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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Stem Cells* (*WJSC*, *World J Stem Cells*) is to provide scholars and readers from various fields of stem cells with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJSC* publishes articles reporting research results obtained in the field of stem cell biology and regenerative medicine, related to the wide range of stem cells including embryonic stem cells, germline stem cells, tissue-specific stem cells, adult stem cells, mesenchymal stromal cells, induced pluripotent stem cells, embryonal carcinoma stem cells, hemangioblasts, lymphoid progenitor cells, *etc*.

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REVIEW

Mesenchymal stem cells as living anti-inflammatory therapy for COVID-19 related acute respiratory distress syndrome

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Abstract

Coronavirus disease 2019 (COVID-19), a pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), is growing at an exponential rate worldwide. Manifestations of this disease are heterogeneous; however, advanced cases often exhibit various acute respiratory distress syndrome-like symptoms, systemic inflammatory reactions, coagulopathy, and organ involvements. A common theme in advanced COVID-19 is unrestrained immune activation, classically referred to as a "cytokine storm", as well as deficiencies in immune regulatory mechanisms such as T regulatory cells. While mesenchymal stem cells (MSCs) themselves are objects of cytokine regulation, they can secrete cytokines to modulate immune cells by inducing anti-inflammatory regulatory Treg cells, macrophages and neutrophils; and by reducing the activation of T and B cells, dendritic and nature killer cells. Consequently, they have therapeutic potential for treating severe cases of COVID-19. Here we discuss the unique ability of MSCs, to act as a "living anti-inflammatory", which can "rebalance" the cytokine/immune responses to restore equilibrium. We also discuss current MSC trials and present different concepts for optimization of MSC therapy in patients with COVID-19 acute respiratory distress syndrome.

Key Words: Mesenchymal stem cells; SARS-CoV-2; COVID-19; Cytokine storm; Acute respiratory distress syndrome; Immunomodulation

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Core Tip: Coronavirus disease 2019 a disease caused by the severe acute respiratory syndrome coronavirus 2, is growing exponentially, with no treatments currently available. Preclinical and clinical studies have shown that mesenchymal stem cells (MSCs) work in reversing acute respiratory distress syndrome caused by other conditions such as influenza virus infection, or sepsis. In this review we discuss the unique ability of MSCs, to act as a "living anti-inflammatory", which can "rebalance" the cytokine/immune responses to restore equilibrium.

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INTRODUCTION

The severe respiratory consequences of the coronavirus disease 2019 (COVID-19) are caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with few effective treatments currently available. SARS-CoV-2 along with SARS-CoV and middle east respiratory syndrome coronavirus are coronaviruses that have caused significant human morbidity and mortality[1]. We are currently in the middle of a SARS-CoV-2 global pandemic. As of August 7, 2020, based on a Johns Hopkins University Coronavirus Resource Center Report, there have been at least 19.4 million confirmed cases worldwide, with at least 722706 deaths, and a mortality rate reaching approximately 3.7%. In the United States alone, approximately 5 million people are infected resulting in 161810 deaths and a mortality rate of 3.3%. COVID-19 infection of the lungs leads to extraordinary intensive care unit resource utilization and mortality.

One of the ways COVID-19 produces morbidity and mortality is by severely impairing lung function, causing a condition called acute respiratory distress syndrome (ARDS). This is characterized by a rapid onset of cytokine storm widespread lung inflammation, and sepsis-like conditions. Currently there is no effective anti-viral treatment for COVID-19. However, a few therapeutic strategies have been tested in the clinic or in trials for the treatment of patients with COVID-19. The anti-viral remdesivir can reduce death risk of severe COVID-19 patients as much as 62% when compared with standard care alone. Other anti-viral drugs such as but not limited to lopinavir-ritonavir, favipiravir, chloroquine and hydroxychloroquine have been proposed to treat COVID-19. Many of these anti-viral agents are currently being tested in clinical trials. Anti-inflammatory drugs such as dexamethasone were found to have beneficial effects in critically ill COVID-19 patients. Additionally, tocilizumab and siltuximab are interleukin-6 inhibitors being studied as therapeutics in critically ill patients with severe respiratory failure and elevated serum IL-6. The immunomodulatory functions of mesenchymal stem cells (MSCs) have been well documented in recent years. While MSCs themselves are objects of cytokine regulation, they can secrete cytokines to modulate immune cells by inducing anti-inflammatory regulatory Treg (T) cells, macrophages and neutrophils; and by reducing the activation of T and B cells, dendritic and nature killer (NK) cells. Consequently, they have therapeutic potential for treating severe cases of COVID-19.

