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Research Article

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

ACE 2: Angiotensin-Converting Enzyme 2; AF: Amniotic Fluid; ALT: Alanine Transaminase; Ang-1: Angiopoietin-1; ARDS: Acute Respiratory Distress Syndrome; AST: Aspartate Transaminase; AT: Adipose Tissue; BALF: Bronchoalveolar Lavage Fluid; BM: Bone Marrow; CFU-F: Colony-Forming Unit Fibroblast; CIK: Cytokine-Induced Killer Cells; CM: Conditioned Media; COVID-19: Coronavirus Disease 2019; CRP: C-Reactive Protein; CT: Computed Tomography; CTL: Cytotoxic T Cells; DC: Dendritic Cell; DP: Dental Pulp; EVs: Extracellular Vesicles; FiO_2: Fraction of Inspiration Oxygen; G-CSF: Granulocyte-Colony-Stimulating Factor; GVHD: Graft-Versus-Host Disease; HGF: Hepatocyte

Growth Factor; HLA: Human Leukocyte Antigen; ICU: Intensive Care Unit; IFITM: Interferon-Induced Transmembrane Protein; IFN-α: Interferon-Alpha; IFN-γ: Interferon-Gamma; IL: Interleukin; IP: Interferon Gamma-Induced Protein; ISG: Interferon-Stimulated Gene; KGF: Keratinocyte Growth Factor; MCP: Monocyte Chemoattractant Protein; MIP: Macrophage Inflammatory Protein; MSCs: Mesenchymal Stem Cells; NK: Natural Killer Cells; PaO_2: Arterial Partial Pressure of Oxygen; PB: Peripheral Blood; PL: Placenta; RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus-2; SF-36: 36 Item Short-Form Health Survey; TGF-β: Transforming Growth Factor-Beta; TMPRSS2: Type II Transmembrane Serine Protease; TNF-α: Tumor Necrosis Factor-Alpha; UC: Umbilical Cord; UCB: Umbilical Cord Blood; WJ: Warton Jelly

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 MCSs 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

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", 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" to bind the population of cases under consideration. Search string for disease groups include [("COVID-19" or "novel coronavirus-2019", "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")]. The initial literature databases were further manually screened with the following rules: 1) non-COVID-19-, non-novel coronavirus-2019-, and non-SARS-CoV-2-related articles were excluded; 2) articles that did not report mesenchymal stem cell transplantation on COVID-19 or novel coronavirus-2019 or SARS-CoV-2 were not considered, such as commentary articles, or editorial; 3) non-peer reviewed articles were not considered to be of a scholarly trustworthy validity; and 4) duplicated and non-English articles were removed. The articles were carefully selected to guarantee the literature quality, which is a trade-off for quantity.

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 (study) 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.

