Mesenchymal Stem Cell Transplantation in Treating Severe COVID-19: A Systematic Review and Meta-Analysis

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Abstract

The objective of the study is to perform a critical review, exploration, and strong summary of the roles of mesenchymal stem cell transplantation in treating various diseases, including COVID-19. A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienceDirect, PubMed, Scopus, ISI Web of Science, and websites of the news. The search was applied to the articles that were published between January 2020 and April 2020. Needed article information was extracted from each article by: 1) direct information including journal (research article, review article, meeting abstract, conference abstract, correspondence, author index, editorial board meeting abstract, discussion), book chapter, title, authors, abstract, full text documents of candidate studies, websites of the news, publishing year; 2) study period; 3) research (study) method used; 4) types of mesenchymal stem cells; and 5) types of human organ system disorder or disease studied. With strict literature search and screening processes, it yielded 6 articles from 76 articles of initial literature databases and websites of the news (January 2020 to April 2020). Anti-inflammatory and immunomodulatory properties of MSCs in the treatment of respiratory diseases were confirmed by at least 17 clinical studies and more than 70 clinical trials are registered in this issue that are available at: https://www.clinicaltrials.gov. MSC transplantation improves the treatment outcome of COVID-19 patients may be due to controlling inflammatory response and promoting tissue regeneration and repair. In conclusion, Human MSCs are currently being evaluated as a stem cell treatment for a number of diseases, particularly severe COVID-19 and have been demonstrated to be safe in clinical trials. There are some promising reports to apply MSCs therapy to treat COVID-19. MSCs may possibly be one of the most ideal therapeutics, or a combination of treatment to treat patients with COVID-19. Nevertheless, further studies are urgently needed to investigate and optimize a number of variables in the human MSC culture environment by developing a bioprocess that can be operated in accordance with the Good Manufacturing Product (GMP).

Keywords: Acute Respiratory Distress Syndrome; COVID-19; Novel Coronavirus-2019; Mesenchymal; Pneumonia; Stem Cell; SARS-CoV-2; Severe Transplantation

Abbreviations


Introduction

In vitro, mesenchymal stem cell (MSC) populations with potentials of similar multi-lineage differentiation have been obtained from several bone marrow (BM) and non-bone marrow tissues [1], including umbilical cord [2-4], placenta [5], amniotic fluid [6,7], adipose tissue [8,9] and peripheral blood [10]. The clonogenic BM-human MSCs fraction ranges from 10 to 100 colony-forming unit-fibroblast (CFU-F) per 106 marrow mononuclear cells (MNCs) [11]. BM-human MSCs are characterized by lacking CD11b, CD14, CD19, CD34, CD45, CD79α, and human leukocyte antigen (HLA)-DR expression; positive expression of surface antigens CD73, CD90, and CD105; multipotency (i.e. chondrogenic, osteogenic and adipogenic); and their adherence to plastic [11]. By the year 2000, clinicians increasingly had become interested in intravenously applied MSC therapy [12]. A previous study demonstrated that both human and murine MCSs can induce immune suppression by attracting and killing autoreactive T cells via FasL, therefore stimulating transforming growth factor-beta (TGF-β) production by macrophages and generation of regulatory T cells [13]. The dying T cells that is caused by the interaction involving the MSC-induced Monocyte Chemoattractant Protein-1 (MCP-1) secretion in turn activate macrophages to produce TGF-β, then stimulating regulatory T cells and promoting immune tolerance [14]. The capacity of MSCs for in vivo differentiation and engraftment and by their efficacy in promoting wound healing highlighted its clinical relevance [15-21].

In 2006, the International Society for Cellular Therapy came up with the guidelines for MSC characterization for standardization the MSC biology, definition, isolation, and characterization criteria, in vivo relevance and ethical and institutional regulations for its clinical use [11]. Since the COVID-19 pandemic, there are several ongoing trials that have been studied in China, such as the ClinicalTrials.gov identifiers: NCT04252118, NCT04273646, NCT04276987, NCT04293692, NCT04302519, NCT04288102, etc. for fighting against severe COVID-19 or COVID-19 pneumonia [22-27]. MSCs can decrease the overproduction of immune cells caused by a reaction to the COVID-19 and decrease excessive levels of inflammatory substances, contributing to regulating the immune system and recovering to the normal status, particularly of the elderly patients [28].