Preclinical and clinical studies have shown that MSCs work in reversing ARDS caused by other conditions such as influenza virus infection, or sepsis. For example, MSCs derived from adipose[2-5], bone marrow[6-25], placental[26], amniotic membrane[27,28], umbilical cord[29-35], menstrual blood[36], and lung[37,38] origin, as well as conditioned media[39-46], have demonstrated reduction of pulmonary injury, and neutrophil accumulation. Early clinical trials[47,48] have shown safety of systemic infusions and bronchial instillations of MSCs for treating ARDS and other pulmonary complications. Most recently small studies[49,50] have also suggested that MSCs can be effective in COVID-19 ARDS; however, these approaches have not been well validated. In this review, we discuss the immunomodulatory effects of stem cells and the role of MSCs as potential therapeutic options for cytokine storm and/or ARDS in COVID-19.

COVID-19 AND ITS PATHOLOGY

SARS-CoV-2 enters host cells through the angiotensin converting enzyme 2 (ACE2) receptor. ACE2 expression was found to be high in the lung, heart, ileum, kidney and bladder[51]. ACE2 is highly expressed on the apical side of lung epithelial cells in the alveolar space, which is how SARS-CoV-2 virus can likely enter and destroy these cells. This is probably why early lung injury was often seen in the distal airway. The issue now becomes in what way does the immune system respond to viral infection in the lung. Innate immunity in the airway mainly includes epithelial cells, alveolar macrophages and dendritic cells. They fight against the virus until adaptive immunity is initiated. T cell mediated responses are initiated by antigen presentation *via* dendritic cells and macrophages. CD4+ T cells activate B cells to promote the production of virus-specific antibody CD8+ T cells which can kill virus infected cells. Approximately 80% percent of patients with COVID-19 are asymptomatic or experience only mild symptoms such as fever, dry cough and shortness of breath. However, some patients deteriorate quickly and develop ARDS[52]. Patients with severe diseases were reported to have increased plasma levels of proinflammatory cytokines, including IL-6, IL-8, IL-10, GM-CSF, macrophage inflammatory protein 1-alpha, and TNF-alpha[53].

Information regarding the pathological findings in COVID-19 is still limited, although several reports on this topic have been published recently. Xu *et al*[54] reported one case where the patient presented 15 d of symptoms. Biopsy samples from both lungs showed bilateral diffuse alveolar damage[55] with cellular fibromyxoid exudates and hyaline membrane formation, indicating ARDS in both lungs. Noteworthy is the observation that the pathological features of COVID-19 greatly resemble those seen in SARS and middle east respiratory syndrome coronavirus infections[56,57]. In addition, over-activation of T-cells was manifested by an increase of Th17 and high cytotoxicity of CD8 T cells, partially accounting for the severe immune injury in the patient.

Tian *et al*[58] described the early histopathological features in two patients who underwent postmortem for lung cancer but were later discovered to have had COVID-19 upon resection. The results of the lung evaluation from the two patients exhibited only nonspecific histologic changes, including edema, proteinaceous exudate, hyperplastic pneumocytes, patchy inflammation, and multinucleated giant cells with no hyaline membrane. Given that the two patients were asymptomatic from COVID-19 at the time of postmortem, they were likely only in the early stages of acute lung injury from the infection[58]. Tian *et al*[59] also conducted another postmortem study of four COVID-19 patients with a minimum of 15 days of symptoms, demonstrated ARDS in all biopsies.

