SCIE DOI: 10.14744/scie.2022.26086
South. Clin. Ist. Euras. 2022;33(3):331-335

Review

Use of Stem Cell Therapy in COVID-19

Mustafa Törehan Aslan,[1,2] Öner Özdemir,[3] İlke Özer Aslan[4]

[1]Department of Pediatrics, Division of Neonatology, Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Türkiye
[2]Advanced Neonatal Research Master Program, Graduate School of Health Sciences, Institute of Child Health, Hacettepe University, Ankara, Türkiye
[3]Department of Pediatrics, Division of Pediatric Allergy and Immunology, Sakarya University Training and Research Hospital, Sakarya, Türkiye
[4]Department of Obstetrics and Gynecology, Tekirdağ Namık Kemal University Faculty of Medicine, Tekirdağ, Türkiye

Submitted: 06.07.2022
Accepted: 18.07.2022

Correspondence: Öner Özdemir, Sakarya Üniversitesi Eğitim ve Araştırma Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, 54100 Sakarya, Türkiye

E-mail: ozdemir_oner@hotmail.com

Keywords: Acute respiratory distress syndrome; COVID-19; stem cell therapy; tissue regeneration.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 is known to cause the new coronavirus disease 2019 (COVID-19), in which many organs and systems such as the lung, heart, and immune system can be severely affected. Currently, the treatment process is generally based on supportive and palliative care. Some potential drugs are being tested for treatment. At this point, perhaps a promising treatment method for many diseases in the future seems to be stem cell therapy in recent times. Stem cell therapy in COVID-19 may be a treatment method that can play an important role, especially in resistant and severe cases. In this review, we summarized the potential mechanisms of stem cell therapy and developments in this treatment modality.

INTRODUCTION

The new coronavirus disease 2019 (COVID-19), which manifests itself with many clinical signs ranging from mild to moderate respiratory symptoms to severe acute respiratory distress syndrome (ARDS), has caused millions of people to become ill and even die around the world. It is thought that the factors that play a major role in the progression of COVID-19 and the formation of organ damage are excessive inflammation and cytokine storm.[1,2]

The immunological cascade initiated by this increased inflammation, especially in the lungs, causes an increase in the permeability of the lung endothelium, as in influenza infections, interstitial edema in the lung, diffuse alveolar damage, dysfunction, and ARDS as the final outcome.[3] Considering this situation, it is an important point that in addition to symptomatic or antiviral treatments, immunomodulatory treatments such as convalescent plasma therapy or mesenchymal stem cell (MSC) may also be effective in preventing the progression of the disease in COVID-19.[4]

MSCs are a current treatment method that has wide clinical applications in regenerative medicine and has also been extensively researched in terms of their immunomodulatory properties.[5] Although many studies are mentioned in the literature regarding the efficacy and safety of MSCs in preventing comorbidities associated with COVID-19,

further studies are needed for scientific evidence to emerge in terms of the side effects and long-term safety and course of these treatments.[6]

Reasons for the use of MSC in the treatment of COVID-19

Stem cells are classified as embryonic or adult according to the tissue from which they originate. Today, MSCs are widely used in clinical practice thanks to their ability to escape from being perceived as foreign by the immune system. In many in vivo and in vitro studies conducted in recent years, it is thought that MSCs on the alveoli act as a barrier in clinical conditions such as ARDS, which are accompanied by disorders in the oxygen–carbon dioxide exchange.[7] In addition to anti-inflammatory and immunomodulatory properties, MSCs also have functions such as self-renewal and versatile differentiation.[8]

MSCs are nonhematopoietic cells that can be isolated from different tissues such as the umbilical cord, adipose tissue, and bone marrow. According to the studies, it has been understood that stem cells from the umbilical cord are more advantageous than those obtained from other tissues due to their higher percentage of stem cells. MSCs can also support the regeneration of type 2 alveolar epithelial cells by secreting many factors such as hepatocyte growth factor, vascular endothelial growth factor, and keratinocyte growth factor, thanks to their regenerative properties.[9] In addition, it has an important advantage that MSCs have the ability to migrate and settle in the damaged area and to initiate tissue repair.[10] It is thought that MSCs, which can be used in the treatment of autoimmune diseases, spinal cord injuries, and degenerative diseases, can be a strong alternative in the treatment of severe COVID-19 by playing an important role in healing lung damage, suppressing overactive inflammatory response, and suppressing pulmonary fibrosis. Bearing in mind the ethical issues, the production and preparation of MSCs must be done in accordance with quality control standards and must be inspected by authorized institutions.

