REVIEW ARTICLE

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Allogeneic Mesenchymal Stem Cells and Its Conditioned Medium as a Potential Adjuvant Therapy for COVID-19

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Recent research has demonstrated that mesenchymal stem cells (MSCs) potentially benefit and enhance coronavirus disease (COVID-19) recovery. This benefit occurs via a mechanism that promotes viral clearance by phagocytes and macrophages. This action occurs through the innate (increase in IL-10 production and decrease in TNF-α and IL-12 production) and the adaptive immune system (decrease in IL-17 production, promote regulatory T cell proliferation and inhibit effectors T cell proliferation). MSCs are expected to act as an anti-inflammatory in the hyper-inflammatory state of COVID-19. MSCs enhance immune cell replacement that have been overwhelmed or have been lost due to cytokine storm. Although vaccines are the answer to this pandemic, MSCs can improve COVID-19 patients, especially in patients with chronic illnesses. The focus on keeping death-rates low is a great opportunity for MSCs-based therapy for severe or critically ill patients. MSCs and conditioned medium have the potential to serve as adjunctive therapy in preventing the body's overactive defense response or the so-called cytokine storm caused by COVID-19.

Keywords: *adjuvant therapy, COVID-19, mesenchymal stem cells, secretome*

Introduction

The coronavirus disease (COVID-19) epidemic was initially informed at the end of December 2019. This disease was found in Wuhan, China which then spread globally, thus becoming a pandemic.[1] This pandemic has progressed rapidly and resulted in severe respiratory distress associated with significant mortality and morbidity worldwide.[2,3] As of October 2021, 237.5 million cases were identified and a total of 4,847,462 deaths were confirmed.[4] This high mortality rate is caused by cytokine storm due to the high levels of pro-inflammatory cells in the body. This condition causes

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damage to immune cells, resulting in hyperinflammation and damage to lung cells.[2,5] Since the pandemic, many treatments have been developed, one of them is a stem cell therapy. Stem cells can treat various diseases and become an alternative treatment of COVID-19.[6] Mesenchymal stem cells (MSCs) are cells that have a high division rate and can differentiate into several cell types.[7] MSCs can be found in organs and tissues, such as umbilical cord, umbilical cord blood, adult connective tissue, placenta, amniotic membranes, dental tissue, and bone marrow.[8,9] MSCs are expected to reduce lung damage, accelerate the recovery of damaged cells and improve patient survival.

COVID-19 Pathogenesis

COVID-19 is a viral disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a virus that comes from the Coronaviridae virus family (CoVs) with the characteristics of enveloped RNA viruses.[10] The virus particle diameter is 60-100 nm, round or oval form.[11] The virus transmission occurs primarily via the respiratory tract and fecal-oral route.[3] This virus is known to have an incubation period of approximately five days, with a range of 1-14 days. Mild respiratory tract disorders characterized by pneumonia, normal or low leukocytes, myalgia, cough, and fever are the symptoms experienced by most COVID-19 patients.[5] These symptoms resemble the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).[12]

SARS-CoV-2 specifically recognizes the angiotensin-converting enzyme 2 (ACE2) receptor through spike (S) protein.[1,2,13] The S glycoprotein is an essential component in SARS-CoV infection or escapes from host immunity.[14] This is a fusion protein of first class that plays a role in initiating receptor binding on host cells.[15] ACE2 receptors are widely distributed on the surface of human cells, especially on capillary endothelial and type II alveolar (AT2) cells.[16] Transmembrane serine protease type 2 (TMPRSS2), which has been reported to play a key role in triggering the SARS-CoV S protein for the viral cell fusion process and could be targeted by neutralizing antibodies by preventing the entry of the virus, is found to be highly expressed in AT2 cells.[17,18] Hence, SARS-CoV-2 prefers infecting the lung cells and promoting lung damage.

In a small proportion of patients, SARS-CoV-2 induces cytokine storm within the lungs, for instance tumor necrosis factor (TNF)-α, macrophage inflammatory protein (MIP)-1A, monocyte chemo-attractant protein (MCP)-1, interferon-γ-inducible protein (IP)-10, granulocyte colony-stimulating factor (GSCF), and interleukin (IL)-7, IL-2, IL-6. The release of these cytokines is caused by damaged immune cells, causing hyper-inflammation and the risk of death, since it often involves lung function. This systemic hyper-inflammatory condition results in monocytic and lymphocytic infiltration in the organs, leading to acute respiratory distress (ARDS), heart failure, or worse, multi-organ failure (MOF). In COVID-19-infected patients with ARDS and fulminant, classic serum biomarkers produced by the release of cytokines have been found, particularly elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), and IL-6, lactate dehydrogenase (LDH).[2,5,19] Therefore, avoiding or reducing cytokine storm is the key to treating COVID-19-infected patients.

