

Mesenchymal Stem Cell Therapy For COVID-19; Is A New Challenge

Review

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Abstract – "Coronavirus" is the word that absolutely isn't forgotten by everybody who lives in the first half of the twenty-first century. COVID19, as a pandemic, has driven numerous researchers from various biomedical fields to discover arrangements or therapies to deal with the pandemic. Nonetheless, no standard treatment for this infection has been found to date. Presumably, preventing the acute severe respiratory infection type of COVID-19 as the most risky period of this disease can be useful for the therapy and decrease of the death rate.

In such manner, mesenchymal stem cells (MSCs)-based immunomodulation treatment has been proposed as a reasonable restorative methodology and a several clinical studies have started. Recently, MSCs as indicated by their immunomodulatory and regenerative properties stand out in clinical trials. After the intravenous transplantation of MSCs, a large population of cells gathers in the lung, which they close by immunomodulatory impact could protect alveolar epithelial cells, recover the respiratory microenvironment, prevent pneumonic fibrosis, and cure lung dysfunction. Given the vulnerabilities here, we checked on detailed clinical preliminaries and theories to give helpful data to scientists and those keen on stem cell therapy.

In this study, we considered this new way to deal with improve patient's immunological reactions to COVID-19 utilizing MSCs and talked about the parts of this proposed treatment. Nonetheless, right now, there are no affirmed MSC-based methodologies for the anticipation or potentially treatment of COVID-19 patients however clinical preliminaries progressing.

Keywords – (COVID-19, Mesenchymal stem cells, stem cell treatment, Immunomodulatory, Clinical trials).

I. INTRODUCTION

At the long term's end, various instances of extreme respiratory infections were reported for in Wuhan, China, and were at first idea to be an occasional influenza sickness, given that some patients had a history of attending or working in the wholesale market for fish and seafood, then the market was promptly closed down on January 1, and environmental sanitation and disinfection were completely executed. A couple of days after the fact, subsequent to dismissing the analysis of occasional flu, avian flu, adenovirus, Covid, SARS, Covid, and other organisms, on Jan. 1, the infection was proclaimed a causative agent of the disease in four of the nine hospitalized patients: another Covid that has a 5% genetic relationship with SARS and is a subset of Sarbecovirus [1]. As of

now, the infection has been momentarily named SARS-CoV-2 infection for additional data and COVID-19, the name was given by the World Health Organization (WHO) to the SARS-CoV-2 infection related disease.

This disease has brought about that clinicians and researchers from various parts of biomedicine were assembled to discover a solution or treatment for the management of this pandemic.

As per a new declaration of the International Society for Stem Cell Research (ISSCR), at present, there are no approved stem cell-based methodologies for the anticipation and treatment of COVID-19 disease. Nonetheless, as of late, mesenchymal undifferentiated cells (MSCs) have presented one of the helpful methodologies for utilizing in the treatment of COVID19 [2]. As we probably are aware, MSCs opposes viral infection because of the presence of specific cytokines improved qualities. These highlights are available in MSCs in the characteristic specialty before their partition cycle occurs. Hence, MSCs can be expected to endure regardless of whether they are relocated into a patient with an affirmed COVID-19. Due to there is difference in MSCs treatment to treat COVID-19, we looked into announced clinical preliminaries and news to introduce supportive data to specialists of the stem-based treatment field. In this study, we considered this proposed way to deal with improve patient's immunological reactions to COVID-19 utilizing MSCs and examined the parts of this helpful methodology.

II. SARS-CoV-2 AND COVID-19

"Coronavirus" the word that positively it isn't forgotten by every individual who lived in the principal half of the twenty-first century. Covid disease 2019 which known as COVID-19 is the aftereffect of one Covid contamination for the sake of SARS-CoV2. Covids (CoV) are a huge group of infections that some of them are more referred to, for example, Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV), yet some of them are not more known like Severe intense respiratory disorder Covid 2 (SARS-CoV-2). SARS-CoV-2 that recently known by the 2019 novel Covid (2019-nCoV), is another strain of Covid that hasn't been distinguished in people up to late December of 2019. Nonetheless, there are reports that exhibit the SARS-CoV-2 infection started from bats and afterward moving into camels, however its careful elements are as of now obscure. In addition, a large part of the pathogenesis data respects to SARS-CoV-2 isn't completely known.

SARS-CoV-2 is from the Nidovirales request, an individual from the class β -Covid (β -CoV) [3]. β -CoV incorporates five subgenera remembering for embecovirus (counting HCoV-OC43 and HCoV-HKU1) [4], nobecovirus (counting BtCoV HKU9) [4], hibecovirus (counting Bat Hp-betacoronavirus Zhejiang2013) [4], sarbecovirus (counting SARSr-CoV and its strains, for example, SARS-CoV, SARS-CoV-2, and Bat SLCoV-WIV1), merbecovirus (counting Middle East respiratory disorder (MERS)-CoV, BtCoV-HKU4, and BtCoV-HKU5) [4, 5].

