MedCrave
Step into the World of Research
Journal of Stem Cell Research & Therapeutics

Editorial

Open Access

Stem cell therapy for COVID-19 patients for combating the proinflammatory cytokine storm and related damages

Editorial

Volume 6 Issue 2 - 2020

Diana Esquivel,[1] Rangnath Mishra,[1,2] Anand Srivastava[1,2]
[1]Global Institute of Stem Cell Therapy and Research, México
[2]Global Institute of Stem Cell Therapy and Research, USA

Correspondence: Anand Srivastava, Global Institute of Stem Cell Therapy and Research (GIOSTAR), 4660 La Jolla Village Drive, San Diego, CA, 92122, USA, Email anand@giostar.com

Received: October 09, 2020 | **Published:** December 04, 2020

By the end of 2019 an outbreak of a novel virus was confirmed which has caused more than 35 million cases, and more than a million deaths all around the globe (https://covid19.who.int/ accessed on Oct 5th, 2020). The emergence of the virus primarily recorded from Wuhan, Hubei Province, China, has caused global concern due to a very high infection rate with a high mortality rate which have been reported to vary in different societies. For example, mortality rate in the USA is estimated to be in the range of 2.9% while that in Italy has reached as high as 11.3%.[1] The reasons for varying mortality rates can depend on several factors like the prevalence of other comorbidities in the population, availability and quality medical services, preparedness plans and their implementation. It has been a well-established fact that the presence of one or more comorbidities enhances chances of developing COVID-19 in a more acute form which may be life-threatening in many cases.[2]

The phylogenetic analysis helped name the causative virus as SARS-CoV-2 primarily affects respiratory organs though, it can affect almost all of the organs. The SARS-CoV-2 virus enters the cells after interacting with the ACE2 receptors, which are richly found on AT2 cells of the lung leading to damages in the structural organization of organ resulting in insufficient gaseous exchange or acute respiratory distress syndrome (ARDS), which is also accompanied by a storm of proinflammatory cytokines.[3] Histopathologic observations have reported pulmonary hemorrhagic infarcts along with alveolar edema accompanied with inflammatory injuries and extensive pulmonary interstitial fibrosis in the epithelial cell linings.[4] At the same time, many other organs have been reported to suffer extensive injuries during the infection. ACE2 is also expressed in endothelial cells, rendering them vulnerable to the infections by the virus. Because of the settling acute infection, and -caused cytokine storm-induced increased myocardial output demand, it becomes probable that pre-existing atherosclerotic plaques get mobilized, which can cause myocardial infarction.[5] It has been reported that patients infected with SARS-CoV-2 developed acute kidney injuries (AKI) also. Regarding the AKI, even though more research studies for deciphering the exact mechanisms of pathogenesis are required, two steps seem more plausible. Acute endothelial necrosis, multi-organ failures are recorded in COVID-19 patients due to the infection as a study based on single-cell transcriptome analysis reported that ACE2 receptor expression at comparatively higher levels in kidney cells.[6] Injuries in the nervous tissues also have been a major indication in many patients of the class as several were diagnosed with damages in the central nervous system in a recent retrospective study on the patients hospitalized in Wuhan, China. The findings demonstrated that 36.4% of infected patients had some degree of neurologic symptoms, and the most affected persons of the group were highly likely to develop acute cerebrovascular disease, impaired memory, and skeletal muscle-related injuries.[7] The study also demonstrated the presence of severe liver injuries during and after the infection were fairly common in the COVID-19 patients. Studies have reported that up to 53% of patients had abnormally high levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin, the well-established parameters to reflect some sort of liver ailment or malfunctioning. Although more research is needed, observations indicate that the some degree of liver damage is a very common indication in COVID-19 patients.[5]

Moreover, new insights into the pathobiology of the novel coronavirus revealed that most of the patients who had recovered from COVID-19 have long term effects and may need additional care to lead a normal life. Up to 87.4% of the patients reported to have at least one symptom persisting even after 3 months of the recovery, of which fatigue and dyspnea were the most common ones.[8] Though more studies are needed to evaluate the long term effects of the disease on various internal organs, so far it is clear that the severe damages caused by the infection lead to reduced capacities of lungs and other highly vascularized organs which may need way longer time to regain normal functionality, and the time needed will depend on their ability to recover.[5]

As of now, the standard care for the patients in discussion, in general, involves treatment with anti-viral drugs for inhibiting viral multiplication, and corticosteroids for inhibiting inflammation. However, these drugs have a number of undesired side effects. Clinicians are still looking for a safer and more effective therapeutic option for treating the disease. The use of Mesenchymal Stem Cells (MSCs) has gained importance in treating various autoimmune disorders like arthritis, inflammatory bowel disease, and respiratory afflictions among other maladies.[9] Although different mechanisms of their action have been suggested, studies support the immunomodulatory and regenerative properties of MSCs could be the principal factors helping in the recovery of the patients.[10,11] During cell to cell communications, it has been documented that MSCs can secrete diverse anti-inflammatory cytokines and trophic factors like TGF-β, HGF, LIF, GAL, NOA1, FGF, VEGF, EGF, BDNF, and NGF which contribute to the regeneration of the lung, kidney, nervous system, liver, and other internal organs.[10,12]