Methods of the Study

Search strategy and inclusion criteria

A comprehensive search was carried out in mainstream bibliographic databases or Medical Subject Headings, including ScienDirect, PubMed, Scopus, ISI Web of Science, and websites of the news. The search was applied to the articles that were published between January 2020 and April 2020. Our first involved performing searches of article abstract/keywords/title using strings of ([“COVID-19” or “novel coronavirus-2019”, or “SARS-CoV-2”, “immune disorders or diseases” or “autoimmune disorders or diseases”, “acute respiratory distress syndrome” or “acute respiratory distress syndrome-related COVID-19 or “acute respiratory distress syndrome-related novel coronavirus-2019”, “pneumonia” or “pneumonia-related COVID-19”, or “pneumonia-related novel coronavirus-2019”, “novel therapeutics on “COVID-19” or “novel coronavirus-2019” or SARS-CoV-2”]). After a first approach of search, published articles focusing on transplantation of mesenchymal stem cells in treating COVID-19 or novel coronavirus-2019 were retained and the information on “COVID-19” or “novel coronavirus-2019”, or “SARS-CoV-2”, “immune disorders or diseases” or “autoimmune disorders or diseases”, “pneumonia” or “pneumonia-related diseases”, “novel therapeutics on “COVID-19” or “novel coronavirus-2019” or SARS-CoV-2” was extracted for having

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a crude knowledge involving their themes. Another round of publication search was conducted for adding the missing published articles that were not identified by the first round.

All keywords combinations from "COVID-19" or "novel coronavirus-2019", "SARS-CoV-2", "immune disorders or diseases" or "autoimmune disorders or diseases", "pneumonia" or "pneumonia-related diseases", "novel therapeutics on COVID-19" or "novel coronavirus-2019" or "SARS-CoV-2" to bind the population of cases under consideration. Search string for disease groups include "[COVID-19] or [severe COVID-19] or novel coronavirus-2019 or SARS-CoV-2" and the inclusion criteria were met with 6 articles from 76 articles of the initial literature database and websites of the news (January 2020 to April 2020).

Results

With strict literature search and screening processes, it yielded 6 articles from 76 articles of initial literature database and websites of the news (January 2020 to April 2020). Needed article information was extracted from each article by: 1) direct information including journal, research article, review article, meeting abstract, conference abstract, correspondence, author index, editorial board meeting abstract, discussion, book chapter, title, authors, abstract, full text documents of candidate studies, websites of the news, publishing year; 2) study period; 3) research method used; 4) types of mesenchymal stem cell variables studied in transplantation; 5) types of organ system disorder or disease studied; and 6) the conclusions made about the mesenchymal stem cell transplantation in treating COVID-19 or novel coronavirus-2019 or SARS-CoV-2. An overview of the information required for the present analysis that was captured by those themes was shown in the figure 1. Results from 6 yielded articles (Reference number to Reference number) was demonstrated in the figure 1 and table 1.
infection can trigger a very intense pro-inflammatory response compared to other influenza viruses, thus the beneficial effects might be a specific consequence of different pathogenic features, as compared to other influenza viruses. In vitro, infection in vitro with N5 strain viral-like particles induced by influenza A (H5N1) infection is more severe. UC-MSCs were more effective than human BM-MSCs at restoring impaired alveolar fluid clearance and permeability. UC-MSC-derived EVs were more effective than UC-MSCs themselves in terms of neutrophil infiltration and injury of the lungs in a preclinical lung injury model. In particular, EVs derived from pig-Derived UC-MSCs with a more reduced number of EVs was administered intravenously but did not significantly improve lung injury model after 12 hours of intervention. Clinical improvement within 3-4 days after MSC administration was observed in a patient with critically severe COVID-19. The mean serum cytokine levels of MSCs vary between 4 and 4.2 x 10^5 cells/kg. The highest dose of MSCs used in non-human primate was 16 x 10^5 cells/kg (SAF: 2x10^6 cells/kg) for 2 daily doses. The MSCs are usually given in a single-dose regimen or as an average frequency of every 2 days.