Published Year	Article Content	Reference
2020	Clinical trial ID (Registry: 1) NCT04293692 (ClinicalTrials.gov, umbilical cord MSCs, randomized, triple blinded, withdrawn, China); 2) NCT04273646 (ClinicalTrials.gov, umbilical cord MSCs, randomized, non-blinded, not recruiting, China); 3) NCT04269525 (ClinicsalTrials.gov, umbilical cord MSCs, non-randomized, non-blinded, recruiting, China); 4) ChiCTR2000030138 (ICTPR, umbilical cord MSCs, randomized, double blinded, not recruiting, China); 5) ChiCTR2000030484 (ICTPR, umbilical cord MSCs and derived exosomes, unspecified randomized, unspecified blinded, not recruiting, China); 6) ChiCTR2000030116 (ICTPR, umbilical cord MSCs, randomized, unspecified blinded, recruiting, China); 7) ChiCTR2000029816 (ICTPR, umbilical cord MSCs, randomized, non-blinded, not recruiting, China); 8) NCT04313322 (ClinicalTrials.gov, Wharton jelly MSCs, non-randomized, non-blinded, recruiting, Jordan); and 9) ChiCTR2000030088 (ICTPR, Wharton jelly MSCs, randomized, unspecified blinded, not recruiting, China)	[29]
	Human umbilical cord MSCs effectively modulated the immune response and repaired injured tissues of critically ill COVID-19 patient with excellent safety by intravenous route three times (5 X 10^7 cells each time) every three days. After second administration, the vital signs were improved, the tracheal tube was pulled off and the serum C-reactive protein (CRP), serum alanine transaminase:aspartate transaminase (ALT:AST), and serum bilirubin were gradually decreased. MSc significantly improved the pulmonary function and clinical symptoms of patients with COVID-pneumonia.	[30]
	MSC transplantation in patients with influenza A (H_7N_9) infection induced ARDS were conducted in a single center and open-label clinical trial. Several parameters, such as computed tomography of the chest (1 week, 1 months, 6 months, and 12 months), pulmonary ventilatory function (6 months and 12 months), 36 Item Short-Form Health Survey (SF-36) (Chinese version) of the Medical Outcome Study (Health-Related Quality of Life (HRQoL) (6 months and 12 months) after MSC transplantation. MSCs have ability to decrease inflammatory effects and defend against cytokine storm. MSCs probably decrease the secretions of the inflammatory factors. MSCs significantly decreased the mortality (16.7% in MSC group versus 54.5% in control group). No serious adverse effects are identified after MSC transplantation during the period of 5 years. Nevertheless, long-term pulmonary dysfunction is still a problem after 2 years of hospital discharge.	[31]
	In animal models, H_9N_2 viral infection increases serum and pulmonary chemokines responsible for pulmonary leukocyte infiltration. Antiviral protein members of the IFITM family members are unique as they prevent infection before a virus can traverse the lipid bilayer of the cell contributing the limitation of infection in cultured cells by many viruses, such as SARS coronavirus, influenza A virus, Ebola virus, dengue virus, etc., whereas knockdown of IFITM3 rendered MSC susceptible to infection by a variety of viruses, such as Zika virus, Yellow Fever virus, etc. Pro-inflammatory cytokines including IFN-γ induced non-constitutive ISGs including CD74, IFNAR2, MT1G, MT1X, SAT1, SERPING1, whereas significantly increasing the expression of constitutive antiviral genes, such as CCL2, IFI6, IFITM1, ISG15, PMAIP1, and SAT1. In a respiratory viral infection including COVID-19, MSCs might present two distinct antiviral mechanisms: 1) constitutively elevated the levels of MSC-specific ISGs to function as mediators of an antiviral protection, and 2) a secondary response to IFN, contributing to ISG induction and broad viral resistance. MSCs could present a mix of inducible and intrinsic innate antiviral defenses that could contribute to treatment benefits in severe COVID-19 patients. BM-MSCs are permissive to avian influenza A (H_5N_1) infection, losing immunoregulatory activities, and viability. Virus-infected MSCs may not be functionally effective at stopping virus replication and pulmonary injury. BM-MSCs and UC-MSCs were more effective than adipose tissue-derived MSCs in decreasing mortality in pre-clinical acute lung injury models (rodents, pig, sheep, and explanted human lungs). Neither synergistic or xenogeneic MSC administration, either alone or as an adjuvant therapy with oseltamivir was effective either when administered prophylactically, prior to H_1N_1 virus inoculation, or when therapeutically administered, similar to the results of both systemic and intratracheal administration of human and mouse MSCs. MSCs did not improve influenza-mediated lung injury regardless of administration route. Avian influenza-virus	[32]