MSC treatment in preclinical studies

Preclinical studies are of great importance in examining the safety and efficacy of a newly developed treatment method. So far, the efficacy of MSCs in the treatment of ARDS and acute lung injury has been demonstrated in many preclinical studies.[11] In a study by Jung et al.,[12] human adipose tissue-derived MSCs were shown to be quite effective in reducing lung damage and inflammation associated with ARDS between 2 and 7 days. In other similar preclinical studies, it has been observed that MSCs can be extremely effective in reducing inflammation, oxidative stress, and apoptosis.[13] These preclinical studies also suggest that the use of MSCs may play a key role in the treatment of COVID-19, considering increased inflammation and cell damage, which are the main pathophysiological process.

Use of MSC treatment in clinical studies of adult COVID-19 patients

As of February 2022, 79 clinical trials evaluating the safety and efficacy of MSCs in patients with COVID-19 have been registered with clinicaltrials.gov. Looking at the literature, the efficacy of many different types of stem cell therapies are tried, such as dental stem cells, umbilical cord stem cells, mesenchymal stromal stem cells, MSCs originating from menstrual bleeding, and adipose tissue in the treatment of COVID-19. Before the trials on the treatment of COVID-19, MSCs were also tried in the treatment of ARDS cases, and a decrease in mortality was found in a significant part of the patients. Although there are no definitive data on which stem cells obtained from different sources can be the best source yet, it is thought that its effectiveness may be the best since the umbilical cord has the highest stem cell concentration, according to our theoretical knowledge.[14] Although invasive procedures are needed for the use of stem cells originating from bone marrow and adipose tissue, millions of stem cells must be applied to achieve adequate therapeutic efficacy. Considering the increased inflammation, hypoxemia, and predisposition to intravascular thrombosis in cases with COVID 19, the use of mesenchymal stromal cell secretomes (MSC-secretome) in the treatment becomes more prominent.[15]

In a study by Häberle et al.,[16] when patients who received and did not receive MSC therapy were compared, the effectiveness of the treatment was demonstrated in patients who received MSC therapy, with significantly lower lung injury, high discharge rates, and near-normal lung function tests. When many studies in the literature were reviewed, no serious adverse events were encountered in stem cell therapy, but it was found that the rates of possible side effects related to inducing any tumor formation or growth, infection, or thrombus formation were generally similar.[17] In a double-blind randomized controlled study by Lanzoni et al.,[18] it was shown that there was a significant decrease in cytokine levels and a significant increase in survival rates on the sixth day following the use of umbilical cord-derived MSCs in the treatment. In another study by Leng et al.,[19] after MSC treatment, the existing symptoms regressed approximately 3 days after the treatment, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR tests became negative 2 days after this application, the cytokine storm was suppressed, and C-reactive protein levels increased rapidly. Regression was detected without any significant side effects.

In a case report, three doses of allogeneic umbilical cord-derived MSC treatment were administered to a patient with severe inflammatory symptoms due to COVID-19 at 3-day intervals, and no side effects were observed on the fourth day following the end of the treatment, but the patient recovered from the intensive care unit with the regression of symptoms due to increased inflammation.[20] In a case report by Zengin et al.,[21] two doses of umbilical

cord-derived MSCs were administered intravenously and intratracheally at 5-day intervals to a patient who was followed up in the intensive care unit with severe COVID-19. Symptoms were decreased, and a significant improvement in the clinical picture was observed.