Seven patients with COVID-19 pneumonia were enrolled and evaluated in the outcomes for MSC transplantation after 14 days. All patients were treated with a single intravenous dose of 16 x 10^5 MSCs/kg. The pulmonary function (transmission of the N5 strain, weight, and symptoms) of all 7 patients were significantly improved without observed adverse effects within 7 days after MSC treatment. Two severe and one common COVID-19 patients were recovered and discharged at 18 days after MSC treatment. After MSC treatment, the CRP decreased, lymphocytes and NK cells increased, and the mRNA levels of IL-6 and TNF-α were decreased in the patients. The cytokine storm was dramatically improved in one patient with severe COVID-19 who was discharged after MSC injection. MSCs were free from COVID-19 infection by demonstrating of ACE2 and TMPRSS2 gene expression profiles.

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<th>Table 1: Demonstrating article contents of mesenchymal stem cell transplantation in treating COVID-19 and references published between January 2020 and April 2020.</th>
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![Figure 1: Literature search and screening flow.](image-url)

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Discussion

Currently, there are no approved therapeutic options for either the prevention or treatment of COVID-19 [29]. MSCs act via a paracrine mechanism [30]. They release biological active substances “secretome” that is made of both growth factors and extracellular vesicles (EVs) [32] and soluble proteins, including a broad spectrum of chemokines and cytokines. EVs are also described as mediators of the protective effects of MSCs in pre-clinical models of bacteria and non-infectious acute pulmonary injury [32]. Additionally, MSCs can secrete angiopoietin-1 (Ang-1), keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) that contribute to the restoration of alveolar-capillary barriers disrupted as part of ARDS pathogenesis [32]. Releasing soluble proteins and EVs interact with the target cells by internalization or ligand-receptor interaction. MSC-secretome acts on several cytokines potentially, simultaneously, and synergistically [30].

MSC-secretome can activate endogenous stem cells, and progenitor cells, regulate the inflammatory response, stimulate angiogenesis and remodeling of the extracellular matrix, suppress apoptosis, mediate chemoattraction, and reduce fibrosis [30]. Nevertheless, mediators responsible for ameliorating respiratory viral-induced lung injury remain unclear [32]. One of the two distinct antiviral mechanisms of the MSCs is the constitutively elevated levels of MSC-specific interferon-stimulated genes (ISGs) to function as mediators of an antiviral protection [32]. The effectiveness of MSC-secretome on autoimmune diseases and ARDS is evidenced, both in vivo and ex vivo. Secretome with highly stability in the blood circulation spread into tissues, particularly lungs and provide immune modulation, restoration of capillary barrier function, resolution of inflammation, and enhance bacterial clearance [30]. Generally, secretome is considered safer than MSCs due to low immunogenicity [30], low emboli formation [30,31] and lacking the potential for endogenous tumor formation [30] in treating COVID-19, virus-induced ARDS and other viral disease, such as H7N9-severe lung disease [30,31]. With fewer costs and ready-to-use product, MSC-secretome treatment seems to be technological advantages [30].

Very recently, MSC-secretome can be formulated as both injectable dosage forms and inhalable dosage form. MSC-secretome therapy emerges as a promising cell-free treatment modality for both acute and chronic pulmonary diseases [30]. Recently, two Chinese clinical trials, NCT04276987 (inhaled secretome for the treatment of critically ill COVID-19 pneumonia) and NCT04313647 (secretome tolerance in healthy volunteers) appeared on the URL: http://www.clinicaltrials.gov [30]. A previous report from China revealed that the levels of serum IL-2, IL-7, G-SCF, IP-10, MCP-1, MIP-1 A, and TNF-α in ICU-COVID-19 patients were higher than those of non-ICU-COVID-19 patients [33]. Nevertheless, there are only a small number of pre-clinical investigations on effects of MSC administration in pre-clinical models of respiratory virus infections and there yet no pre-clinical data investigating the effects of MSC administration in the models of coronavirus respiratory infection, mostly due to lacking an established animal model [32].