SARS-CoV-2 is encompassed, positive-sense, single-stranded RNA infection (with nucleocapsid) by 79.6% arrangement character the equivalent to SARS-CoV [6], that known as the biggest found RNA infections by around 30 kb long genome structure.

It was first detached utilizing human aviation route epithelial cells [7] yet can be separated from the bronchoalveolar lavage liquid from a COVID-19 patient [6, 7]. For the most part, both of the SARS-CoV and the SARS-CoV-2 are confined and filled promptly in Vero cells [7, 8] (a genealogy of cells that was detached from kidney epithelial cells of an African monkey [9]). Additionally, this infection as SARS-CoV-2 enters its host cell by binding to the angiotensin converting enzyme 2 (ACE2) receptor [10, 11].

On March 11, 2020, the World Health Organization (WHO) described the spread of COVID-19 as a pandemic that it has caused unreasonable fear and led to unnecessary suffering and death [12]. Until now, as indicated by the Worldometer site report in excess of 199 nations and domains around the globe have been influenced, with significant episodes individually in the USA, Italy, China, Spain, Germany, and Iran. The mortality rate of COVID-19 has been accounted for from 0.7% [13] to 15.2% [14] as per various investigations in assorted regions and nations. Too, its most extreme incubation period has been accepted fourteen days [15] to about two months [14, 16]. Coronavirus has brought about that numerous specialists from various parts of biomedicine were pulled in to discover an answer or treatment for the administration of this pandemic. Notwithstanding, to date haven't been found the standard solution for this disease.

Several investigations have indicated that the principal phase of the pathogenesis of this kind of infection is the ID of angiotensin-converting enzyme 2 (ACE2) receptor by its spike protein [17]. Hence, ACE2-positive cells are infected by this infection [17]. Another study has demonstrated that the cell protease TMPRSS2 is likewise needed to permit the passage of Covid into host cells [18]. It is possible that the ACE2 receptor is generally circulated on the outside of human cells, particularly alveolar type 2 (AT2)

and capillary epithelium, and AT2 cells to a great extent express TMPRSS2 [18]. Then again, curiously, bone marrow, lymph nodes, thymus, spleen, and immune cells, for example, T and B lymphocytes and macrophages are consistently negative for ACE2 [19]. These discoveries recommend that immunoglobulin treatment can help treat patients with the virus infection. Along these lines, it ought to be noticed that the limit of the infection is enormously reduced by the cytokine-induced storm of the virus. The current sign of SARS-CoV-2 pathogenesis is the cytokine storm in the lung. Virally-set off intense cytokine arrival of GSCF, IP10, MCP1, MIP1A, IL-2, IL-6, IL-7, and TNF brings about pneumonic edema, dysfunction of air-exchange, acute respiratory distress syndrome (ARDS), and acute cardiac injury, and leading to death [2].

Until now, there is no particular remedy for Covid-19, albeit clinical management of these patients includes prevention or control of the infection and supportive care, including supplemental oxygen and mechanical ventilation when required. Recently, in the viral surface glycoprotein, a few epitopes, remembering for 5 CTL epitopes, 3 successive B cell epitopes, 5 spasmodic B cell epitopes of immune cells [20], and 13 MHC-I and 3 MHC-II antigenic epitopes [21], have been accounted for through immunoinformatics approach that a portion of these epitopes perhaps had potential candidates for the development of 2019-nCoV vaccines.

A progression of endorsed drugs for different indications is in progress in clinical preliminaries for these patients, including Chloroquine, Hydroxychloroquine, and Remdesivir around the world. This since, protected, ideal and powerful strong medicines are the unavoidable guideline in patients who create serious signs of COVID19.

III. MESENCHYMAL STEM CELL THERAPY

Right now, cell-based treatment and particularly stem cell therapy has become a promising remedial field, in which many see opportunities to cure incurable diseases [22]. Notwithstanding the significant development of the stem cell-based treatment field, immunogenicity, restricted cell source and moral issue as the primary limits of this helpful methodology have not been addressed at this point. Among these, MSCs has stood out because of source potential, a high proliferation rate, low invasive procedure, and free ethical issues. There is a lot of predominance in utilizing MSC treatment in correlation with different medicines [23], including in;

- I. They are easily accessible and can be isolated from different tissues, for example, bone marrow and fat tissues, remembering for umbilical cord, dental pulp, menstrual blood, buccal fat pad, fetal liver, etc.
- II. They are multipotent stem cells.
- III. MSCs can without much of a stretch grow to clinical volume in an appropriate time frame.
- IV. MSCs can be stored for repetitive therapeutic usage.
- V. Clinical preliminaries of MSCs so far haven't indicated unfavorable responses to allogeneic MSC.
- VI. Safety and viability of MSCs have been clearly reported in a several clinical preliminaries [23].

