Stem Cell Research and Therapeutics
SCRT, 7(1): 210-213
www.scitcentral.com

ISSN: 2474-4646

Short Communication: Open Access

Stem Cell Therapy: A Feasible Novel Therapeutic Option for COVID-19 and Long-COVID Patients

Diana Esquivel[1,2*], Rangnath Mishra[1,2] and Anand Srivastava[1,2]

[*1]*Global Institute of Stem Cell Therapy and Research, México.*

[2]*Global Institute of Stem Cell Therapy and Research, San Diego, CA-92122, USA.*

Received March 03, 2022; Revised April 03, 2022; Accepted April 06, 2022

Following the worldwide outbreak of highly infectious novel coronavirus that took place by the end of 2019, a great concern regarding the pathology and biological characteristics alarmed the medical community. The virus, named SARS-CoV-2, causes severe affliction to internal organs, more often to the lungs, and thereby, causes the disease commonly known as COVID-19. The virus enters the cells via the ACE2 receptor frequently found on the membranes of the respiratory system and circulatory system cells, especially in the lungs. This leads to an acute respiratory distress syndrome (ARDS), usually accompanied by a serious cytokine decompensation known as cytokine storm [1]. It has been documented that interstitial fibrosis, pulmonary hemorrhagic infarcts, alveolar edema, and inflammatory injuries to epithelial cells are among the most common pathological changes in COVID-19 patients [2]. Furthermore, the observed effects on different systemic organs are reported to develop following the acute inflammation observed after the cytokine storm. The virus induced injuries are more severe in the organs having a rich presence of ACE2 receptors. In addition, the infection leads to several complications including neurological manifestations, skeletal muscle injuries, malfunctioning of the liver, myocardial infarction, acute kidney injuries are also reported to be commonly affected organs after the infection [3-5]. Understanding the structural aspects of SARS-CoV-2 and underlying molecular mechanisms leading to pathological manifestations has led to several treatment plans primarily keeping the focus on reducing the ill-effects of the cytokine storm, promoting the patient's own immune system to counteract the viral infection; and thereby, help recover the damaged tissues and organs. Recently, different vitamin supplements like vitamin D have been reported to prevent the infection as well as to improve the clinical outcomes even after the infection [6]. A high dose of vitamin D (50,000 IU of ergocalciferol) has been described to improve the clinical recovery of COVID-19 patients [7]. This finding can be attributed to the activation of vitamin D receptors, which directly reduce the secretion of inflammatory cytokines. Similarly, the administration of Hyperbaric Oxygen (HBO_2) therapy in COVID-19 patients is reported to decrease the degrees of lung inflammation, shortness of breath, and dyspnea while increasing the blood oxygen levels. Moreover, HBO_2 therapy has been proven to promote the regeneration of several tissues and angiogenesis via the activation of a number of growth factors [8,9]. In pursuit to find effective therapeutic interventions for treating acute as well as long COVID-19 effects, Mesenchymal Stem Cell (MSC) therapy has been tried which already has gained a reputation in inhibiting effects of inflammatory cytokines and in upregulating the immune system response even in critical cases [10]. Regardless of the source of origin of the cells, promising results are possible because of the remarkable immunomodulatory properties of the MSCs. It has been reported that the primary abilities of MSCs are immunomodulatory, anti-fibrotic, angiogenic, chemo-attractor, and anti-apoptotic properties [11]. According to several studies, MSC administrations have been proven to be safe and efficient in different types of maladies including systemic diseases, respiratory conditions, and those caused by immune imbalance. Although dosage will vary depending on the patient's condition and response, administration of 1 x 10^6 MSCs per kilogram of body weight, has proven to be efficient for a variety of maladies [12-15].