Two COVID-19 autopsies on the lungs of a 77-year-old man revealing diffuse alveolar damage, the most common histopathologic correlation with ARDS, and on the lungs of a 42-year-old man presenting no evidence of diffuse alveolar damage/ARDS[60]. Magro *et al*[61] demonstrated in a report of five cases that diffuse alveolar damage was not prominent with the presentation of hyaline membranes, inflammation, and type II pneumocyte hyperplasia, all hallmarks of classic ARDS. These pulmonary findings were accompanied by significant deposits of terminal complement components C5b-9, C4d, and mannose binding lectin-associated serine protease 2, in the microvasculature, consistent with sustained, systemic activation of the alternative and lectin-based complement pathways. There was co-localization of COVID-19 spike glycoproteins with C4d and C5b-9 in the interalveolar septa and the cutaneous microvasculature of two cases examined. This indicated the pathophysiologic importance of complement in COVID-19. The results suggest that at least a subset of severe COVID-19 infection involves a catastrophic, complement-medicated thrombotic microvascular injury syndrome with sustained activation of the alternative and lectin-based cascades, possible pathways apart from virus spike protein engagement.

In general, ARDS is a common manifestation of cytokine storms and as well could be the cause of death in many COVID-19 patients, although other mechanisms may also be involved. A better understanding of COVID-19 patients' underlying pathogenesis will pave the way for formulating a timely therapeutic strategy to reduce mortality.

MSCS IMMUNOMODULATORY EFFECTS

MSCs are fibroblast-like and multipotent stromal cells. Human MSCs are positive for a number of cell surface markers including CD73, CD44, CD90, and CD105 and negative for the hematopoietic markers of CD34, CD45 and HLA-DR[62]. MSCs are traditionally isolated from bone marrow, and a variety of fetal, neonatal and adult tissues, including cord blood, peripheral blood, fetal liver and lung, adipose tissue, compact bone, dental pulp, dermis, endometrial, human islet, adult brain, skeletal muscle, amniotic fluid, synovium, and the circulatory system[63-65]. MSCs can differentiate into a variety of cell types of mesodermal origin, including osteoblasts, chondrocytes, cardiomyocytes, neural cells, smooth muscle cells and adipocytes[62,66-68]. MSCs are likely the only stem cell type that possesses both regenerative and immunomodulatory capabilities. Consequently, they have been used widely in the treatment of many degenerative and inflammatory diseases.

One property that greatly increases the value of MSCs in therapeutic applications is their ability to modulate immune responses. MSCs can exert their immunomodulatory function by producing many molecules having immunomodulatory effects, these include prostaglandin E2 (PGE2)[69], nitric oxide[70], indolamine 2,3-dioxigenase (IDO)[71], transforming growth factor beta[72,73], IL-6[74,75], hemoxygenase-1[76], leukocyte inhibitory factor[77], HLAG5 and chemokines[78], PDL1/2[79] and other surface markers-FasL[80]. MSCs can escape the immune system because bone marrow derived MSCs (BM-MSCs) are not recognized by NK cells as they lack expression of HLA Class I surface markers. They also lack expression of HLA Class II antigens, which is desirable for transplantation applications.

The immunosuppressive activity of MSCs is well described, with recent reports providing some mechanistic insights into key soluble factors and receptors. Programmed death-ligand 1/CD274 also known as B7 Homolog 1 (B7-H1) has been shown to be expressed in cultured MSCs and is strongly upregulated following IFN-γ stimulation. Combination therapy using rapamycin and MSCs induced immune tolerance to allografts, but monoclonal antibodies against B7-H1 were shown to abrogate this tolerance leading to allograft rejection[81]. The immunomodulatory effects of MSCs were mediated in part through upregulation of regulatory immune cells including $CD4^+CD25^+FoxP3^+$ T cells[82,83] and tolerogenic dendritic cells[84] and a decrease in alloantibody levels. MSCs that expressed B7H1 may also induce the apoptosis of activated T-cells as a co-culture of CD4+CD25- T cells with MSCs resulting in significant upregulation of programmed cell death-1 receptor (PD-1) on activated T cells[85]. Similar results were reported by Chinnadurai *et al*[86] who further examined the role of IFN-γ in the "licensing" of MSCs to inhibit the proliferation of activated T cells[86]. Both MSCs and IFN-γ licensed MSCs inhibited T-cell proliferation; however, only IFN-γ licensed MSCs significantly inhibited Th1 cytokine (IFN-γ, TNFα and IL-2) production as well as T-cell degranulation. This IFN-γ licensed MSCs inhibitory effect on T-cells is thought to be dependent on IDO[71]; however, Chinnadurai showed that MSC IDO catalytic function is dispensable with regard to MSC driven T-cell inhibition. Chinnadurai *et al*[86] identified the B7-H1 PD1 pathways as essential effectors in blocking T-cell function. Further complexity was also suggested by a recent report that IFN-γ treatment of MSCs upregulated HLA-DR /Class II MHC after 48 h, and MSCs ability to inhibit T cells through B7-H1 was dependent upon the presence of HLA-DR[87].