Although MSC applications in the treatment of COVID-19 are new, considering the onset of the pandemic, and long-term results are not available, there are many studies on stem cell therapies in patients who develop ARDS due to other viral infections. In a study including 61 patients with H7N9 influenza virus, 17.6% of the patients who received stem cell therapy died, while 54.5% of the patients in the untreated group died. In addition, no side effects or morbidity was encountered in the 5-year follow-up of the patients who were given stem cell therapy.[22] However, the presence of increased thrombogenic risk after stem cell therapy infusion still creates a significant concern, especially in patients with hypercoagulopathy.[23] In the light of all these studies in the literature, "expanded access/compassionate use" approval has now been given by the US-FDA for COVID-19 patients who have a serious course.

COVID-19 and MSC treatment in pediatric and pregnant groups

COVID-19 in pediatric cases has been studied in many studies around the world. In a large study conducted at the Chinese Center for Disease Prevention and Control, including 72 314 cases, children less than 10 years of age were shown to be <1% of all COVID-19 cases.[24] In another study involving 1391 pediatric patients, 171 of the cases were proven to be positive for SARS-CoV-2, only 3 of these cases required intensive care, and only 1 patient died.[25] In many large studies, in which 149 082 SARS-CoV-2 positive cases were included, it was found that only 1.7% of these cases were formed by children under the age of 18 years, and the group in need of hospitalization in this group was children under the age of 1 year.[26] In many studies like these, it has been shown that the childhood age group has a low rate of being infected with SARS-CoV-2, and in case of infection, children can have the disease with asymptomatic or mild symptoms, unlike adults.

Similar to children, it was shown in a study published by the World Health Organization that included 147 pregnant women that being pregnant in SARS-CoV-2 positive cases does not increase the risk of developing severe pneumonia.[27] In another study reported by Pierce-Williams et al.,[28] no maternal mortality was reported in pregnant women infected with SARS-CoV-2. Although the results of these studies seem to be positive for pregnant women, considering that different immune responses may occur in different trimesters, it is obvious that there is a need for more extensive studies on the subject.

Considering these data regarding COVID-19 in both children and pregnant women, the ratios of active and dormant stem cells and angiotensin-converting enzyme (ACE)/ACE-2 receptors may differ from the normal adult population. As the first stage of the pathogenesis of SARS-CoV-2, it has been determined that the spike protein of the virus can cause infection by entering the host cell with the recognition of the ACE-2 receptor. Therefore, it has been reported that all cells expressing the ACE-2 receptor can be infected with this virus, and SARS-CoV-2 enters the host cell through the activation of the transmembrane serine protease enzyme.[29] At this point, the question arises whether the increased resistance to COVID-19 in children and pregnant women is due to these changes.[30] Contrary to adults, active stem cell rates are quite high in both children and pregnant women. In addition, multipotent stem cells in pregnant women are more active than MSCs in adults. In a study by Samara and Herlenius, it was shown that fetal MSCs are present in the maternal blood circulation, and accordingly, pregnant women can experience the disease with asymptomatic or mild symptoms.[31] In essence, the excess number of active stem cells in pregnant and children suppresses the entry and reproduction of the virus into the cell and also prevents fibrosis and inflammation caused by the infection. The fact that newborns are infected at a higher rate among infected children compared with other pediatric age groups is thought to be due to the higher number of ACE-2 receptors in the lungs of newborns.[32] The fact that MSCs do not have ACE-2 receptors also ensures that these cells are not infected with COVID-19, thus creating a significant advantage against infection.[33] In the study of Leng et al.,[19] it was shown that ACE-2 negative MSCs are much more effective in COVID-19 pneumonia, supporting this view.

Based on this information, the question arises whether stem cell therapy can be a new and promising treatment method in stopping the progression of the disease and supporting its regeneration after the damage it has caused. However, unfortunately, there are no sufficient data in evidence-based medicine regarding the efficacy or safety of stem cell use in pregnant women and children.

CONCLUSION

MSC therapy in the patient group infected with SARS-CoV-2 and in whom the disease has a serious course, such as the presence of ARDS, is a current and very prominent choice. It is at the top of the promising treatment approaches that can play a key role in the treatment of COVID-19 patients. While it is clear that there is a need for a large number of studies on this subject that can include various patient groups, MSC therapy is promising not only in severe COVID-19 cases but also in the treatment of many chronic lung diseases, especially those associated with lung fibrosis.