One of the first studies published assessing the effectiveness of the MSC therapy in patients with SARS-CoV-2 infection was reported from Beijing, China. Single intravenous administration (1x10^6 MSCs per kg bw) was performed to 7 critically ill patients along with conventional care protocols. A dramatic reduction in the levels of serum proinflammatory cytokines and chemokines was observed in the stem cell-treated patients. The induction of regulatory dendritic cells

Corresponding author: Diana Esquivel, Global Institute of Stem Cell Therapy and Research, México, Tel: +52(646)1218423; E-mail: dianae@giostarmexico.com

Citation: Esquivel D, Mishra R & Srivastava A. (2022) Stem Cell Therapy: A Feasible Novel Therapeutic Option for COVID-19 and Long-COVID Patients: A Mini-Review. Stem Cell Res Ther, 7(1): 210-213.

in the MSC-treated group supported the immunomodulatory properties reported previously in these cells [15]. A portion of approximately 80% of MSCs administered via the intravenous route settles in the respiratory system, which improves the pulmonary microenvironment, reduces the cytokine over-expression, and thereby, can support the regeneration of various organs. After the MSC administration in COVID-19 patients, expression levels of several growth factors like fibroblast growth factor (FGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), are reported to be increased. These findings indicate that MSCs can mitigate the cytokine imbalance during the critical stages of the infection, and eventually can promote the regeneration of damaged tissue [10-15]. Up to the date of preparation of this publication, 93 clinical trials were still undergoing.

The details of the trial studies and their current status can be checked at https://clinicaltrials.gov

Moreover, the regenerative capability of MSC makes them a feasible therapy in treating long COVID-19 sequelae. On a recent clinical follow-up study, a cohort of 1733 adult patients diagnosed with this virus, revealed that six months after the infection, 76% of the patients presented at least one persistent symptom. Conditions include fatigue, muscle weakness, and reduced hearth and pulmonary function. Furthermore, 50% of the patients reported with residual chest imaging abnormalities [16]. The novelty of the disease complicates the prediction of time of recovery, nevertheless, long term effects of COVID-19 is starting to gain attention and research. It is well known that MSC have the ability to differentiate into several cell types, including myogenic, pulmonary and cardiac lineages. The remarkable capacity for tissue regeneration of MSC has been well documented in several studies. Therefore, MSC therapy might be good option for patients to recover normal organ function through tissue regeneration, after been struggle with COVID-19 infection.

The cytokine storm formed during the infection, leaves behind excessive oxidative stress, which induce damage to multiple organs, including the skeletal muscle. Consequently, the muscle undergoes degenerative transformation and shrinkage. Interestingly, unbalanced levels of cytokines also interfere with muscular integrity hormones like testosterone [17]. Although research is still in progress, MSC therapy has proven to be a feasible and safe option in treating muscle degeneration and dystrophy, both in animal models and clinical trials [18,19]. Similarly, the inflammation process, along with the increased metabolic and myocardial demand occurred during the infection of COVID-19, are reported to contribute to the persistent cardiovascular symptoms after the disease. One of the most common long COVID-9 effects is the postural tachycardia syndrome (POTS). This syndrome leads to changes in hearth rate with positional changes, accompanied with palpitations and excessive fatigue. It is presumably related to the interaction of SARS-CoV-2 and the ACE2 protein expressed; however more research is needed to clarify this hypothesis [20,21]. Nevertheless, the administration of allogenic MSC, has proven to be safe and effective on many hearth conditions, including ischemic, infarct and chronic heart failure. MSC interaction with damaged tissue promotes the secretion of growth factors, which leads to decrease of apoptosis; at the same time induces angiogenesis, and the recruitment of other stem cells, to reduce fibrotic tissue. Specifically, it is thought that thymosin β4 and Wnt antagonist SFRP-2 are directly involved in hearth regeneration, since they promote wound healing and protect cardiomyocytes form hypoxia-induced apoptosis respectively [22,23].

