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MINI-REVIEW ARTICLE

Feasibility of Mesenchymal Stem Cell Therapy for COVID-19: A Mini Review

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Abstract: Patients infected with SARS-CoV-2 carry the coronavirus disease 2019 (COVID-19) which involves multiple systems and organs with acute respiratory distress syndrome (ARDS) as the most common complication, largely due to cytokine storms or dysregulated immunity. As such, there are many severe patients with complications such as cytokine storm syndrome (CSS), who have a high fatality rate. Neither specific anti-SARS-CoV-2 drugs nor vaccines exist currently. Current treatment relies mainly on self-recovery through patients' immune function. Mesenchymal stem cells (MSCs) is a kind of multipotent tissue stem cells, which have powerful anti-inflammatory and immune regulatory functions, inhibiting the cytokine storms. In addition, MSCs have a strong ability to repair tissue damage and reduce the risk of severe complications such as acute lung injury and ARDS, and hopefully, reduce the fatality rate in these patients. There are several clinical types of research completed for treating COVID-19 with MSCs, all reporting restoration of T cells and clinical safety. Here we discuss the clinical prospect and conclude the therapeutic effects and potential mechanism for MSCs in treating COVID-19.

Keywords: Mesenchymal stem cells, immune, regulate, repair, COVID-19, secretome.

1. INTRODUCTION

Coronavirus Disease 2019 (COVID-19), an emerging global health challenge, demands global efforts to develop effective treatment strategies. Most patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presented mild to moderate course of the disease, and recovered within two or three weeks [1]. However, about 15% of the patients have progressed to severe stages with complications such as acute respiratory distress syndrome (ARDS) and cytokine storm syndrome (CSS) [2].

The SARS-CoV-2 infection may affect primarily T lymphocytes, resulting in significant decrease in cellular density [3]. As noticed, mild to moderate lymphocytopenia, in association with a high WBC-count, is often seen in severe COVID-19 patients [4]. Flow analysis of peripheral blood of patients showed a decreased number but increased activity of CD4+ and CD8+ T cells. Both T helper cells 17 (Th17) and highly cytotoxic CD8+ T cells cause severe immune damage [4, 5]. High plasma concentrations of both pro-inflammatory cytokines and anti-inflammatory cytokines or cytokine storms might be associated with disease severity. Suppressing the excessive immune response has become the key difficulty in therapeutic strategies.

Currently, the treatment of COVID-19 is either supportive or symptomatic, including antiviral, antibiotics and traditional Chinese medicine [5]. Since it takes a long time to develop a specific vaccine, cell-based therapy and especially stem cell therapy has become a promising therapeutic approach [6]. Mesenchymal stem cells (MSCs) have been employed extensively in cell therapy, which includes a plethora of preclinical research investigations as well as a significant number of clinical trials [7]. As early as February 21, 2020, four patients with severe COVID-19 were recovered and discharged by MSCs therapy in China [8]. Besides, there have been reports of early phase clinical studies in COVID-19 patients from China registered on the website ClinicalTrails.gov [9]. At present, MSCs have become one of the most potential options for COVID-19 treatment. Here we

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reviewed the recently published articles about MSCs and COVID-19, concluding all the completed researches and proposing the underlying mechanisms of this novel therapy in order to provide guidance for future treatment.

2. MSCs AND COVID-19

We reviewed published studies of MSCs treatment for COVID-19 with electronic searches of MEDLINE/PubMed, EMBASE, and Cochrane Libraries using the terms "COVID-19" and "mesenchymal stem cells". Recently published completed clinical researches about MSCs for treating COVID-19 are concluded and listed in Table **1**.

MSCs, derived from various tissues such as bone marrow and adipose tissues, including those in umbilical cord, dental pulp, menstrual-blood, buccal fat pad, fetal liver, *etc*., have been used for immune modulation in various autoimmune disorders [10]. As recently reviewed, treatment with MSCs improved disease-associated parameters in ARDS as well as bronchopulmonary dysplasia, chronic obstructive pulmonary disease, pulmonary hypertension and idiopathic pulmonary fibrosis [11]. Some clinical trials for evaluating the efficacy and safety of MSCs treatment on acute lung injury (ALI)/ ARDS have begun [8], which are eagerly awaited and will shed light on our understanding of the therapeutic role of MSCs to combat with COVID-19.