MSCs express the adhesion molecules VCAM-1 and ICAM-1, which allow T-lymphocytes to adhere to their surface. Subsequently MSCs can affect them by molecules which have a short half-life. Their effect is in the immediate vicinity of the cell[70]. Examples of such molecules include nitric oxide, PGE2, HGF[88], and activation of receptor PD-1. MSCs reduce T cell proliferation between G0 and G1 cell cycle phases G[89], and decrease the expression of IFNγ of Th1 cells while increasing the expression of IL-4 of Th2 cells[90]. MSCs also inhibit the proliferation of B-lymphocytes between G0 and G1 cell cycle phases.

A novel mechanism for MSC-induced immunosuppression was recently proposed by Obermajer and colleagues who showed that cells of the Th17 type, predominantly associated with the rejection of allogeneic solid organ grafts, can be directly converted into a regulatory T cell type[91]. The induction of Tregs was preceded by development of a CD11b(hi)Gr1(int) myeloid-derived immunosuppressive cell-mediated Th17. They identified retinoic acid receptor-related orphan receptor γ as a common factor in the differentiation of T and Th17 cells. The identification of a specific subset of T cells IL-$17A^+Foxp3^+$ double-positive and ex-IL-17^- producing IL-17A-$Foxp3^+$ in this paper argues for direct conversion as the mechanism for MSC-mediated immuno-tolerance. This proposed mechanism where MSC-induced myeloid-derived immunosuppressive

cells act as mediator for immune tolerance without complete immunosuppression may have significant implications for therapeutic applications.

MSCs have an effect on macrophages, neutrophils, NK cells, mast cells and dendritic cells in innate immunity and effector T cells, regulatory T cells, and B cells in adaptive immunity illustrated in Figure 1. In severe COVID-19 patients, their immune responses to SARS-CoV-2 infection are usually over-activated. MSCs are able to exert their anti-inflammatory effect by regulating immune cells and balancing the immune responses. Furthermore, MSCs can migrate to the site of injury, where they polarize through GE2 macrophages into phenotype-2 which is characterized by an anti-inflammatory effect[92,93]. Further, PGE2 inhibits the ability of mast cells to degranulate and produce TNF-α. Proliferation and cytotoxic activity of NK cells are inhibited by PGE2 and IDO. MSCs also reduce the expression of NK cell receptors-NKG2D, NKp44 and NKp30[94], MSCs inhibit respiratory flare and apoptosis of neutrophils by production of cytokines IL-6 and IL-8[95]. Differentiation and expression of dendritic cell surface markers is inhibited by IL-6 and PGE2 of MSCs[96]. The immunosuppressive effects of MSCs also depend on IL-10, but it is not certain whether they produce it alone, or only stimulate other cells to produce it[97,98].

MSCS THERAPY FOR INHIBITION OF ACUTE INFLAMMATION AND CYTOKINE STORM

MSCs have been shown to possess a comprehensive and powerful immunomodulatory function to suppress excessive activation of the immune system, thus promoting endogenous repair by improving the microenvironment. There have been 13 MSCs therapies approved for treating a number of conditions (Table 1) outside of the United States, mainly in the EU, Japan, South Korea and India. Among the conditions, two adipose tissue derived MSC products, Alofisel® and Cupistem®, have been used for complex perianal fistulas in Crohn's disease. The underlying mechanism of action is the MSC immunomodulatory and anti-inflammatory effects at the inflammation sites. Specifically MSCs impair proliferation of activated lymphocytes and reduce the inflammatory cytokines. Two BM-MSC products, Prochymal® and Temcell® HS, have been used for treating GvHD, due to MSCs immunomodulatory effects.

