac surgery . There are 2 case series, one on polycystic kidney disease and one on CKD. Most of the studies used bone marrow MSCs, whereas 2 studies used human umbilical cord MSCs, and one study used adipose-derived MSC. Mesenchymal stromal cells were administered intravenously in 7 trials, whereas they were given intraaortic in one study, and via intrarenal artery in one study. Out of the 9 studies, only 3 studies had favorable outcomes (bone marrow mononuclear cells were used in only one of these trials). Two of these trials treated lupus nephritis and one treated patient with renovascular disease. Both the lupus studies showed improvement in SLEDAI (systemic lupus erythematosus disease activity index) scores, British Isles Lupus Assessment Group scores, and glomerular filtration rate. One of these studies also reported 60.5% partial or complete remission resulting in tapering the doses of the prednisone and immunosuppressive drugs. Cortical perfusion and renal blood flow improved in the renal vascular disease study. The rest of the studies failed to show any improvement in renal function. No complications were noted.

Clinical Trials for Biologics to Treat Seriously Ill COVID-19 Patients

Although there are numerous media reports purporting the success of parenteral expanded stem cells in treating COVID-19 patients, there have been very few published clinical trials. In the first reported study, 7 patients who were severely affected by COVID-19 and not responding to conventional treatment were treated with an IV dose of 1 million/kg cultured umbilical cord stem cells and compared with 3 patients in the control group receiving traditional treatment (40). Approximately 2 to 4 days after MSC treatment, patients had significant recovery with major resolution of the pulmonary computed tomography changes. Other organs apart from the lung were also involved in the patients of this trial. Biochemical indicators in the blood test showed that aspartic aminotransferase, creatine kinase activity, and myoglobin increased sharply, indicating severe damage to the liver and myocardium and decreased glomerular filtration rate (GFR), which reflected kidney failure. However, the levels of these functional biochemical indicators were decreased to normal reference values in 2 to 4 days after MSC treatment. The decrease in GFR also normalized after the infusion. All patients in the treatment arm recovered. However, in the control group, one patient died, whereas one patient developed ARDS, and the third patient recovered. No complications from MSC infusion were reported.

The second trial infused exosomes into 24 critical patients with COVID-19 who had moderate to severe ARDS (65). Significant improvements in oxygenation, neutrophil/lymphocyte counts, D-dimer, ferritin, and C-reactive protein were seen; 71% of patients recovered, 13% remained critically ill, and 16% died. No adverse reactions from the treatment were reported.

A case report of a 65-year-old woman diagnosed with COVID-19 was admitted as she was worsening symptomatically. She continued to deteriorate for the next 9 days with decreasing oxygen saturation coinciding with ground glass appearance on the x-ray and computed tomography scan. She also developed gastrorrhea and anemia necessitating blood transfusion. Elevated bilirubin and ALT/AST indicated liver failure. Because she was not responding to conventional treatment, including steroids, antivirals, antibiotics, and immunoglobulins, 3 doses of 50 million umbilical cord (UC) MSCs were infused 3 days apart. After the second dose, her liver and blood indices normalized, and she was eventually taken off the ventilator 5 days later. The patient was discharged from the ICU after 9 days (66).

There were 17 patients with ARDS from influenza A (H7N9) who were treated with 3 to 4 IV doses

of 1 million/kg of cultured menstrual stem cells in conjunction with standard treatment. Forty-four similar patients receiving conventional therapy without stem cell therapy served as controls. Matching was comparable except that patients in the treatment group had a higher incidence of shock, circulatory failure, fatigue, and shortness of breath than the control cohort. Regardless, the survival rate was significantly higher in the stem cell–treated groups versus control group (82.4% vs. 45.5%). Among patients who survived, stem cell group patients had significant improvement in procalcitonin, serum creatinine, 5-aminolevulinic acid, creatinine kinase, PT, and D-dimer levels when compared with the control group indicating improvement in multiorgan failure. No complications were noted during the trial and also among 4 of these patients who were followed for 5 years (39).

Early and preliminary data with small numbers seem to suggest that biologics can be promising and safe in patients with severe COVID-19 illness, especially if they are not responsive to conventional treatments.

