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MESENCHYMAL STEM CELL THERAPY FOR COVID-19: A LITERATURE REVIEW

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Abstrak

Coronavirus Disease (COVID-19), merupakan penyakit saluran pernapasan akut yang telah menjadi krisis kesehatan yang mengancam dunia. Diperlukan terapi yang dapat bertujuan untuk mengurangi jumlah kematian akibat COVID-19 dan salah satu pengobatan yang potensial adalah terapi sel punca. Dalam beberapa tahun terakhir, terapi sel punca merupakan kemajuan dalam kedokteran dengan peluang besar untuk pengobatan COVID-19 karena dianggap menjanjikan dan mutakhir dalam penelitian. Tinjauan pustaka ini dibuat dengan pencarian data komprehensif di database PubMed dan bertujuan untuk memberikan gambaran tentang sel punca mesenkim dan potensinya dalam mengobati COVID-19. Sel punca mesenkim diketahui memiliki fungsi regeneratif, imunomodulasi, dan antiinflamasi. Ada beberapa tantangan terapi sel punca mesenkim pada COVID-19, seperti produktivitasnya yang terbatas dalam situasi mendesak seperti COVID-19 dan disertai dengan beberapa risiko kesehatan dan tindakan pencegahan yang harus diperhitungkan. Namun, sel punca mesenkim masih merupakan terapi yang menjanjikan untuk COVID-19 karena potensi regenerasi dan perbaikan jaringannya, sifat imunomodulator dan anti-inflamasi yang kuat, kurangnya respons imun dalam transplantasi sel, dan kurangnya ekspresi reseptor ACE2.

Kata Kunci: covid-19; sel punca mesenkim; penyakit menular

Abstract

Coronavirus Disease (COVID-19), is an acute respiratory disease that has become a health crisis that threatens the world. A treatment plan that can aim to reduce the number of deaths caused by COVID-19 is needed and one of the potential treatments is stem cell therapy. In recent years, stem cell therapy has become an advancement in medicine with great opportunity for COVID-19 treatment because it is considered promising and cutting-edge in research. This literature review was constructed by comprehensive data searching in database PubMed and aims to provide an overview of mesenchymal stem cells and their potential in treating COVID-19. Mesenchymal stem cells are known to have regenerative, immunomodulation, and anti-inflammatory function. There are several challenges of mesenchymal stem cell therapy on COVID-19, such as their limited productibility in urgent situations like COVID-19 and it comes with a few health risks and precautions that should be taken into account. However, mesenchymal

stem cell is still a promising therapy for COVID-19 because of their regeneration and tissue repair potential, potent immunomodulatory and anti-inflammatory properties, the lack of immune response in cell transplantation, and the lack of ACE2 receptor expression.

Keywords: *covid-19; mesenchymal stem cell; infectious disease*

Introduction

Coronavirus Disease (COVID-19), is an acute respiratory disease that has become a public health crisis that threatens the world (Singhal, 2020) Diseases that originating from zoonotic transmission from bats in Wuhan, China, are now becoming human-to-human transmission with rapid spread and resulting in death toll which continues to increase and resulted in a number of countries carrying out social distancing and lockdowns to reduce transmission rates between countries. (Yuki, Fujiogi, & Koutsogiannaki, 2020) In Indonesia, there have been around 4,266,649 confirmed cases of COVID-19 with a total of 144,136 deaths due to covid to date (10/01/2022). (Satuan Tugas Penanganan COVID-19, 2022) To overcome the pandemic, Indonesia carried out a strategy issued by WHO on March 26, 2020, namely conducting training, mobilizing and expanding the coverage of health workers, establishing a system to find suspected cases, increasing screening and the availability of screening tools, expanding corona health centers by maximizing existing facilities, develop a patient quarantine plan, and focus on suppressing the spread of the virus. (World Health Organization, 2020) This strategy focuses on reducing the number of COVID-19 transmissions. Although it has been done for a long time, this strategy is not effective in reducing mortality in COVID-19 patients. (Satuan Tugas Penanganan COVID-19, 2022) Therefore, a treatment plan is needed that aims to reduce the number of deaths caused by COVID-19 and one of the treatments that can be suggested is stem cell therapy. (Nugraha, Kloping, Yudhawati, Purwandhono, & Hidayati, 2020) In recent years, stem cell therapy has become an advance in medicine that gives great hope because it is considered promising and cutting-edge in research. Previously, stem cells have been used as a treatment option, including as a solution for organ and tissue transplantation and cardiovascular and neurodegenerative treatment. (Zakrzewski, Dobrzyński, Szymonowicz, & Rybak, 2019) Previously, several studies have shown that stem cell therapy was once used as an emerging treatment for respiratory diseases, including viral infections. (Du et al., 2020) Several studies have shown that COVID has the same immunopathogenesis as SARS and Avian influenza, which cause cytokine storms and produce Acute Respiratory Distress Syndrome (ARDS). (Sadeghi, Soudi, Shafiee, & Hashemi, 2020) Mesenchymal Stem Cells are known as stem cells that can treat ARDS because they are able to secrete anti-inflammatory, anti-fibrosis, and anti-apoptotic cytokines, which will eventually reduce the cytokine storm. (Leng et al., 2020) Mesenchymal stem cells can also promote lung regeneration through growth and transdifferentiation. (Tian Sheng Chen et al., 2010; Lai et al., 2012) This review aims to provide an overview of Mesenchymal Stem