COVID-19 Therapy

Current therapeutic approaches for COVID-19 comprises assertive supportive care and therapy of other co-infections. Lopinavir-ritonavir and remdesivir, or lopinavir-ritonavir and interferon (IFN)-1β are being investigated, but safety and conceivable effectiveness for both antiviral drugs remain to be decided. IFN-1β and remdesivir are more potent antiviral agents than lopinavir and remdesivir against MERS-CoV, as shown with *in vitro* assays, but whether they have the same effects to SARS-CoV-2 infection remains to be elucidated.[20] The use of hydroxychloroquine in COVID-19 patients has been recently approved by the United States Food and Drug Administration, although it does not prevent COVID-19 compatible disease when given within four days of exposure as post-exposure prophylaxis.[21] Lung cytokine storms induced by the virus are responsible for eliciting ARDS; hyper-inflammation is the reason for developing targeted anti-inflammatory drugs, such as anti-IL-6 or anti-IL-1.[10] Currently, there is no specific drug or vaccine available on the market to cure COVID-19 patients. Therefore, developing practical and secure therapies for COVID-19 patients are necessary, especially in severe cases.[2]

ARDS

ARDS patients infected with COVID-19 have worse symptoms than ARDS patients with other causes. The hospital and emergency care unit mortality rates from

typical ARDS are 40.0% and 35.3%, respectively.[22] ARDS patients infected with COVID-19 have a relatively high mortality rate ranging from 26-61.5%, while the mortality rate in patients using displacement ventilation ranges from 65.7-94%. The occurrence of complications of COVID-19 and ARDS in patients can be influenced by several factors, such as the presence of comorbidities (increased D-dimer, kidney injury, lower lymphocyte count, diabetes mellitus, cardiovascular disease, and hypertension) and older age. These complications in patients are caused by myocardial damage and circulatory failure (7%), respiratory failure combined with heart failure (33%), respiratory failure (53%), and the remainder is unknown in detail.[23]

Critically ill patients have been reported to have increased levels of TNF-α, macrophage inflammatory protein-1 alpha (MIP-1α)/chemokine ligand (CCL) 3, monocyte chemoattractant protein-1 (MCP-1)/CCL2, interferon gamma-induced protein 10 (IP10)/chemokine (C-X-C motif) ligand (CXCL)-10, granulocyte colony-stimulating factor (G-CSF), and IL-6, suggesting the presence of cytokine storm.[24] The occurrence of acute cardiac injury, infection, ARDS, dysfunction of air exchange, pulmonary edema, and even the risk of death can be caused by viruses that trigger acute cytokine secretion.[25] A typical ARDS pathology can be observed in COVID-19 patients, where hyaline membranes in the alveoli are accompanied by edema and dilated interstitials in the acute stage, whereas fibroblast proliferation can be observed at an advanced stage.[1,26] Pulmonary fibrosis with functional decline can damage lung tissue resulting from an inappropriate immune response and/or aberrant repair process.[22] The persistence of cytokine storm in COVID-19 proceeds to cause severe multiple-organ injury and death.[24] Critically ill patients are only given glucocorticoids to cope with sit-in storms as there are no other options. This leads to severe side effects due to viral delay, hypo-immunity, and osteoporosis.[1,27] This has spurred researchers and doctors to find strategies to treat patients with severe and critical respiratory distress due to COVID-19.[24]

MSCs Potential

The utilization of MSCs has many advantages, including rapid *ex vivo* expansion, simple harvesting, and acquisition procedures under properly defined culture conditions. In addition, MSCs have the potential to enhance tissue repair, since they can carry out trophic paracrine secretion and multi-lineage differentiation.[28] Therefore, MSCs can be developed into various specialized mesenchymal tissues, including connective tissue, fat/adipose tissue, ligaments, tendons, marrow stroma, muscle, cartilage, and bone.[29]