	infection can trigger a very intense pro-inflammatory response compared to other influenza virus, thus the beneficial effects might be a specific consequence of different pathogenic features as compared to swine-origin H_1N_1 infection. *In vitro* airway epithelial cell models and experimental lung injury induced by Influenza A (H_5N_1) infection in female mice, UC-MSCs were more effective than human BM-MSCs at restoring impaired alveolar fluid clearance and permeability. MSCs-derived EVs were more effective than MSCs themselves in some H_5N_1 cases inflammation and injury of the lungs in pre-clinical lung injury models, particularly EVs isolated from pig BM-derived MSCs in reducing virus shedding in nasal swabs, influenza replication in the lungs, BALF pro-inflammatory cytokines and chemokines, and histopathologic changes in a mixed swine (H_3N_2, H_1N_1) and avian (H_9N_2, H_7N_2) influenza-induced pig lung injury model after 12 hours of administration. Clinical improvement within 2 - 4 days after MSC administration was observed in a patient with critically severe COVID-19. The intravenous dosing range of MSCs varies between 0.4 and 42 X 10^6 cells/kg. The highest dose of MSCs used in non-viral ARDS was 10 X 10^6 cells/kg (START trial). The MSC dosing strategy ranged between a single and 5 doses with an average frequency of every 2 days.	
	Seven patients with COVID-19 pneumonia were enrolled and evaluation of the outcomes for MSC transplantation after 14 days of MSCs injection (January 23, 2020 - February 16, 2020). The pulmonary function (One million MSCs per kilogram body weight) and symptoms of all 7 patients were significantly improved without observed adverse effects within 2 days after MSC injection. One severe and two common COVID-19 patients were recovered and discharged in 10 days after MSC treatment. After MSC transplantation, the CRP decreased, peripheral lymphocytes increased, and the overactivated cytokine-secreting immune cells (CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells) disappeared in 3-6 days. CD14+CD11c+CD11b^{mid} regulatory DC cell population increased. TNF-α level was significantly reduced. IL-10 level increased. The cytokine storm was dramatically improved in one patient with critically severe COVID-19 in 2-4 days after MSCs injection. MSCs were free from COVID-19 infection by demonstration of ACE2 and TMPRSS2 in gene expression profile.	33
	Much superiority in using MSC treatment in comparison with other treatment modalities includes: 1) easily accessible and can be isolated from various tissues (BM, AT, UC, buccal fat pad, fetal liver, menstrual blood, etc.), 2) are multipotent stem cells, 3) MSCs can be stored for repetitive therapeutic usage, 4) MSCs can easily expand to clinical volume in a proper period of time, 5) clinical trials of MSCs have not demonstrated adverse side effects or reactions to allogeneic MSC, and 6) several clinical trials demonstrated safety and effectiveness of MSCs. MSC treatment probably can prevent the cytokine storm releasing by the immune system and promote endogenous repair by reparative properties of the MSCs. MSCs could protect pulmonary alveolar epithelial cells, recover the pulmonary microenvironment, intercept pulmonary fibrosis, and cure pulmonary dysfunction and COVID-19 pneumonia. MSCs can be isolated from BM, PB, AT, PL, UC, WJ, AF, UCB, and neonatal birth-associated tissues. MSC transplantation is also widely used in the treatment of graft-versus-host disease (GVHD), spinal cord injury, autoimmune disease, type 2 diabetes mellitus, and other high immunity diseases. Second and third intravenous injections of UC-MSCs in combination with lopinavir/ritonavir, α1-thymosin, IFN-α, and oseltamivir as well as intravenous injection of immunoglobulin, methylprednisolone, Xuebijing, and moxifloxacin in a 65-year-old female patient with critically ill COVID-19 demonstrated the improvement of COVID-19 pneumonia 2 days after the third injection of MSCs.	[34]

Table 1: *Demonstrating article contents of mesenchymal stem cell transplantation in treating COVID-19 and references published between January 2020 and April 2020.*

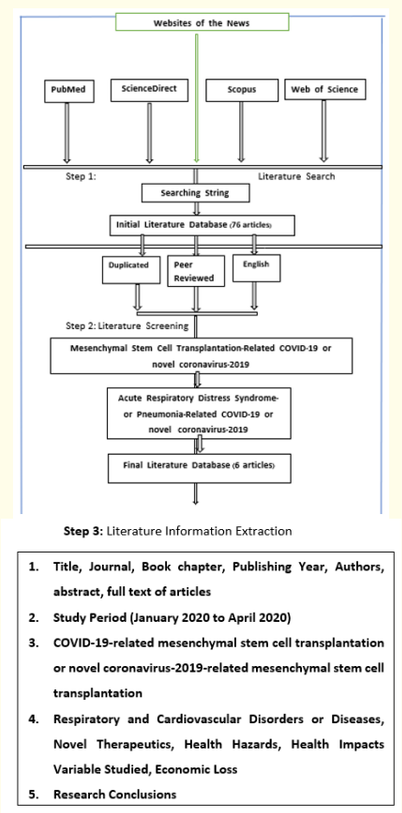

Figure 1: *Literature search and screening flow.*

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 mediating 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-

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 (PaO_2)/fraction of inspiration oxygen (FiO_2) 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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