Cells and their potential in treating COVID-19 and to review the possible risk and benefit of mesenchymal stem cell therapy on COVID-19 patients.

Method

This literature review was constructed by comprehensive data searching in database PubMed. We searched all relevant related articles with keywords such as stem cell, mesenchymal stem cells, COVID-19, SARS-CoV-2, and its synonym during the search strategy. Boolean operators (AND, OR, NOT) were applied to broaden and narrow the search results with the following combination (STEM CELL OR Mesenchymal Stem Cell) AND (COVID-19 OR SARS-CoV2). Subsequently, we included all articles including comprehensive cohort studies, case reports, randomized controlled trials, and systematic reviews.

Result and Discussion

A. Stem Cell

Stem cells are unique cells in the human body with a special ability called potency. It can differentiate itself into different cell types and self-renewal. (Nawab, Bhere, Bommarito, Mufti, & Naeem, 2019) Because of its unique ability, scientist starts to search for the possibility of using stem cells as a treatment. (Aly, 2020) Stem cells are studied as a solution for tissue and organ transplantation that needs their ability to differentiate into the type of cell that needs to be repaired and it's currently believed as the next future in medicine because of its ability of considerable therapeutic and biotechnical benefit to cure diseases such as cardiovascular and neurodegenrative. Stem cell can be found everywhere, from embryos until adult cells (Zakrzewski et al., 2019).

1. Classification of Stem Cell

Stem cells can be classified according to their cell origin and their potency. Based on their cells origin, stem cell can be classified into four types, embryonic stem cell; fetal stem cell; infant stem cell; and adult stem cell. (Barky, Ali, & Mohamed, 2017)

a) Embryonic Stem Cell

Embryonic stem cell can be found since the first entity of life, the fertilized eggs. Embryonic stem cell can be isolated from the inner cell mass of 5–8 days old embryos. It has the ability to make the entire organism, called totipotency. But, when it reach the formation blastocyst, the cell are no longer totipotent even though it still can develop into all cell type or known as pluripotent. (Choudhery & Harris, 2020; Wobus & Boheler, 2005) It can be stored in culture and then stimulated to differentiate to any cell. The embryonic stem cell also has a great ability in tissue regeneration therapy. (Xinyue Zhang & Huang, 2010) However, the clinical use of ESCs is restricted due to a number of religious, ethical, and legal controversies. (Choudhery & Harris, 2020)

b) Fetal Stem Cell

Fetal stem cell are primal cell that can be found in numerous fetal tissue. Fetal tissue, with the exception of pancreatic cells, are easier to culture and proliferate than adult tissue cell. (Ishii, 2014) It's known to have the potential to treat congenital genetic, hematologic, immune, and metabolic disorder. (Witt, MacKenzie, & Peranteau, 2017)

c) Infant Stem Cell

Umbilical cord stem cell used to thrown away when the baby was born, but now the scientist found out that it can be the sources of Human Stem Cell (HSCs) which can be found in the peripheral blood and bone marrow. It has the ability to self-renewing and multipotent by continuously proliferating and differentiating. Under certain conditions, they will proliferating and differentiating into one or more cell type that form human tissue or organ. They also affect the immune response. (Xie et al., 2020) The umbilical cord stem cell is covered by simple epithelial layer and surrounded by wharton's jelly that protect the blood vessel, prevent it to clumping, and makes it flexible. (Alatyyat, Alasmari, Aleid, Abdel-maksoud, & Elsherbiny, 2020).