The homing capacity moderates MSCs regeneration capacity into the sites of inflammation or injury.[30] MSCs release trophic factors that are responsible for re-establishing tissue homeostasis and cell proliferation in damaged tissue.[31] MSCs can also be used as autologous and allogeneic therapies due to their immunosuppressive properties.[32,33] In addition, the utilization of MSCs as cell therapy is also easier compared to the safety profile of induced pluripotent stem cells or embryonic stem cells. This is because MSCs can be extracted from postnatal tissues, so there is little ethical concern in their use.[34] MSCs are also less sensitive to IFN-induced expression of human leukocyte antigen (HLA)-II, hence they are less affected by the host.[35]

The immunomodulatory ability of MSCs can be utilized to mitigate cytokine storm.[2] Immune cells interact directly with MSCs, resulting in paracrine modulation as an immune response through the release of anti-inflammatory cytokines, such as the production of indoleamine 2,3 dioxygenase (IDO) and nitric oxide (NO), IL-1RA, IL-10, and transforming growth factor (TGF)-β.[36] These cytokines will stimulate the adaptive and innate immune responses toward an anti-inflammatory phenotype, especially matrix metalloproteinases (MMP)-12, MMP-9, MMP-2, IFN-γ, CXCL-2, CXCL-1, IL-6, IL-1, MIP-2, MCP -1, IL-17, IL-12, and TNF-α become anti-inflammatory cytokine by depleting tryptophan resulting in an antiproliferative effect. MSCs suppress T cell proliferation induced by nonspecific mitogenic stimuli and inhibit naive T cell responses and antigen-specific memory. MSCs suppress T cell proliferation by secreting NO, IDO, prostaglandin E (PGE)-2, chemokine (C-C motif) ligand (CCL)-18, TGF-β, IL-10, IL-4, and inflammation resolving lipoxin A4 (LXA4) which can repair endogenous tissue and inflammation.[37,38]

MSCs are safe and beneficial for patients with COVID-19-related pneumonia or patients with acute illnesses, and they can alter the levels of immune function. The epithelial-mesenchymal transition of alveolar epithelial cells is inhibited by the MSCs and is partly mediated by keratinocyte growth factor (KGF)/fibroblast growth factor (FGF)-7. This transition is regulated by inhibiting transforming growth factor (TGF)-gene transcripts, such as zinc finger E-box binding homeobox-1 (ZEB-1), twist-related protein-1 (TWIST-1), and connective tissue growth

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factor (CTGF). Claudin-4, a protein implicated in the development of tight junctions, is necessary for MSCs to clear alveolar fluid.[39-41]

MSCs for ARDS

MSCs transplantation in preclinical ARDS models has indicated the effectiveness and safety of MSC transplantation for lung damage therapy.[42,43] In an *ex vivo* assay on the human acute lung injury (ALI) model induced by lipopolysaccharide (LPS), MSC has been reported to restore alveolar fluid clearance, reduce extravascular lung water[43-45] and prevent ARDS.[43,45] MSCs reduce alveolar damage and inflammation in LPS-induced ARDS mouse model.[42] Compared to vehicle or fibroblasts, MSCs treatment improves lung architecture, lung compliance, and reduces alveolar edema/lung permeability.[46]

Paracrine substances, such as antimicrobial peptides, growth factors, and anti-inflammatory cytokines, have been shown to alter lung endothelial and epithelial permeability following MSC transplantation.[47] MSCs release KGF and angiopoietin-1 (Ang-1), which help to re-establish the alveolar-capillary barriers damaged during ARDS development[48] and protect from both non-infectious bacterial and acute lung injuries in pre-clinical models.[49] MSCs transplantation has been reported to attenuate lung neutrophil infiltration, decrease TNF-α level, and increase IL-10 level.[42,50] MSCs-secreted growth factors, such as KGF, vascular endothelial growth factor (VEGF), and hepatocyte growth factor (HGF) promote AT2 cells regeneration, prevent endothelial cells apoptosis, and restore the alveolar-epithelial barrier in the ARDS.[44,51-53] MSC transplantation has been shown to protect against sepsis-ARDS by enhancing macrophage capacity in a PGE2-dependent pathway to generate IL-10.[52] MSCs can facilitate the resolution of inflammation by generating LXA4, which increases survival and lowers pulmonary edema in LPS-induced ARDS mice.[54] SCs transplantation increases KGF production, lowers neutrophil chemoattractant-1 and IL-6 expression, and reduces inflammatory cell infiltration into the damaged alveolus, improving alveolar fluid evacuation.[47]