As referenced, Following the COVID-19, may trigger a destroying immune overreaction in the body. In COVID-19 patients, the safe framework creates a lot of inflammatory factors, causing a cytokine storm including, in an overproduction of immune cells and cytokines [24].

It is the beginning of the MSC therapy idea in the treatment of COVID-19 patients, MSC therapy can prevent the storm release of cytokines by the immune system and stimulate endogenous repair by reparative properties of the stem cells.

After intravenous infusion, part of the MSC population entraps in the lung, which frequently in systemic infusion it is recognized as a limit. In any case, here these MSCs could recover the pulmonary microenvironment, intercept pulmonary fibrosis, and cure lung dysfunction and COVID-19 pneumonia [25].

In any case, one of the principal limitations in this methodology is the suppling wellspring of clinical-grade MSCs and therefore the speed of preparation for clinical utilization that here stem cell banks can play a significant part. Additionally, MSCs can be isolated from various adult tissues, including ideally bone marrow (BM), peripheral blood (PB) and fat tissues (AT), (for example, stomach fat, infrapatellar fat pad, and buccal fat pad) and neonatal birth-related tissues, including placenta (PL), umbilical cord (UC), Warton jelly (WJ), amniotic liquid (AF), and cord blood (CB), and afterward put away for future potential applications. In this manner, it appears MSCs-based therapy may possibly be an ideal candidate for clinical trials or at least the combination of treatment to treat COVID-19 patients.

IV. MSC CLINICAL TRIALS FOR COVID-19

Recently, China, USA, Jordan, Iran, and a few different nations have started cell-based treatment clinical studies and a few reports have been distributed. Curiously, one of the accessible strategies to evaluate its efficacy in the maintenance or repair of damaged vital organs is the utilization of mesenchymal immature cells (MSCs) treatment that broadly utilized in the treatment of type 2 diabetes, immune system disease, spinal cord injury, GVHD and several other diseases specially with high immunity rates have been used [23, 26–28].

MSCs, utilizing their immunomodulatory properties and their differentiation ability, can prevent lung tissue death by counteracting the cytokine storm and regeneration and reconstruction of damaged tissues. As of late, the utilization of these cells in the clinical treatment of H5N1 viral diseases that affect the lung has additionally been recommended [29].

Moreover, as of late a case study was accounted for in China on a female patient with an intense COVID19 condition that the aftereffects of lab tests and CT pictures gave incredibly powerful outcomes following 21 days of therapy with umbilical cord MSCs. A new contextual analysis of a case report of a 65-year-old female patient determined in basic condition to have COVID-19, at that point distinguished the specific 2019nCoV variation presently called SARS-CoV-2 [30]. The patient had a neutrophil increment of 87% and a lymphocyte reduction of 9.8% and was treated with antiviral medications, for example, lopinavir/ritonavir, IFN- α and oseltamivir just as intravenous infusion of moxifloxacin, Xuebijing, methylprednisolone and immunoglobulin. The patient was likewise exposed to noninvasive mechanical ventilation to encourage breathing and soothe muscle weakness because of poor oxygenation. As the imperative signs deteriorated, the patient was treated with line MSCs alone and with $\alpha 1$ thymosin 5×10^7 cells every multiple time. The aftereffects of the study demonstrated that after the subsequent infusion, serum albumin, CRP, and ALT/AST slowly diminished, just as other fundamental signs improved. From that point, the patient was taken out from the ventilator and ready to walk, and the quantity of white blood cells and neutrophils in the patient diminished to an ordinary level, while the quantity of lymphocytes increased to their typical level. Above all, CD3+ T cell, CD4+ T cell and CD8+ T cell numbers were altogether increased. Additionally, the subjective outcomes acquired from CT pictures after the second and third infusions of cord stem cells demonstrated that the pneumonia was exceptionally very relieved, 2 days after the third infusion the patient was released from the ICU ward and most of the vital signs and clinical laboratory parameters were typical. The outcomes recommended that umbilical cord mesenchymal stem cells could be an ideal treatment alternative alone or in combination with other immune modulators for severe COVID-19 patients [30]. In another study delivered as of late in China and as a team with the United States, 7 patients with COVID19 pneumonia in Beijing YouAn Hospital from January 23 to February 16 experienced mesenchymal stem cell transplantation and clinical manifestations, changes in immune function levels [25]. Likewise, inflammation was evaluated inside 14 days after transplantation. The outcomes demonstrated that the clinical symptoms of all patients improved altogether 2 days after stem cell transplantation. Among the patients considered, one was exceptionally severe and two patients with milder conditions were released from the medical clinic 10 days after transplantation. Their outcomes additionally demonstrated that peripheral lymphocyte levels increased, activated cytokine-secreting immune cells, for example, CXCR3+ CD4+ T cells, CXCR3+ CD8+ T cells and NK CXCR3+ cells disappeared on day 6–6.