d) Adult Stem Cell

The true gold standard for regenerative medicine is the adult stem cell and it already shown the evidence to success. Beside there's no ethical baggage regarding their isolation, it's also approved in many recent clinical trials and at all stages of testing by the Food and Drug Administration due to their practical advantages over pluripotent stem cells. (Prentice, 2019) Adult stem cells can be sourced from neonatal sources (cord blood, cord tissue, placenta, and menstrual blood) and from adult tissues (bone marrow, adipose tissue, dental pulp, and peripheral blood). (Choudhery & Harris, 2020) The example of adult stem cell is Mesenchymal stem cell. Mesenchymal stem cell or MSCs one of adult multipotent cell that have the ability to differentiate into various mesodermal liniage. It can be found almost in all parts of the body, but mostly were isolated from bone marrow and umbilical cord blood for therapeutic uses. (Brignier & Gewirtz, 2010)

B. COVID-19

Coronavirus Disease 2019 (COVID-19) is a highly contagious acute respiratory disease caused by *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2), a new coronavirus strain that was first identified in Wuhan, China, in end of 2019. COVID-19 has spread rapidly globally and was officially declared a pandemic by the *World Health Organization* (WHO) in March 2020 (Tenda et al., 2020).

The complete genome sequence of the 2019 novel-Coronavirus (hereinafter name changed to COVID-19) strain obtained from five patients in the early stages of the outbreak, was nearly identical by 79.6% with SARS-CoV. Further research revealed that the entire genome of this virus shared a 96% identical genome sequence to that of the bat coronavirus. In addition, a large number of infected people have been exposed to a wet market selling animals in Wuhan, China, leading to the

hypothesis that SARS-CoV-2 originated in bats which then mutated and infected humans (Rothan & Byrareddy, 2020; Zhou et al., 2020).

The clinical manifestations of COVID-19 are fever, dry cough, shortness of breath, anosmia, dysgeusia, headache, sore throat, rhinorrhea, nausea, and diarrhea. Palpitations have also been reported in some cases. The main cause of death in patients with COVID-19 increases in patients with underlying conditions such as old age, comorbid diseases such as diabetes and hypertension, increased levels of D-Dimer, signs of sepsis (Garima & Singh, 2020; Leung, 2020).

1. Transmission

   Coronavirus is zoonotic (transmitted between animals and humans) and can spread either directly through droplets or indirectly through contaminated surfaces. (Lotfi, Hamblin, & Rezaei, 2020) Individuals infected with COVID-19 can spread the SARS-CoV-2 virus in several ways, including spread through droplets with a particle size of >5 m and aerosols with a particle size of 5 m. In general, the droplets produced when a person talks, coughs and sneezes can be spread over a distance of 1-2 meters. (Rothan & Byrareddy, 2020) There is also an indirect transmission line through objects that are widely used in daily life that are exposed to droplets from infected people (Kementerian Kesehatan Republik Indonesia, 2020).

2. Pathophysiology

   The COVID-19 virus is composed of several glycoprotein structures, one of which is protein S which has a role as the main key to bind to receptors on the target cells, namely Angiotensin Converting Enzyme-2 (ACE2) which is located in the plasma membrane of human body cells, especially in cells that are lining the alveoli. (Bohn et al., 2020; Tao Zhang, Wu, & Zhang, 2020) Genetic material and viral proteins that enter the cell will duplicate and form new virions on the surface of cells that have been infected. (Tao Zhang et al., 2020) Basically, viruses that enter cells will activate the human body's immune response. After the viral material enters the host cell, the antigen from the virus will be presented to the antigen presenting cell (APC) which will respond to the immune system mediated by T and B cells. (Geng Li et al., 2020) this results in the formation of a humoral immune system consisting of Immunoglobulin M (Ig M) which will disappear on day 12 and Immunoglobulin G (Ig G) which will last longer. (Geng Li et al., 2020) the interaction of viral material with the body's immune system produces an immune response that determines the severity of this COVID-19 virus infection. (Bohn et al., 2020) Even though the body has an immune system, the virus can escape by inducing double membrane vesicles that do not have a Pattern Recognition Receptor (PPR) and replicate in these vesicles so that they cannot be recognized by immune cells. (Xiaowei Li, Geng, Peng, Meng, & Lu, 2020) Viruses have a cytopathic effect and the ability to overwhelm and hide from the immune response affects the severity. In addition, excessive immune reactions

will increase the severity of tissue damage. (Bohn et al., 2020; Geng Li et al., 2020)