In an animal model, the pro-inflammatory chemokines, such as MIP-1, MCP-1, and granulocyte-macrophage colony-stimulating factor (GMCSF), are reduced by MSCs intravenous injection.[55] *In vitro* tests show that MSC treatment enhances protein permeability and alveolar fluid clearance generated by H5N1 and H7N9 influenza viruses.[10] Intra-tracheal and intravenous infusion of MSCs improve the influx of inflammatory cells into wounded alveoli, lung permeability, lung compliance and permeability, as well as arterial oxygenation. MSCs have direct antibacterial action via antimicrobial peptides or proteins such as lipocalin-2 or antimicrobial peptides of cathelicidin-related, which increase bacterial clearance and macrophage/monocyte bacterial phagocytosis.[56] MSCs and their secretion might be seen as renewed practical and potential therapeutic agents for ARDS treatment and its complications.[53]

MSCs can limit virus activity through small ubiquitin-like modifier 2 (Sumo2)- and chromatin assembly factor 1a (Chaf1a)-mediated epigenetic control, a process known as proviral silencing.[57] Several phase II and III clinical trials have established the favorable and safety benefits of MSC treatment in patients with ARDS.[58,59] Up to now, there are no reported morbidities of the patients with ARDS treated with MSCs. In these pandemics, there are twenty clinical trials that are still ongoing for the application of MSCs in COVID-19 patients with ARDS registered in the Chinese registry of clinical trials.[60]

Potential of MSCs Conditioned Medium

The problem of MSCs utilization can be overcome by utilizing conditioned medium (CM) or secretomes obtained in stem cell culture. The use of CM is urgently needed for people with COVID-19 because of blockage due to cytokine storms and occlusion of blood vessels in the lungs that impede the transport of MSCs. Currently, there are nine clinical trials for COVID-19 treated with adjuvant MSCs and one clinical trial using MSC-exosomes in the clinical trials.gov registry. Several studies show that CM from human Wharton's jelly MSCs (hWJMSCs-CM) contains various essential proteins including cytokines, growth and angiogenic factors.[61] Various stimulation of regeneration and growth factors, including hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), VEGF-α, epidermal growth factor (EGF), and Ang-1, which is secreted by MSCs, recreate an essential position in the regeneration and repair process. In addition, MSCs paracrine activity generally recreates a position in tracing the inhibition of attraction of immune cells to the damage site and their immunomodulatory components through the inhibition of adaptive and innate immune responses.[62] The main driver in extracellular vesicle (EV) action is carried out by several identified growth factors and cytokines, such as stromal cell derived factor 1 (SDF-1), HGF, EGF, Ang-1, and KGF.[63]

MSCs-derived EVs have been shown to deliver the same, or perhaps even more practical ability than MSCs themselves in repairing injury and inflammation in various preclinical lung injury models.[64,65] EV isolates from porcine bone marrow-derived MSCs (BM-MSCs) have been reported to be able to reduce nasal swab virus release, pro-inflammatory cytokines and chemokines in bronchoalveolar lavage (BALF), as well as influenza replication in the lungs. Furthermore, histopathological changes are observed upon virus inoculation of avian (H9N5, H7N2) and swine (H3N2, H1N1) influenza viruses mixture administered after 12 hours in a swine influenza-induced lung injury model.[66] To overcome virus-induced lung injury, a potential cell-free strategy is applied through systemic EV administration.[10] A meta-analysis and systematic review of recent preclinical studies report that increased inflammation occurs in CM-MSCs and has a comparable effect with MSCs in many animal lung disease models such as ARDS, pulmonary hypertension, bronchopulmonary dysplasia, and asthma.[67]

Allogeneic MSCs Potential

MSCs is a good candidate for cell therapy.[33,68] MSCs can reduce inflammation and increase cell growth. In inflamed lung cells, blood vessels are blocked, and lung tissue permeability is decreased. Administered MSCs release anti-inflammatory factors IL-10 and IL-4 to suppress lymphocyte activation and inflammatory cytokines, such as IL-1α, IL-1β, IL-6, IL-17, and TNF-α. In promoting cell healing, MSCs reduce neutrophil overproduction and promote neutrophil-mediated phagocytosis, promote macrophage differentiation into M1, which induces phagocytosis, and M2, which promotes tissue repair by attenuating inflammation in infection site. In addition, MSCs promote the proliferation of regulatory T cells and inhibit the proliferation of effectors T cells, thereby reducing the immune response and repairing lung damage.[69]