MSCs suppress overactive immune responses. This immunoregulatory effect of MSCs has potential therapy in severe COVID-19 patients with dysfunction of the adaptive immune system after SARS-CoV-2 infection. MSCs also bring about tissue regeneration and repair [12]. Therefore, infusion of multipotent MSCs may help alleviate COVID-19, as these cells could not only inhibit excessive immune response but also promote the endogenous repair of pulmonary epithelial cells by improving the microenvironment [13].

Based on previous experiences with MSCs therapy in COVID-19 patients, it can be hypothesized that administering the patients with an infusion of multipotent MSCs can help to combat with COVID-19 as these cells could inhibit the exaggerated immune response, prevent the triggering of cytokine storms and promote endogenous repair of the lung epithelial cells [13].

2.1. Immunoregulation

MSCs can alter the behavior of both adaptive and innate immune systems by regulating immune cells, including T cells, B cells, dendritic cells (DCs), natural killer (NK) cells, neutrophils, and macrophages, and a variety of cytokines to suppress the excessive immune activation.

To alleviate acute respiratory symptoms in SARS-CoV-2-infected patients, MSCs inhibit the activation of cytotoxic CD8+ T cells, thereby reducing direct injury to lung parenchyma [14]. MSCs can change the cytokine secretion profile of subset T cells and then inhibit the activation of TH1 and TH17 cells. Besides, activated Tregs can regulate T cell activity and decrease the production of inflammatory cytokines [15]. MSCs can also inhibit the excessive proliferation of B cells and prevent their differentiation to plasma cells, thus reducing the production and secretion of immunoglobulin [16].

As for the innate immunity, MSCs can alter the cytokine secretion profile of DCs subsets and reduce the activity and maturity of DCs. Besides, MSCs can down-regulate the expression of NK activation receptors, decreasing the release of interferon γ (IFN-γ) and inhibiting its cytotoxic activity. It has been proved that MSCs can decrease the chemotaxis of neutrophils. MSCs can enhance the differentiation of macrophages by inhibiting the expression of M1 macrophage specific genes, and then promote M1 macrophages transform to M2 macrophages [17].

Previous studies have shown that MSCs can decrease the production of cytokine storm-related inflammatory factors, such as (interleukin-1a) IL-1a, (interleukin-6) IL-6, IFN-γ and tumor necrosis factor-alpha (TNF -α). Immune cells, including T cells are suppressed and the levels of anti-inflammatory factors increase, especially interleukin-10 (IL-10). In addition, MSCs can modulate the activation and effector function of immune cells, and prevent the CSS [18].

2.2. Repair Effect

Pathological examination reveals diffuse alveolar damage in the lungs of COVID-19 patients. SARS-CoV-2 could over-activate the immune system while invading alveolar epithelium and blood vessels, leading to ARDS and other acute lung injuries.

Table 1. Completed researches on MSCs for treating COVID-19. This table summarizes published clinical researches about MSCs treatment of COVID-19*.

Study	Sources of MSCs	Numbers of Participants	Research Period	PaO_2/FiO_2	CRP	T Cell Counts	Safety Evaluation
Liang 2020	hUCMSCs	1	January 3 - February 21, 2020	↑	↓	↑	Yes
Guo 2020	hUCMSCs	31	January 3 - April 4, 2020	↑	↓	↑	Yes
Leng 2020	MSCs	7	January 23 - February 16, 2020	↑	↓	↑	Yes
Zhang 2020	hWJCs	1	February 24 - March 2, 2020	↑	↓	↑	Yes
Sengupta 2020	bmMSC	24	April 8 - April 28, 2020	↑	↓	↑	Yes

* bmMSCs: bone marrow MSCs; hUCMSCs: human umbilical cord MSCs; hWJCs: human umbilical cord Wharton's jelly-derived MSCs; CRP: C-reactive protein; PaO_2: partial pressure of oxygen; FiO_2: Fraction of inspiration O_2; ↑: increase; ↓: decrease.