Discussion

There is no treatment for COVID-19 complicated by ARDS, septic shock, and multiorgan failure, which is usually associated with a high mortality rate. Conventional treatments, such as antivirals, immunomodulators, such as chloroquine, hydroxychloroquine, and convalescent plasma, have not shown to be very effective. In a large trial, touted as one the best antiviral drugs for COVID-19, Remdesivir had a mortality rate of 8.0% versus 11.6% for the placebo group and this result was not statistically significant (67). Therefore it is urgent to find a safe and effective therapeutic approach to treat COVID-19 complications. Preliminary small studies with MSCs are showing promise in managing organ failures from different etiology and also in seriously ill COVID-19 patients who are not responding to traditional treatments. These studies have demonstrated that MSCs are capable of improving organ function by regeneration. Bone marrow stem cells have a 30-year history of safety and efficacy in the musculoskeletal arena (68). A meta-analysis of various studies using biologics to treat back pain has been encouraging (69). Because bone marrow MSCs seem to be FDA allowed, as they meet the "minimal manipulation" and "homologous use" criteria, they have been the most commonly used MSCs in the United States (68,70). Despite spending billions of dollars, conventional treatment has been uninspiring in treating back pain. MSC therapy seems to be filling this void and hopefully can mitigate the numerous problems associated with intractable pain, including opioid abuse (71). Early clinical trials have demonstrated that MSCs can be a valuable alternative for joint replacements and spinal fusions (68,70). Because preliminary evidence shows that MSCs have the potential to make strides in recalcitrant back and joint pain, especially in those who have failed conventional therapies, it is worthwhile to explore the role of MSCs in complicated COVID-19 patients, as meaningful alternatives do not currently exist. Based on early evidence that MSCs are safe and effective in seriously ill COVID-19 patients, a call for FDA approval for compassionate use was published as early as March 2020 (72). Fortunately, the FDA has been considerate and has approved various types of stem cell treatments to treat COVID-19, and as per media reports, the initial response is encouraging.

Organ failure is the culmination of various insults resulting in cellular death and dysfunction. Currently, there are no pharmaceuticals that can reverse cellular injury and unfortunately organs are not capable of meaningful self-regeneration. The only remaining option for severe liver, heart, or kidney failure is organ transplantation, but has inherent shortcomings, such as expense, accessibility (usually performed in tertiary settings), availability of donor organs, surgical complications, and lifelong immunosuppression. For certain organs, such as the brain, it is not an option. Based on the clinical evidence presented earlier, although stem cells cannot engraft (regardless of the route of administration) and differentiate into organ cells, they are, however, through their paracrine activity, capable of organ regeneration, restoring function and increasing the survival rates. Most importantly, as numerous studies have demonstrated, if MSC therapy is conducted appropriately, the complication rate seems to be negligible. Although MSCs are immunoprivileged they are not immune evasive. However, immune rejection, even after repeated doses of allogeneic MSCs, is a rare phenomenon (73). The concern of tumorigenicity exists for embryonic and iPSCs, however, it seems to be extremely low for adult and fetal stem cells (74). Because these donor cells rarely engraft and disappear within a few weeks, the risk of altering the recipient's karyotype or chimerism seems unlikely (75).

MSC therapy is fledgling science and hence draws skepticism, which is only partially justified (76). Unfortunately, this field has attracted a lot of unconscionable actors who prey on desperate patients primarily for financial reasons. Every step should be taken by the regulatory agencies to curb this malpractice. However, unwarranted criticism of the whole MSC therapy can be a grave disservice to suffering patients, conscientious physicians, and medical progress. Calls for responsible and safe use of MSCs have been made by principled physician organizations (77-79). Clearly more research needs to be performed to streamline the process of MSC therapy to achieve consistent outcomes as this field is still in its infancy. Some of the questions that remain unanswered are:

1. Which is the best MSC?
2. What is the best route of administration?
3. What is the optimal dose?
4. How many doses should be given?
5. What is the ideal passage number?
6. What is the best device to manufacture cells for "off-the-shelf" use?
7. What is the best medium to expand cells?
8. How to best cryopreserve the cells to preserve high viability?

Hopefully, in the near future, robust long-term research will provide answers to these seemingly resolvable issues culminating with a modern and novel therapy that can have a tremendous therapeutic potential.

MSC therapy has risks and they have been well summarized by Bauer et al (80). A total of 35 cases describing acute/chronic complications and death from MSC administration were identified: 19 cases came from the scientific literature, and 16 cases were mass media reports. Five of these were neoplastic in nature, 6 were related to infections, 2 neurologic, 6 cardiovascular, 2 autoimmune, and loss of vision in 3 patients. Eight deaths were also reported in this article. Additionally, 12 serious infections were reported from another report from using tainted umbilical cord product (81). Moreover, the CDC reported 6 more cases of infections from exosome therapy (82). To avoid complications, it is paramount that these procedures are performed by well-trained physicians using appropriate MSCs, which are produced under the strictest standards.

Conclusions

Serious complications from COVID-19 have a high mortality due to pulmonary and multiorgan failure. Currently, there are no treatments other than supportive care. MSC therapy, which is presently in infancy, seems to be promising in restoring functions of damaged tissues and organs because it can function as a "broad-spectrum" therapy. The medical community should harness the immunomodulatory, antiinflammatory, regenerative properties of these cells to heal patients who are refractory to conventional methods. Clearly more research is urgently needed to maximize the benefits of this novel treatment.

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