The allogeneic MSC transplantation for ARDS has been conducted previously, in which patients transplanted with MSCs were reported to have a lower mortality rate in H7N9-induced ARDS (17.6% vs 54.5%). Since patients with severe COVID-19 develop profound local or systemic inflammation and subsequently progresses into ARDS and the related multi-organ dysfunction, MSCs-based therapy could become a considerable option for those patients.[70] Based on promising preclinical data, there are three preceding clinical trials that test the feasibility and safety of MSCs for ARDS treatment. One clinical trial (NCT01775774) is a multicenter analysis that assesses the safety of dose-escalation of allogeneic human BM-MSCs that are administered intravenously (10^5-10^6 cells/kg of body weight (bw)) in patients with moderate or severe ARDS. Results from this clinical trial shows that there are no exceptional cases of adverse effects among nine patients in this experiment. In three patients, serious adverse events (SAEs) are observed after weeks of infusion. However, SAEs occur in these patients but are not related to MSCs administration.[71] Another randomized, double-blind, placebo-controlled trial study (NCT01902082) investigates the efficacy and safety of allogeneic adipose-derived MSC therapy (10^6 cells/kg bw). This clinical trial shows that there are no severe side effects or infusion toxicity due to MSC administration, indicating that allogeneic adipose-derived MSCs are safe and appropriate for treating ARDS.[59] Nevertheless, the ideal dosage and method of MSC administration remain unknown.[47]

Allogeneic MSCs application is an encouragement beginning point for a more significant randomized, multicenter, phase II clinical trial research that screened 1,038 individuals in the United States (NCT02097641). The experiment includes 60 adult ARDS patients who are given either a single dose of allogeneic BM-MSCs (10^6 cells/kg bw) or a placebo (Plasma-Lyte A) intravenously.[72] There are no predefined respiratory adverse or MSC-related hemodynamic effects in any of the patients. One patient that received MSCs died after 24 hours of treatment, although the cause is determined to be unrelated. The groups do not vary in terms of 28-day mortality (15% in the placebo group vs. 30% in the MSC group; 95% confidence interval (CI) =0.5–15.1; odds ratio =2.4). The hazard ratio for death at 28 days is 143 after adjusting for Acute Physiology and Chronic Health Evaluation (APACHE)-III score (95% CI=0.40–5.12, p=0.58). According to this research, one dosage of intravenous MSCs is safe for individuals with mild to severe ARDS.[73]

Recently, an Indonesian multicenter-double blind-randomized clinical trial (NCT04457609) evaluates the safety of single intravenous infusion (10^6 cells/kg bw) of allogeneic human umbilical cord-derived MSCs (UC-MSCs) in patients with critical disease (intubated with severe pneumonia clinically and radiologically) or severe ARDS. This clinical trial shows that the survival rate in the UC-MSCs group is 2.5 times higher than in the control group (p=0.047). UC-MSCs therapy increases the survival

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rate in patients with comorbidities by 4.5 times than the control group. The use of ventilators and the stay duration in the critical care unit are not statistically significant. The use of UC-MSCs in the COVID-19 therapy is noticed to repress proinflammatory cytokines, such as interleukin 6 (IL-6) (p=0.023). As an adjunct therapy for critically ill COVID-19-infected patients, intravenous infusion of MSCs is known to improve survival by regulating the immune system to an anti-inflammatory state.[74]

Based on the theoretical framework above, the multiple organ failures that occur suddenly are preceded by cytokine storms. The therapeutic modality for modulating the inflammatory process, which leads to cytokine storms is under investigation. Stem cells with anti-inflammatory, anti-fibrotic and immunomodulatory properties can be used as adjuvant therapies to overcome or prevent cytokine storms, so that clinical deterioration and laboratory parameters can be overcome and the length of stay will be shorter (Figure 1). Currently, our ongoing multicenter, randomized-controlled, open-label clinical trial in four main hospitals for COVID-19 centers in Jakarta, Bandung, Solo and Yogyakarta, Indonesia (Study Protocol No. 01/COVID19/11 June 2020) is using either allogeneic UC-MSCs (10^6 cells/kg bw for 3 times) or standard therapy alone (antivirus therapy along with symptomatic therapy) for severe COVID-19 patient. This preliminary study shows promising results (unpublished data).

