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

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Abstract

The outbreak of novel virus SARS-CoV-2 by the end of 2019 caused a great concern in the medical and global community. The virus enters the cell through the ACE2 receptor affecting primarily the respiratory and circulatory system, causing the disease commonly known as COVID-19. Patients infected with the virus develop acute respiratory distress syndrome (ARDS), usually accompanied by a cytokine storm.

Several treatment plans focus on reducing the effect of cytokine decompensation while promoting the patients' immune system to counteract the infection. Recently, high doses of vitamin D (50,000 IU of ergocalciferol) and administration of Hyperbaric Oxygen (HBO2) therapy, have proven to reduce the secretion of inflammatory cytokines as well as promote tissue regeneration in COVID-19 infected patients. Similarly, given the remarkable properties of Mesenchymal Stem Cells (MSC), intravenous administration of MSC has been reported to improve the pulmonary microenvironment, reduce the cytokine storm and support the regeneration of various organs.

A combination of these therapies can give the patient the strength to reduce or prevent hospitalization caused by cytokine imbalance and promote the regeneration of tissue and organs via the production and secretions of growth factors.

Keywords: *COVID-19, Mesenchymal stem cells therapy, Vitamin supplementation, Hyperbaric chamber*

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 haemorrhagic 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 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 (HBO2) 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, HBO2 therapy has

been proven to promote the regeneration of several tissues and angiogenesis via the activation of several 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 of 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-attractors, 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 [12-14].

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 of MSCs was performed on 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 in the MSC-treated group supported the immunomodulatory properties reported previously in these cells [15]. A portion 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, 83 clinical trials were still undergoing. The details of the trial studies and their current status can be checked at https://clinicaltrials.gov.

Conclusion

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 are 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 an acute form of the disease [16]. Is important to mention that the principal mechanism 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 HBO2 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, 9, 10].

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