Acknowledgment

All of the authors thank those who actively participate both in the field and on the scientific platforms during

these hard days when the COVID-19 pandemic happens all over the world.

Peer-review

Internally peer-reviewed.

Authorship Contributions

Concept: M.T.A., Ö.Ö.; Design: M.T.A., Ö.Ö.; Supervision: M.T.A., Ö.Ö., İ.Ö.A.; Materials: M.T.A., İ.Ö.A.; Data: M.T.A., İ.Ö.A.; Analysis: M.T.A., Ö.Ö., İ.Ö.A.; Literature search: M.T.A., İ.Ö.A.; Writing: M.T.A., Ö.Ö., İ.Ö.A.; Critical revision: M.T.A., Ö.Ö., İ.Ö.A.

Conflict of Interest

None declared.

REFERENCES

1. Kuri-Cervantes L, Pampena MB, Meng W, Rosenfeld AM, Ittner CAG, Weisman AR, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol 2020;5:eabd7114. [CrossRef]
2. Song JW, Zhang C, Fan X, Meng FP, Xu Z, Xia P, et al. Immunological and inflammatory profiles in mild and severe cases of COVID-19. Nat Commun 2020;11:3410. [CrossRef]
3. Metcalfe SM. Mesenchymal stem cells and management of COVID-19 pneumonia. Med Drug Discov 2020 5:100019.
4. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, et al; Sinai Immunology Review Project. Immunology of COVID-19: Current state of the science. Immunity 2020;52:910–41. [CrossRef]
5. Samsonraj RM, Raghunath M, Nurcombe V, Hui JH, van Wijnen AJ, Cool SM. Concise review: Multifaceted characterization of human mesenchymal stem cells for use in regenerative medicine. Stem Cells Transl Med 2017;6:2173–85. [CrossRef]
6. Gorman E, Shankar-Hari M, Hopkins P, Tunnicliffe WS, Perkins GD, Silversides J, et al. Repair of acute respiratory distress syndrome by stromal cell administration in COVID-19 (REALIST-COVID-19): a structured summary of a study protocol for a randomised, controlled trial. Trials 2020;21:462. [CrossRef]
7. Lee JW, Krasnodembskaya A, McKenna DH, Song Y, Abbott J, Matthay MA. Therapeutic effects of human mesenchymal stem cells in ex vivo human lungs injured with live bacteria. Am J Respir Crit Care Med 2013;187:751–60. [CrossRef]
8. Atluri S, Manchikanti L, Hirsch JA. Expanded umbilical cord mesenchymal stem cells (UC-MSCs) as a therapeutic strategy in managing critically Ill COVID-19 patients: The case for compassionate use. Pain Physician 2020;23:E71–E83. [CrossRef]
9. Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regen Med 2019;4:22.
10. Ullah M, Liu DD, Thakor AS. Mesenchymal stromal cell homing: mechanisms and strategies for improvement. iScience 2019;15:421–38.
11. Fan E, Beitler JR, Brochard L, Calfee CS, Ferguson ND, Slutsky AS, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? Lancet Respir Med 2020;8:816–21. [CrossRef]
12. Jung YJ, Park YY, Huh JW, Hong SB. The effect of human adipose-derived stem cells on lipopolysaccharide-induced acute respiratory distress syndrome in mice. Ann Transl Med 2019;7:674.
13. El-Metwaly S, El-Metwaly S, El-Senduny FF, El-Demerdash RS, Abdel-Aziz AF. Mesenchymal stem cells alleviate hydrochloric acid-induced lung injury through suppression of inflammation, oxidative stress and apoptosis in comparison to moxifloxacin and sildenafil. Heliyon 2019;5:e02710.
14. Arutyunyan I, Elchaninov A, Makarov A, Fatkhudinov T. Umbilical cord as prospective source for mesenchymal stem cell-based therapy. Stem Cells Int 2016;2016:6901286. [CrossRef]
15. Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145–47.
16. Häberle H, Magunia H, Lang P, Gloeckner H, Körner A, Koeppen M, et al. Mesenchymal Stem Cell Therapy for Severe COVID-19 ARDS. J Intensive Care Med 2021;36:681–8. [CrossRef]
17. Centers for Disease Control and Prevention. Stem cell and exosome products. 2019. Available at: https://www.cdc.gov/hai/outbreaks/stem-cell-products.html. Accessed Feb 12, 2021.
18. Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, et al. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: A double-blind, phase 1/2a, randomized controlled trial. Stem Cells Transl Med 2021;10:660–73. [CrossRef]
19. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020;11:216–28.
20. Liang B, Chen J, Li T, Wu H, Yang W, Li Y, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report. Medicine (Baltimore) 2020;99:e21429. [CrossRef]
21. Zengin R, Beyaz O, Koc ES, Akinci IO, Kocagoz S, Sagcan G, et al. Mesenchymal stem cell treatment in a critically ill COVID-19 patient: a case report. Stem Cell Investig 2020;7:17. [CrossRef]
22. Chen J, Hu C, Chen L, Tang L, Zhu Y, Xu X, et al. Clinical study of mesenchymal stem cell treatment for acute respiratory distress syndrome induced by epidemic influenza a (H7N9) infection: A hint for COVID-19 treatment. Engineering (Beijing) 2020;6:1153–61.
23. Coppin L, Sokal E, Stéphenne X. thrombogenic risk induced by intravascular mesenchymal stem cell therapy: Current status and future perspectives. Cells 2019;8:1160.
24. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239–42.
25. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al, Chinese Pediatric Novel Coronavirus Study Team. SARS-CoV-2 infection in children. N Engl J Med 2020;382:1663–5.
26. CDC COVID-19 Response Team. Coronavirus disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep 2020;69:422–6. [CrossRef]
27. WHO. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). Geneva: WHO; 2020.
28. Pierce-Williams RAM, Burd J, Felder L, Khoury R, Bernstein PS, Avila K, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM 2020;2:100134. [CrossRef]
29. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433. [CrossRef]
30. Sanie-Jahromi F, NejatyJahromy Y, Jahromi RR. A review on the role of stem cells against SARS-CoV-2 in children and pregnant women. Int J Mol Sci 2021;22:11787.
31. Samara A, Herlenius E. Is there an effect of fetal mesenchymal stem cells in the mother-fetus dyad in COVID-19 pregnancies and vertical transmission? Front Physiol 2021;11:624625. [CrossRef]
32. Zhang Z, Guo L, Lu X, Zhang C, Huang L, Wang X, et al. Clin-