In order to minimize the ill-effects of the cytokine storm of pro-inflammatory cytokines recorded in the early stages of coronavirus

infection, intravenous administration of MSCs has proven to be efficient in reducing the level of pro-inflammatory cytokines and chemokines while inducing cell-mediated immunity by activating regulatory dendritic cell population.[13] Our group (unpublished data) including other scientific groups have recorded in few case studies reporting recovery of a critically ill patient infected with the virus after the infusion of MSCs.[13] The patient presented with severe multi-organ damages caused by COVID-19-induced inflammatory responses resulting in severe pneumonia, acute respiratory distress, moderate anemia, hypertension, type 2 diabetes, electrolyte disturbance, immunosuppression among other internal conditions. MSC therapy along with other immune modulating agents (thymosin α1) has demonstrated excellent outcomes on the regulation of cytokine storm and the recuperation of the internal organs. While the immunomodulation mechanisms would be regulating the cytokine storm, the regeneration properties of MSCs would be helping the damaged organs to regain their functions, even long after the infection is eliminated, and thereby, help recover the individual from post-COVID-19 syndrome.[14]

Finally, MSC therapy is starting to garner attention of the scientists and clinicians in pursuit of an effective treatment for COVID-19 also. However, more studies are still needed on patients treated with MSCs to decipher the underlying mechanisms responsible for the excellent outcomes recorded in humans so far in terms of regulating the cytokines levels and in the regaining functionality of organs.[13,14] It is important point worth keeping in mind that MSC therapy is a safe and it is proving to be an effective option in numerous indications. In addition, unlike almost all pharmacologic agents, MSCs have been reported to be very safe in clinical use, and only rarely mild undesired adverse events like fever are recorded.[15] Considering these facts, MSCs could be a very useful and safe therapeutic option for COVID-19 patients suffering from active infection; and even after that by helping repair and regenerate affected internal organs. Keeping the various mechanisms of stem cell-mediated therapeutic benefits in mind, it is logical to infer that MSCs could be a good tool for treating the post-COVID-19 syndrome as well.

References

1. Johns Hopkins University & Medicine. Mortality Analyses. Johns Hopkins University & Medicine 2020.
2. Goh HP, Mahari WI, Ahad NI, et al. Risk Factors Affecting COVID–19 Case Fatality Rate: A Quantitative Analysis of Top 50 Affected Countries. *Europe PMC* 2020.
3. Garima S, Singh N. Fatality in COVID 19: An Overview of Causes of Death and Organ Involvement. *Int J Adv Med.* 2020;7:1190.
4. Luo WR, Yu H, Gou JZ, et al. Histopatological Findings in the Explant Lungs of a Patient with COVID–19 Treated With Bilateral Orthotopic Lung Transplant. *Transplantation.* 2020;2020.
5. Zaim S, Chong JH, Sankaranarayanan V, et al. COVID–19 and Multiorgan Response. *Current Problems in Cardiology.* 2020;45:100618.
6. McIntosh K. Coronavirus disease 2019 (COVID–19): epidemiology, virology, clinical features, diagnosis, and prevention. *UpToDate.* 2020.
7. Mao L, Wang M, Chen S, et al. Neurological Manifestations of Hospitalized Patients with COVID–19 in Wuhan, China: A Retrospective Case Series Study. *JAMA Neurol.* 2020;77:683–690.
8. Carfì A, Bernabei R, Landi F. Persistent Symptoms in Patients after Acute COVID–19. *JAMA* 2020;324:603.
9. Larijani B, Esfahani EN, Amini P, et al. Stem cell therapy in treatment of different diseases. *Acta Med Iran*. 2012;50:79–96.
10. Esquivel D, Mishra R, Soni P, et al. Stem Cells Therapy as a Possible Therapeutic Option in Treating COVID–19 Patients. *Stem Cell Rev and Rep.* 2020, *In Press*.
11. da Silva Meirelles L, Fontes AM, Covas DT, et al. Mechanisms Involved in the Therapeutic Properties of Mesenchymal Stem Cells. *Cytokine & Growth Factor Reviews.* 2009;20:419–427.
12. Fan XL, Zhang Y, Li X, et al. Mechanisms Underlying the Protective Effects of Mesenchymal Stem Cell–Based Therapy. *Cell Mol Life Sci*. 2020;77:2771–2794.
13. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2– mesenchymal stem cells improves the outcome of patients with COVID–19 pneumonia. *Aging and Disease.* 2020;11:216.
14. Liang B, Chen J, Li T, et al. Clinical remission of a critically Ill COVID–19 patient treated by human umbilical cord mesenchymal stem cells. *ChinaXiv*. 2020:202002.00084.
15. Thompson M, Mei SHJ, Wolfe D, et al. Cell Therapy with Intravascular Administration of Mesenchymal Stromal Cells Continues to Appear Safe: An Updated Systematic Review and Meta–Analysis. *EClinicalMedicine.* 2020;19:100249.