In patients with mild symptoms, an increase in T cells, especially CD8 was found on days 7-9, then follicular T helper and Antibody Secreting Cells (ASCs) were found, and a progressive increase in IgM and IgG was found until day 20, without any increase in proinflammatory chemokines and cytokines. (Wang, Horby, Hayden, & Gao, 2020) Otherwise, in patients with severe symptoms, the lymphocyte count was low, with lower monocytes, basophils, and eosinophils, while proinflammatory mediators such as TNF-a, IL-1, IL6, and IL8 were increased. However, T helper, T suppressor and regulatory T cells were decreased. (Zumla, Hui, Azhar, Memish, & Maeurer, 2020) Patients with COVID-19 who have Acute Respiratory Distress Syndrome (ARDS) have decreased CD4 and CD8 T cells, and CD4 and CD8 lymphocytes are hyperactivated. ARDS cases in COVID-19 became one of the causes of death due to an increase in proinflammatory mediators or an uncontrolled cytokine storm, so that the body gave an excessive immune reaction and damaged body tissues, one of which was lung damage with the formation of fibrotic tissue, causing functional failure (Zumla et al., 2020).

3. Current Update on COVID-19 Therapy

Currently, there are plenty of ongoing trials on COVID-19 therapy, mostly revolving around drugs for the treatment of other diseases. The available treatment for COVID-19 is mostly supportive. (Mishra & Tripathi, 2021) There are a few therapy options that are safe for COVID-19 patients recommended by World Health Organization (WHO):

a. Casirivimab and imdevimab (neutralizing monoclonal antibodies) Conditional recommendation for patients at highest risk of hospitalization.
b. IL-6 receptor blockers (tocilizumab or sarilumab) Recommended for patients with severe or critical COVID-19 infection.
c. Remdesivir Conditional recommendation against administering remdesivir in addition to usual care.
d. Systemic corticosteroids Recommended for patients with severe and critical COVID-19 Conditional recommendation against for patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection). (World Health Organization, 2020)

C. Potential Mechanism of Stem Cell Therapy for COVID-19

In recent years, stem cell therapy has been a very promising and cutting-edge research topic. Advances in treatment have given rise to great hope. (Zakrzewski et al., 2019) Many studies have shown that stem cell therapy can be used as one of the emerging treatment strategies for respiratory diseases with no known treatments, including viral infections (Du et al., 2020) Until now, there's still a lot of studies to search for the cure of covid-19. Recent studies have shown that COVID-19 have a similar immunopathogenesis to SARS and avian influenza, which we know as

cytokine storm, and eventually will develop as acute respiratory distress syndrome (ARDS). (Sadeghi et al., 2020) Many studies have used Mesenchymal Stem Cell as the therapy for ARDS due to the ability of Mesenchymal Stem Cell to secrete anti-inflammatory, anti-fibrosis, and anti-apoptosis cytokines, which eventually will reduce the cytokine storm. (Leng et al., 2020) Mesenchymal Stem Cell has been shown to exert immunomodulatory effects through several mechanisms. Mesenchymal Stem Cell is known to promote lung regeneration through growth and trans differentiation. However**,** recent studies have shown that paracrine plays a role in Mesenchymal Stem Cell in lung regeneration. The Mesenchymal Stem Cell benefit**s** from releasing extracellular vesicles such as microvesicles and exosomes known as paracrine mechanisms. Exosomes contain a variety of chemokines, growth factors, messenger RNAs**,** and microRNAs**.** These products have anti-inflammatory and immunomodulatory properties, so they act as immune system regulators. (Tian Sheng Chen et al., 2010; Lai et al., 2012) In addition, exosomes have enormous regeneration potential for repairing and regenerating damaged organs and tissues. (Choudhery & Harris, 2020) Through several immunomodulatory factors, T cell activation can be inhibited by mesenchymal stem cells. (Laing et al., 2019) The regulatory T cells and anti-inflammatory TH2 cells are increased, NO and IDO are released and suppressed the production of T cell cytokine. The regulatory T cells and anti-inflammatory TH2 cells are increased, NO and IDO are released and suppressed the production of T cell cytokine, and then there's another mechanism of MSCs that suppresses the NK cell cytotoxicity and decreases the expression of IFN-γ. MSCs also can prevent the dendritic cell maturation and then retain the dendritic cells in a tolerogenic phenotype and induce anti-inflammatory M2-macrophage polarization with the increased levels of PGE2, TSG-6, and IL-1RA. (Pittenger et al., 2019) Although many of the identified factors have been used individually to inhibit the immune response**,** MSCs can establish an immunomodulatory environment through the secretion of many immunomodulators**.** MSC has been shown to reduce the inflammatory response and protec**t** the host from low mortality cytokine storms without serious side effects. this studies make a lot of changes in the output management of respiratory disease like H7N9, and since it's similar with COVID-19, this approach could be apply for COVID-19 treatment (Jiajia Chen et al., 2020).