As reported, the production of multiple cytokines, exosomes and vesicles promoted by MSCs can influence multiple signaling pathways and repair lung injuries [19]. MSCs' role in orchestrating development, tissue maintenance, and repair by producing several growth factors is unquestionable. Besides their stem-cell potency, their therapeutic properties can also be attributed to the capacity of secreting multiple critical cytokines for tissue regeneration [20]. It has been found that MSCs could differentiate into alveolar epithelial cells and pulmonary vascular endothelial cells, playing a protective role in lungs. MSCs can secrete cell health factors such as keratinocyte growth factor (KGF), vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), suppress inflammatory factors like transforming growth factor-beta (TGF-β), TNF-α, and reduce the content of collagen. All these molecules make a contribution to protecting and repairing alveolar epithelial cells and endothelial cells. Besides, the repairing effect of MSCs can be partly attributed to the increased secretion of alveolar surface active substances and the regeneration of alveolar epithelial cells and angiogenesis [21]. And then all these molecules and substances can help repair alveolar epithelial barrier, alleviate the pulmonary fibrosis and improve the microenvironment.

2.3. Exosome of MSCs

It has been reported that MSCs carry a paracrine mechanism [11], known as secretome or exosomes releasing biologically active substances [22]. After intravenous MSCs injection, the secretome remains highly stable in the blood flow and distributes through to the lungs. Then the secretome spreads into tissues and it provides immune modulation, resolution of inflammation, restoration of capillary barrier function and enhances bacterial clearance.

MSC-secretome contains a broad spectrum of cytokines, chemokines and growth factors, which are released in the form of extracellular vesicles (EVs) with micro- and nano-size [11, 23]. These soluble molecules can diminish inflammation and the EVs can stimulate tissue reparation. These MSC-released EVs can deliver microRNA, messenger RNA (mRNA), DNA, proteins, and metabolites into recipient cells in specific injuries of the lung to promote lung repair as well as regeneration and to restore lung function [24]. Once released, EVs and soluble proteins interact with the target cells (by ligand-receptor interaction or by internalization) and modulate cellular responses. More specifically, secretome can activate endogenous stem cells and progenitor cells, suppress apoptosis, ameliorate the inflammatory response, stimulate the remodeling of the extracellular matrix and angiogenesis, reduce fibrosis and mediate the chemoattraction [25].

A recent study with a single intravenous dose of bone marrow derived exosomes has demonstrated profound reversal of hypoxia, immune reconstitution, and down-regulation of cytokine storms in severe COVID-19 patients, without any adverse effects [26], which suggested that MSCs might be a worthwhile option in COVID-19 patients, especially for the severe or critical cases.

3. ADVANTAGES AND EFFECTIVENESS

It has been found that after infusion of MSCs in COVID-19 patients, the number of peripheral lymphocytes increased while the levels of C-reactive protein (CRP) decreased. The overactivated cytokine-secreting immune cells (CXCR3+ CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells) dwindled in the circulating blood within 6 days. Furthermore, after the MSCs treatment, the population of CD14+CD11c+CD11bmid regulatory DCs increased in size. The major pro-inflammatory cytokine, TNF-α, presents a decline in its levels in the MSCs treated COVID-19 patients, accompanying an elevation in concentration of the anti-inflammatory protein IL-10 [27]. The patients showed significantly improved pulmonary function with no adverse effects based on a 14-day follow-up [28].

There is much superiority in using MSCs therapy, comparing to other treatments. Firstly, MSCs are multipotent stem cells which can easily expand to clinical volume in a suitable period of time. Secondly, MSCs can be stored for repetitive therapeutic usage, with easy accessibility and isolation [29]. Thirdly, the safety and effectiveness of MSCs have been well documented in several clinical trials, without any adverse reactions. Fourth, MSCs are negative for angiotensin converting enzyme 2 receptor (ACE2) and transmembrane protease serine 2 (TMPRSS2) and thus resistant to SARS-CoV-2 infections, as confirmed by 10 x RNA-sequencing [27]. In addition, the expression of interferon-stimulated genes (ISGs) in MSCs may play an important role in preventing viral infection [13]. As MSCs are free of ethical and social issues, with a high proliferation rate and a low invasive nature, this kind of therapy is preferred over other therapeutic strategies for COVID-19.

CONCLUSION

MSCs have been confirmed effective in the treatment of COVID-19, and at the same time, to reduce the mortality caused by complications such as ARDS and CSS, especially in severe patients. However, the evidence for effective immune response modulation is not very strong thus far and the mechanism of action remains unclear. It is quite necessary and also feasible to conduct clinical researches on MSCs-based treatment for COVID-19 patients. More data and results of randomized controlled trials (RCTs) will help to find out whether MSCs can truly be a standard treatment for COVID-19. Moreover, there are other drugs in trials for tackling CCS, such as tocilizumab, which was recently approved in China and the US for the treatment of severe COVID-19 cases and may exemplify a future research effort.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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