Conclusion

Clinical trials using stem cells are not cheap, especially at large-scale production of clinical grade stem cells and its

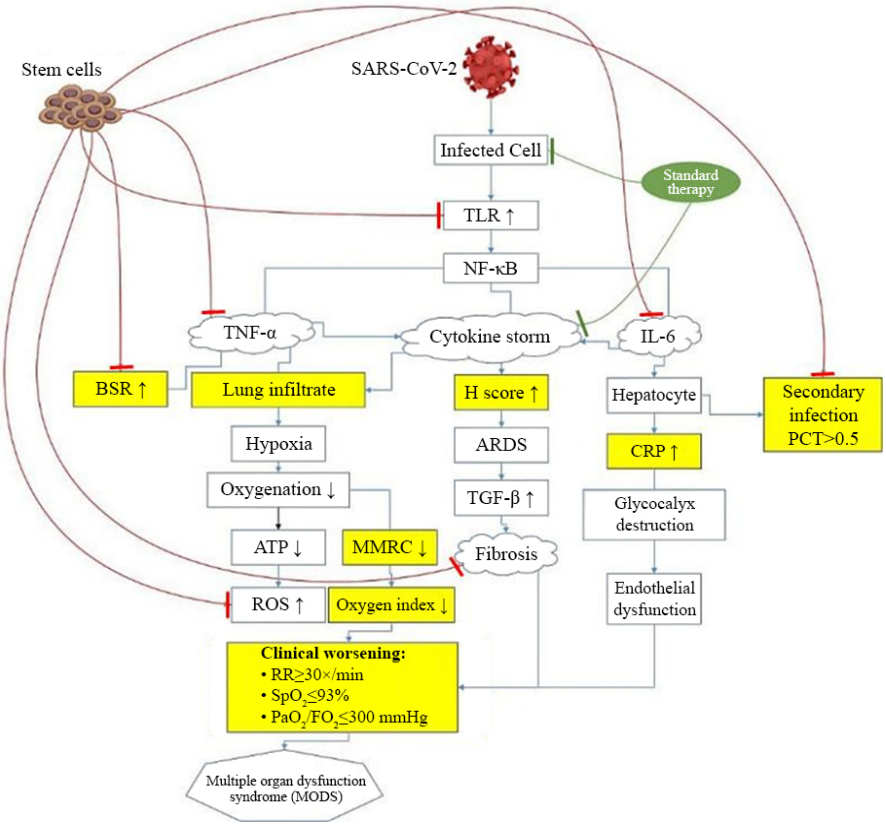

Figure 1. SARS-CoV-2 causes pulmonary damage and stimulates a terrible cytokine storm in the lung, ARDS or even MODS. Patients with fulminant COVID-19 and ARDS have classical serum biomarkers of cytokine release syndrome, including CRP, LDH and IL-6.[2,5] TLR: toll-like receptor; NF-κB: nuclear factor kappa B; BSR: blood sedimentation rare; H score: reactive hemophagocytic syndrome score; PCT: pro-calcitonin; ATP: adenosine triphosphate; mMRC: modified Medical Research Council score; ROS: reactive oxygen species; RR: respiratory rate; SpO_2: oxygen saturation; PaO_2/FiO_2: ratio of arterial oxygen partial pressure (PaO_2) to fractional inspired oxygen (FiO_2); yellow highlight: the primary endpoint that we hope to enhance in our upcoming clinical trial; red line: UC-MSCs inhibition; green line: Antiviral inhibition.

use as COVID-19 therapy. Studies focusing on reducing mortality rate due to COVID-19 using MSCs and its CM are important and need to be supported. Not only vaccines that potentially prevents ones from COVID-19, but MSCs and its CM also have their own roles in reducing the death rate in COVID-19 patients.

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Authors Contribution

WW, AF and YH were involved in concepting the review article and collecting the references. WW, AF, HWSK and ABH drafted the manuscript. YH and TD designed the figures. All authors took parts in giving critical revision of the manuscript and have read and approved the final manuscript.

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