Likewise, due to the severe damaged observed on pulmonary system after COVID-19 infection, lungs are highly prone to present long-term injury. As observed in 2003 outbreak of severe acute respiratory syndrome (SARS), affection of alveolar epithelial cells is observed during the acute phase of infection. This promotes cellular changes, mitochondrial dysfunction, and ultimately, dysregulation in repair mechanisms and fibrosis. Furthermore, deficit on the diffusion capacity for carbon monoxide (DLCO) is still present after hospital discharge in most patients, and is associated with the most severe cases [24,25]. Intravenous or intrathecal administration of MSC in treating lung conditions has proven to be efficient and safe. Chronic lung diseases, such as obstructive bronchiolitis, idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease, are reported to have positive outcomes when using MSC therapy. Through cell communication, MSC promotes the secretion of VEGF, FGF-10, interleukin 10 (I-10), prostaglandin E2, angiopoietin 1 (ANGPT-1), Lipoxin A4, among other angiogenic factors; which leads to the recruitment of endothelial progenitor cells (EPCs), responsible of repair the vascular damaged commonly observed in lung conditions [26,27].

Almost two years have passed since the outbreak of the pandemic took place. The remarkable efforts by the scientific, medical, and healthcare communities, along with the several vaccination programs by almost all governments around the globe give hope about minimizing the pandemic-caused social and financial losses to the world community. Nevertheless, investigations into more efficient approaches to treat COVID-19 and long COVID-19 is still desirable. It is being reported that almost 80% of COVID-19 patients have at least one residual symptom even six months after the patient has recovered from acute form of the disease [28]. Is important to mention that the principal mechanisms of action against the viral infection of COVID-19, is an efficient immune system able to cope with the challenge. Although more clinical trial results are needed to elucidate the effectiveness of the MSC therapy; considering the different curative properties of the stem cells, MSC therapy appears to

be a feasible option for treating COVID-19 and long-COVID patients. Its combination with other therapies such as vitamin supplementation and/ or HBO_2 can give the patient's own system the strength to reduce or prevent altogether the duration of hospitalization caused by the cytokine imbalance. The combination therapy can promote the production and secretion of the necessary growth factors to regenerate damaged organs and tissues [6-10].