Preclinical study has demonstrated that MSCs can inhibit the progress of acute inflammation in the lungs and alleviate symptoms of respiratory distress[99]. The feasibility of utilizing MSCs for the treatment of ARDS has been demonstrated in animal models and extracorporeal lung models[100]. MSCs of adipose, bone marrow, placental, amniotic membrane, umbilical cord, menstrual blood, and lung, origin, as well as conditioned media with secreted exosomes, have demonstrated a reduction of pulmonary injury and neutrophil accumulation. In a recent study using a sheep model of ARDS[9], both endobronchial and intravenous administration of bone marrow-derived multipotent adult progenitor cells were effective for the treatment of ARDS.

Additionally, an analysis of 342 systemic infusions and 57 bronchial instillations (204 recipients) of cells of various origins for ARDS and other pulmonary issues demonstrated safety in early human clinical trials[47]. Recently, a study involving two patients with severe refractory ARDS, both showed improvement[99]. Both patients received 2×10^6 cells per kilogram of body weight. Subsequently, each of the patients improved with resolution of respiratory, hemodynamic, and multiorgan failure. In parallel, a decrease was seen in multiple pulmonary and systemic markers of inflammation, including epithelial apoptosis, alveolar-capillary fluid leakage, proinflammatory cytokines, microRNAs, and chemokines. *In vitro* studies of the MSCs demonstrated a broad anti-inflammatory capacity, including suppression of T-cell responses and induction of regulatory phenotypes in T cells, monocytes, and neutrophils. Some of these *in vitro* potency assessments correlated with, and were relevant to, the observed *in vivo* actions.

RECENT SUCCESS OF MSCS FOR COVID-19 PATIENTS AND CLINICAL TRIALS

Currently, drugs alone or in combination with other therapeutic approaches have not afforded a cure; however a number of investigational drugs in clinical trials, including antivirals such as chloroquine/hydroxychloroquine, remdesivir, immune-based

Table 1 Approved mesenchymal stem cell therapies outside of United States in the past 20 years

	Product name	Source	Autologous/Allogeneic	Indication	Company/Country
1	Alofisel	Adipose tissue-derived stem cells	Allogeneic	Complex perianal fistuals in Crohn's disease	TiGenix NV/Takeda PharmaceuticalEU
2	Chondrocytes-T-Ortho-ACI	Chondrocyte	Autologous	Cartilage damage, lesions and defects	Ortho Cell, Australia
3	Spherox	Chondrocyte	Autologous	Symptomatic articular cartilage defects	CO.DON AG, Germany and EU
4	Ossgrow	BM-MSCs	Autologous	Avascular necrosis	Regrow, India
5	Stempeucel	BM-MSCs	Allogeneic	CLI	Stempeutics, India
6	Porchymal	BM-MSCs	Allogeneic	GvHD in children	Osiris Therapeutics, Canada
7	Temcell HS	BM-MSCs	Allogeneic	GvHD	JCR Pharmaceuticals, Japan
8	NeuroNata-R	BM-MSCs	Autologous	Lou Gehrig's disease, or ALS	Corestem, Korea
9	Cupistem	AT-MSCs	Autologous	Crohn's fistula	Anterogen, Korea
10	Cartistem,	UC-blood-derived MSCs	Allogeneic	Damaged cartilage	Medipost Inc., Korea
11	Cellgram-AMI	BM-MSCs	Autologous	Acute myocardial infarction	Pharmicell, Korea
12	AstroStem	AT-MSCs	Autologous	Alzheimer's disease	Nature cell, Korea
13	Stemilac	BM-MSCs	Autologous	Alzheimer's disease	Nipro and Sapporo Medical University, Japan