D. Mesenchymal Stem Cell on COVID-19

Mesenchymal stem cells, an example of adult stem cell, are a special focus of stem cell-related therapies currently due to their immunomodulatory and regenerative potential. Several sources such as adipose tissue, bone marrow, cord blood, and cord tissues can be sourced in a large number for the mesenchymal stem cells. Mesenchymal stem cells from allogenic sources are the better option of treatment for severely ill patients because it can be cryopreserved and readily available for repetitive uses. Meanwhile, autologous sources are better for COVID-19 patients

who are at high risk of developing the more severe disease (older patients with comorbidities) (Choudhery & Harris, 2020).

Mesenchymal stem cells migrate and work by regenerating and inducing damaged tissues repair by secretion of various bioactive molecules to stimulate resident cells. (Choudhery & Harris, 2020) Mesenchymal stem cells also work by their potent immunomodulatory and anti-inflammatory properties. It is hypothesized that mesenchymal stem cells therapy can prevent the cytokine storm production. Mesenchymal stem cell also lacks the expression of the ACE2 receptor that is the mediator of entry for SARS-CoV-2 into the host cell. Transplantation of ACE2-negative mesenchymal stem cells was effective in treating patients with COVID-19 pneumonia and that the cells used remained resistant to infection with SARS-CoV-2. (Saleh & Ghazzawi, 2021) All these characteristics have made MSCs a potential candidate for the treatment of COVID-19. (Choudhery & Harris, 2020)

Mesenchymal stem cells are also known as hypoimmunogenic cells because they lack important histocompatibility complex class II (MHCII) antigens and other cell surface molecules that help induce and regulate the immune response. These cells play a significant role in transplantation. The regulatory mechanism of these cells is a complex process involving pro-inflammatory and anti-inflammatory molecules. Various theories have been proposed based on in vitro and in vivo studies. There is no clear theory of how these cells regulate the immune system in such an organized way, but much is known about their interaction with the cells that maintain the immune system. Increase. T cells, B cells, and natural killer cells work with mesenchymal stem cells in ways that are not clearly understood but are sufficient to develop therapeutic strategies (Shah, Kumar, & Ambasta, 2011).

E. Challenges on Mesenchymal Stem Cell Therapy on COVID-19

Stem cell therapy is currently still under clinical trials and hasn't been approved yet for prevention or therapy for COVID-19. Recent clinical trials of stem cell therapy on COVID-19 haven't brought any conclusion and most trials would need a larger sample size, randomization, proper control groups, and long-term follow-ups. Stem cells are also limited in production. It is not possible to produce a big amount of stem cells in a short period of time, especially in urgent situations like COVID-19 (Saleh & Ghazzawi, 2021).

Mesenchymal stem cell infusion risks promoting thrombus formation especially in patients suffering hyper-coagulopathy. The risk is promoted by higher mesenchymal stem cell doses and higher passage. This risk is prevented by lowering the quantity of stem cell passage. (Saleh & Ghazzawi, 2021) In a retrospective study of 25 severe COVID-19 patients that were injected mesenchymal stem cells saline solution at a speed of ~20 drops per minute, there was a patient that experienced heart failure while on treatment. The research also found that only 3 out of 25 patients experienced side effects, noting that serum levels of LAC, cTnT, and CK-MB were elevated significantly after the administration of mesenchymal stem cell therapy. Therefore, mesenchymal stem cell therapy should be used with caution in

patients with metabolic acidosis or coronary heart disease (Xian Chen, Shan, Wen, Sun, & Du, 2020).

F. Limitation of Evidence

COVID-19 is still considered new and there is very little information available on stem cell therapy as a treatment option. The clinical trials results of stem cell therapy on COVID-19 patients are still considered inconclusive and it would need more randomized controlled trials with longer periods of follow-ups and a bigger sample size to come to a conclusion of the therapy effectiveness. However, this study managed to evaluate the potentials of mesenchymal stem cell in treating COVID-19.

Conclusion

There are several challenges of mesenchymal stem cell therapy on COVID-19, such as its limited productibility in urgent situations like COVID-19 and it comes with a few health risks and precautions that should be taken into account. However, mesenchymal stem cell is still a promising therapy for COVID-19 because of their regeneration and tissue repair potential, potent immunomodulatory and anti-inflammatory properties, the lack of immune response in cell transplantation, and the lack of ACE2 receptor expression. However, since mesenchymal stem cell therapy is still a very new topic, there is very little information on it and more clinical trials with longer periods of follow-ups and bigger sample sizes should be conducted to evaluate the effectiveness and safety of the therapy.

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