REFERENCES

1. Singh GS (2020) N. Fatality in COVID 19: An Overview of Causes of Death and Organ Involvement. Int J Adv Med 7(7): 1190.
2. Luo WR, Yu H, Gou JZ, Li XX, Sun L (2020) Histopathological Findings in the Explant Lungs of a Patient With COVID-19 Treated with Bilateral Orthotopic Lung Transplant. Transplantation 104(11): e329-e331.
3. Mao L, Wang M, Chen S, He Q, Chang JH (2020) Neurological Manifestations of Hospitalized Patients with COVID-19 in Wuhan, China: A Retrospective Case Series Study. JAMA Neurol 77(6): 683-690.
4. Zaim S, Chong JH, Sankaranarayanan V, Harky A (2020) COVID-19 and Multiorgan Response. Curr Probl Cardiol 45(8): 100618.
5. Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, et al. (2020) Clinical Findings in a Group of Patients Infected with the 2019 Novel Coronavirus (SARSCov2) Outside of Wuhan, China: Retrospective Case Series. BMJ 368: m606.
6. Moscatelli F, Sessa F, Valenzano A, Polito R, Monda V, et al. (2021) COVID-19: Role of Nutrition and Supplementation. Nutrients 13(3): 976.
7. Ohaegbulam KC, Swalih M, Patel P, Smith MA, Perrin R (2020) Vitamin D Supplementation in COVID-19 Patients: A Clinical Case Series. Am J Ther 27(5): e485-e490.
8. Ortega MA, Fraile-Martínez O, García-Montero C, Callejón-Peláez E, Sáez MA, et al. (2021) A General Overview on the Hyperbaric Oxygen Therapy: Applications, Mechanisms and Translational Opportunities. Medicina 57(9): 864.
9. Esquivel D, Mishra R, Soni P, Srivastava A (2021) A Possibility of Using Mesenchymal Stem Cell Therapy in Combination with Hyperbaric Oxygen Therapy for Treating COVID-19 Patients. Ann Stem Cell Res Ther 5(1): 1040.
10. Esquivel D, Mishra R, Soni P, Seetharaman R, Mahmood A, et al. (2020) Stem Cells Therapy as a Possible Therapeutic Option in Treating COVID-19 Patients. Stem Cell Rev Rep 17(1): 144-152.
11. Silva-Meirelles L, Fontes AM, Covas DT, Caplan A (2009) Mechanisms Involved in the Therapeutic Properties of Mesenchymal Stem Cells. Cytokine Growth Factor Rev 20(5-6): 419-427.
12. Vizoso F, Eiro N, Costa L, Esparza P, Landin M, et al. (2019) Mesenchymal Stem Cells in Homeostasis and Systemic Diseases: Hypothesis, Evidences, and Therapeutic Opportunities. IJMS 20(15): 3738.
13. Rad F, Ghorbani M, Roushandeh AM, Roudkenar MH (2019) Mesenchymal Stem Cell-Based Therapy for Autoimmune Diseases: Emerging Roles of Extracellular Vesicles. Mol Biol Rep 46(1): 153349.
14. Behnke J, Kremer S, Shahzad T, Chao CM, Böttcher-Friebertshäuser E, et al. (2020) MSC Based Therapies-New Perspectives for the Injured Lung. JCM 9(3): 682.
15. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, et al. (2020) Transplantation of ACE2- mesenchymal stem cells improve the outcome of patients with COVID-19 pneumonia. Aging Dis 11: 216.
16. Huang C, Huang L, Wang Y, Li X, Ren L, et al. (2021) 6-month consequences of COVID-19 in patients discharged from hospital: A cohort study. Lancet 397(10270): 220-232.
17. Ali AM, Kunugi H (2021) Skeletal Muscle Damage in COVID-19: A Call for Action. Medicina 57(4): 372.
18. Wilschut KJ, Ling VB, Bernstein HS (2012) Concise Review: Stem Cell Therapy for Muscular Dystrophies. Stem Cells Transl Med 1(11): 833-842.
19. Tedesco FS, Cossu G (2012) Stem cell therapies for muscle disorders. Curr Opin Neurol 25(5): 597-603.
20. Chilazi M, Duffy EY, Thakkar A, Michos ED (2021) COVID and Cardiovascular Disease: What We Know in 2021. Curr Atheroscler Rep 23(7): 37.
21. Johansson M, Ståhlberg M, Runold M, Nygren-Bonnier M, Nilsson J, et al. (2021) Long-Haul Post-COVID-19 Symptoms Presenting as a Variant of Postural Orthostatic Tachycardia Syndrome. JACC: Case Rep 3(4): 573-580.
22. Joggerst SJ, Hatzopoulos AK (2009) Stem cell therapy for cardiac repair: Benefits and barriers. Expert Rev Mol Med 11: e20.
23. Povsic TJ, Gersh BJ (2021) Stem Cells in Cardiovascular Diseases: 30,000-Foot View Cells 10(3): 600.
24. Fraser E (2020) Long term respiratory complications of Covid-19. BMJ. 370: m3001.
25. Blanco J-R, Cobos-Ceballos M-J, Navarro F, Sanjoaquin I, Arnaiz de las Revillas F, et al. (2021) Pulmonary long-term consequences of COVID-19

infections after hospital discharge. Clin Microbiol Infect 27(6): 892-896.

26. Hosseinirad H, Rashidi M, Moghaddam MM, Tebyanian H, Nouraei S, et al. (2018) Stem cell therapy for lung diseases: From fundamental aspects to clinical applications. Cell Mol Biol (Noisy-le-grand) 64(10): 92.
27. Parekh KR, Nawroth J, Pai A, Busch SM, Senger CN, et al. (2020) Stem cells and lung regeneration. Am J Physiol-Cell Physiol 319(4): C675-C693.
28. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, et al. (2021) More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. Sci Rep 11: 16144.