MSCs: Mesenchymal stem cells; BM-MSCs: Bone marrow derived mesenchymal stem cells; EU: European Union; UC-MSCs: Umbilical cord mesenchymal stem cells; AT-MSCs: Adipose tissue-derived mesenchymal stem cells.

therapies and adjunctive therapies have shown promise, particularly in mitigating certain systemic markers according to NIH COVID-19 Guidelines. Potential antiviral drugs: remdesivir, chloroquine or hydroxychloroquine, hydroxychloroquine plus azithromycin, lopinavir/ritonavir and other HIV protease inhibitors. Immune-based therapy under evaluation: Convalescent plasma, Immunoglobulins: SAR-CoV-2-specific and non-SAR-CoV-2 specific, MSCs, Corticosteroids, Interferons alpha and beta, IL-1 and IL-6 inhibitors, Kinase inhibitors: Bruton's tyrosine kinase inhibitors and Janus kinase inhibitors; Adjunctive therapy: antithrombotic therapy, vitamin C and vitamin D, zinc supplementation.

To date, there are over 50 clinical trials using MSCs to treat COVID-19 patients based on the registration in clinicaltrial.gov website, we listed the most relevant studies in Table 2. Umbilical cord MSCs (UC-MSCs), BM-MSCs, AT-MSCs and other MSCs, as well as exosomes from MSCs are used in clinical trials, among them UC-MSCs are the most desirable for treating severely compromised COVID-19 patients due to its rich and extensive source of stem cells, scalable expansion capability, and ability to be allogeneic as low MHC-I expression[49]. The dose and delivery times are also varied in different trials. Recent reviews have described the potential for and rationale of using different types of MSCs for treating severe COVID-19 patients to protect alveolar epithelial cells, to reclaim the pulmonary microenvironment, to induce anti-inflammatory macrophages, regulatory T and B cells, and regulatory dendritic cells. In addition, MSCs can inactivate T cells in order to prevent cytokine storm, prevent pulmonary fibrosis and cure lung dysfunction[101-104]. Details of MSCs clinical trials for COVID-19 have also been discussed in other reviews[101,104-106].

MSCs have been used effectively to treat patients with COVID-19 in recent reports[50,107,108]. The underlying processes involve preventing the cytokine storm from occurring as well as reversing the cytokine storm in compromised patients. A total of seven patients with COVID-19 were enrolled in the study[50], the results have shown that MSCs significantly improved the functional outcome without observed adverse effects. The pulmonary function and symptoms of these patients were significantly improved in two days after MSC transplantation. Among them, two common and one severe patient recovered and were discharged within 10 d after the treatment. Compared to the placebo control group, the level of TNF-alpha was significantly decreased, and IL-10 increased in the MSCs treatment group. The gene profile showed MSCs were ACE2- and TMPRSS2- which indicate MSCs are free from COVID-19

Table 2 The most relevant clinical trials of mesenchymal stem cell treating COVID-19 patients