ical analysis and pluripotent stem cells-based model reveal possible impacts of ACE2 and lung progenitor cells on infants vulnerable to COVID-19. Theranostics 2021;11:2170–81. [CrossRef]

33. Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med 2020;76:14–20. [CrossRef]

Kök Hücre Tedavisinin COVID-19'da Kullanımı

SARS-CoV-2'nin akciğer, kalp ve bağışıklık sistemi gibi birçok organ ve sistemin ciddi şekilde etkilenebildiği yeni koronavirüs hastalığı 2019'a (COVID-19) neden olduğu bilinmektedir. Şu an için tedavi süreci genel anlamda destekleyici ve palyatif bakım üzerine kurulmuştur. Potansiyel olabilecek bazı ilaçlar ise tedavide denenmektedir. İşte bu noktada, son dönemlerde belki de birçok hastalıkta ileride umut verici bir tedavi yöntemi olabilecek kök hücre tedavisi gündeme gelmektedir. COVID-19'da kök hücre tedavisi özellikle dirençli ve ağır vakalarda anahtar rolü üstlenebilecek bir tedavi yöntemi olabilir. Bu derlemede, kök hücre tedavisinin potansiyel mekanizmalarını ve bu tedavi yöntemindeki gelişmeleri özetledik.

Anahtar Sözcükler: Akut solunum sıkıntısı sendromu; COVID-19; doku rejenerasyonu; kök hücre tedavisi.