A previous study on both human and mouse MSCs administration demonstrated that MSCs did not improve influenza (H1N1)-mediated pulmonary injury regardless of administration route [32]. Nevertheless, there are evidence-based studies that MSC therapy can inhibit the overactivation of the immune system and promote endogenous repair by improving the microenvironment [33]. At least 4 of the trials will utilize either MSC-derived conditioned media (CM) or EVs. Two of these propose aerosol inhalation of MSC-derived EVs, one from adipose-derived MSCs, for which there is no pre-clinical supporting data. Six studies will utilize other cells including UCB-derived mononuclear cells, cytotoxic T cells (CTL), dendritic cells (DC), natural killer cells (NK), umbilical cord blood stem cells (UCB-SC), or cytokine-induced killer cells (CIK). Only the latter study describes dosing and frequency of MSC injections [32]. Apparent pre-clinical data are not available to support the rationale for any of these therapeutic interventions. More pre-clinical data involving the models of coronavirus-induced pulmonary injuries are needed to initiate trials of MSC-based studies with highest standards for rationale and properly designed investigations. These are the only ways that a rationale evidence-based framework for potential cell-based therapies can be developed [32]. A recent study of 7 COVID-19 patients in China (one with critical severe type, 4 with severe type, and the other 2 with common type of COVID-19 syndrome) were received 1 million MSCs per kilogram body weight and were closely observed their symptoms for 14 days. This study revealed that all symptoms disappeared by 2-4 days after MSCs intravenous administration with no apparent adverse effects [32-34]. The majority of patients demonstrated negative results of the reverse transcriptase polymerase chain reaction (RT-PCR) tests for COVID-19 or SARS-CoV-2 or novel coronavirus-2019 nucleic acid over a week or two weeks as well as the significant resolution of pneu-

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Monic infiltration in the chest computed tomographic (CT) imaging after MSC intravenous administration [32-34]. The National Health Commission of China classifies the clinical grading of the COVID-19 as the following: 1) Mild type-mild clinical manifestation, none imaging performance, 2) Common type-fever, respiratory symptoms, pneumonia performance on chest X-ray or CT, 3) Severe type-meet any of the followings: 3.1) respiratory distress, respiration rate at least 30/minute, 3.2) oxygen saturation not higher than 93% at rest state, and 3.3) arterial partial pressure of oxygen (PaO2)/fraction of inspiration oxygen (FiO2) not higher than 300 mmHg (1 mmHg = 0.133kpa), and 4) critically severe-meet any of the followings: 4.1) respiratory failure needs mechanical ventilation, 4.2) shock and 4.3) combined with other organ failure, patients need ICU monitoring and treatment [33]. Anti-inflammatory and immunomodulatory properties of MSCs in the treatment of respiratory diseases were confirmed by at least 17 clinical studies and more than 70 clinical trials are registered in this issue that are available at: https://www.clinicaltrials.gov [34]. MSC transplantation improves the treatment outcome of COVID-19 patients may be due to controlling inflammatory response and promoting tissue regeneration and repair [33].

Conclusion

Human MSCs are currently being evaluated as a stem cell treatment for a number of diseases, particularly severe COVID-19 and have been demonstrated to be safe in clinical trials. There are some promising reports to apply MSCs therapy to treat COVID-19. MSCs may possibly be one of the most ideal therapeutics, or a combination of treatment to treat patients with COVID-19. Nevertheless, further studies are urgently needed to investigate and optimize a number of variables in the human MSC culture environment by developing a bioprocess that can be operated in accordance with the Good Manufacturing Product (GMP).

Authors Contributions

Dr. Attapon Cheepsattayakorn conducted the study framework and wrote the manuscript. Associate Professor Dr. Ruangrong Cheepsattayakorn contributed to scientific content and assistance in manuscript writing. Both authors read and approved the final version of the manuscript.

Competing Interests

The authors declare that they have no actual or potential competing financial interests.

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Bibliography

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