NCT number	Cell type	Autologous	Phase	Sponsor
NCT04490486	UC-MSCs	Allogeneic	I	Joshua M Hare, United States
NCT04456361	UC-MSCs	Allogeneic	I	Instituto de Medicina Regenerativa, Mexico
NCT04313322	UC -MSCs	Allogeneic	I	Stem Cells, Arabia
NCT04288102	MSCs	NA	II	Beijing 302 Hospital
NCT04346368	BM-MSCs	NA	I/II	Guangzhou Institute of Respiratory Disease
NCT04366323	Adipose-derived MSCs	Allogeneic	I/II	Andalusian Network for Design and Translation of Advanced Therapies
NCT04273646	UC-MSCs	Allogeneic	I	Wuhan Union Hospital, China
NCT04349631	Adipose-derived MSCs	Autologous	II	Hope Biosciences
NCT04339660	UC-MSCs	Allogeneic	I/II	Puren Hospital Affiliated to Wuhan University of Science and Technology
NCT04366063	MSCs	NA	II/III	Royan Institute
NCT04352803	Adipose-derived MSCs	Autologous	I	Regeneris Medical
NCT04355728	UC-MSCs	Allogeneic	I/II	Camillo Ricordi
NCT04366271	UC-MSCs	Allogeneic	II	Hospital Infantil Universitario Niño Jesús, Madrid, Spain
NCT04348461	Adipose-derived MSCs	Allogeneic	I	Instituto de Investigación Sanitaria de la Fundación Jiménez Díaz
NCT04345601	BM-MSCs	Allogeneic	I	Baylor College of Medicine
NCT03042143	UC-MSCs (CD362 enriched)	Allogeneic	I/II	Belfast Health and Social Care Trust
NCT04361942	MSCs	Allogeneic	II	Red de Terapia Celular
NCT04269525	UC-MSCs	Allogeneic	II	Zhi-Yong Peng, Hospital
NCT04333368	UC-MSCs	Allogeneic	I	Assistance Publique - Hôpitaux de Paris
NCT04299152	Cord blood stem cells (CB-SC)	Allogeneic	II	Tianhe Stem Cell Biotechnologies Inc.
NCT04341610	Adipose-derived MSCs	Allogeneic	I/II	Rigshospitalet, Denmark
NCT04276987	Adipose MSC-derived exosomes (inhalation)	Allogeneic	I	Ruijin Hospital
NCT03857841	BM-MSC derived extracellular vesicles (UNEX-42)	Allogeneic	I	United Therapeutics

MSC: Mesenchymal stem cells; BM-MSC: Bone marrow derived mesenchymal stem cells; UC-MSCs: Umbilical cord mesenchymal stem cells.

infection. In another case report[107], UC-MSCs were infused into a severely compromised COVID-19 patient. The pulmonary function and symptoms of the patient were significantly improved in 2 d after UC-MSCs transplantation. The patient recovered and was discharged in 7 d after treatment. The percentage and counts of lymphocyte subsets (CD3, CD4, and CD8 T cell) were increased, and the level of IL-6, TNF-α, and C-reactive protein was shown to have significantly decreased after UC-MSCs treatment. Guo *et al*[108] reported a 31-patient trial with UC-MSCs infusion. After the first infusion of UC-MSCs, the SARS-CoV-2 PCR results of 30 patients (96.8%) became negative after a mean time of 10.7 d (SD, 4.2 d). Laboratory parameters tended to improve after UC-MSCs therapy compared to the status before treatment, including elevated lymphocyte count, decreased C-reactive protein and IL-6 levels. Thus far, the intravenous transplantation of MSCs has been shown to be effective for the treatment of patients with COVID-19 pneumonia, especially for the patients in critical condition.

Exosomes derived from MSCs have been studied in clinical trials for treating severely compromised COVID-19 patients[104,109,110]. Exosomes (ExoFlo™) derived from allogeneic bone marrow MSCs in a single 15 mL dose were evaluated in a 24-patient trial[110] for both safety and efficacy from days 1 to 14 post-treatment. No adverse events were observed; a survival rate of 83% was observed; 71 patents recovered, 13% remained critically ill though stable, and 16% patients expired for reasons unrelated to the treatment. Overall, after one treatment, patients' clinical status and oxygenation improved with an average pressure of arterial oxygen to fraction of inspired oxygen

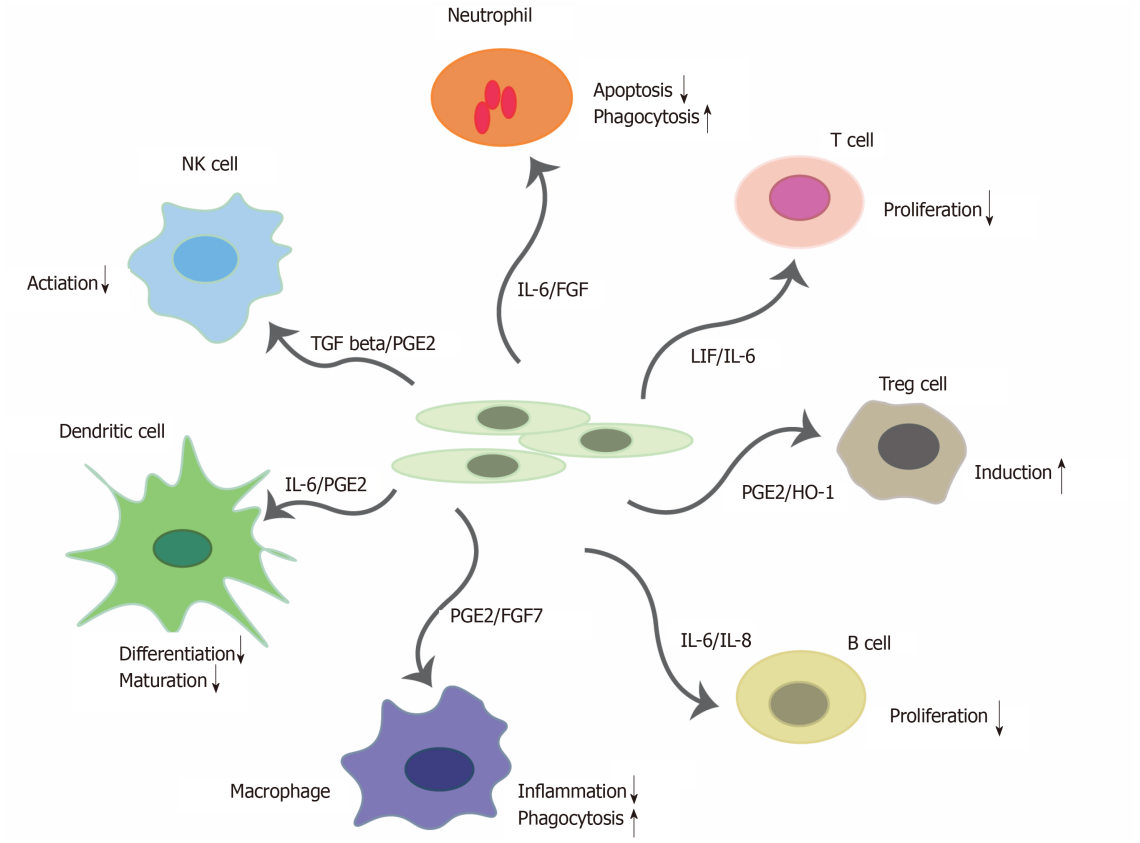

Figure 1 Immunomodulatory effects of mesenchymal stem cells on immune cells. Mesenchymal stem cells secrete cytokines to modulate immune cells by inducing anti-inflammatory regulatory Treg cells, macrophages and neutrophils, reducing the activation of Treg and B cells, dendritic and nature killer cells. T cell: Treg cell; PGE2: Prostaglandin E2; NK cell: Nature killer cell.

ratio (PaO_2/FiO_2) increase of 192%. Laboratory values revealed significant improvements in absolute neutrophil count and lymphopenia with average $CD3^+$, $CD4^+$, and $CD8^+$ lymphocyte counts increasing by 46%, 45%, and 46%, respectively. Likewise, acute phase reactants declined, with mean C-reactive protein, ferritin, and D-dimer reduction of 77%, 43%, and 42%, respectively. The study demonstrated the excellent safety profile and capacity to restore oxygenation, downregulate cytokine storm, and reconstitute immunity. Exosome derived from MSCs is a promising therapeutic candidate for severely compromised COVID-19 patients.

CONCLUSION

The social burden of COVID-19 is growing with the global pandemic. However, there is no effective or curative therapy for COVID-19, and preventive vaccines, other than the vaccine recently approved in Russia, but for which there is limited information, are still under development and will not be available until next year. The most recent clinical trials with MSCs may fulfill the unmet medical need of COVID-19, to reduce the related ARDS and cytokine storm. There are several issues that need to be addressed in order to move forward: dose, delivery times, type of MSCs, efficacy and cost-effectiveness. An understanding of all facets of MSCs and pathomechanism of COVID-19 is necessary to fully translate the MSCs therapy into a meaningful treatment for COVID-19. The next therapeutic strategies may focus on a combination approach using two or more types of MSCs, certain type of MSCs, and immune-based therapies or antiviral therapies to achieve maximal therapeutic efficacy.

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