A gathering of CD14+ CD11c+ CD11bm^{id} regulatory DC cell population likewise increased significantly. Simultaneously, TNF- α levels were essentially diminished, though IL-10 was expanded in patients treated with MSCs compared with patients treated with conventional treatment. What's more, gene expression profiling of mesenchymal stem cells showed that these cells are ACE2- and TMPRSS2-, which demonstrated that mesenchymal stem cells are free of COVID19 infection [25]. In this way, they presumed that MSCs would be safe and effective for treating patients with COVID19 pneumonia, especially for patients with very acute conditions.

V. CONCLUSION

Immunomodulatory and anti-inflammatory properties of MSCs in the treatment of respiratory infections were affirmed by 17 completed clinical investigations, and furthermore in excess of 70 preliminaries are enrolled in such manner.

Umbilical cord, umbilical cord blood, Wharton's jelly, menstrual blood, and dental pulp, are the significant MSC sources that will be utilized in these preliminaries. Notwithstanding, the process of developing new therapeutic and bringing it to clinical application has important practical implications and not over for MSC therapy of COVID-19.

Nonetheless, the cost-effective and speed of therapeutic preparation are the capable discussed topic for MSC based therapy for COVID-19, however unquestionably, the life of a human is more commendable and COVID-19 is so risks. Along these lines, the clinical utilization of MSCs treatment to treat COVID-19 is still some time away, yet there are some encouraging reports to apply stem cell treatment and particularly MSCs may potentially be is quite possibly the best therapeutics, or a combination of treatment to treat COVID-19 patients. Nonetheless, scientists are trying incessantly to develop therapeutics to treat this disease.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

Authors have equally participated and shared every item of the work.

REFERENCES

- [1] Wu, Fan, et al. "A new coronavirus associated with human respiratory disease in China." *Nature* 579.7798 (2020): 265-269.
- [2] Metcalfe, Su M. "Mesenchymal stem cells and management of COVID-19 pneumonia." *Medicine in drug discovery* 5 (2020): 100019.
- [3] Golchin, Ali, Ehsan Seyedjafari, and Abdolreza Ardeshirylajimi. "Mesenchymal stem cell therapy for COVID-19: present or future." *Stem cell reviews and reports* 16.3 (2020): 427-433.
- [4] Wong, Antonio CP, et al. "Global epidemiology of bat coronaviruses." *Viruses* 11.2 (2019): 174.
- [5] Woo, Patrick CY, et al. "Comparative analysis of twelve genomes of three novel group 2c and group 2d coronaviruses reveals unique group and subgroup features." *Journal of virology* 81.4 (2007): 1574-1585.
- [6] Zhou, Peng, et al. "A pneumonia outbreak associated with a new coronavirus of probable bat origin." *nature* 579.7798 (2020): 270-273.
- [7] Zhu, Na, et al. "China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019." *N Engl J Med* 382.8 (2020): 727-733.
- [8] Park, Wan Beom, et al. "Virus isolation from the first patient with SARS-CoV-2 in Korea." *Journal of Korean medical science* 35.7 (2020).
- [9] Govorkova, E. A., et al. "African green monkey kidney (Vero) cells provide an alternative host cell system for influenza A and B viruses." *Journal of virology* 70.8 (1996): 5519-5524.
- [10] Hoffmann, Markus, et al. "The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells." *BioRxiv* (2020).
- [11] Li, Fang, et al. "Structure of SARS coronavirus spike receptor-binding domain complexed with receptor." *Science* 309.5742 (2005): 1864-1868.
- [12] Shankar, Abhishek, et al. "Cancer care delivery challenges amidst coronavirus disease–19 (COVID-19) outbreak: specific precautions for cancer patients and cancer care providers to prevent spread." *Asian Pacific journal of cancer prevention: APJCP* 21.3 (2020): 569.
- [13] Ji, Yunpeng, et al. "Potential association between COVID-19 mortality and health-care resource availability." *The Lancet Global Health* 8.4 (2020): e480.
- [14] Spychalski, Piotr, Agata Błażyńska-Spychalska, and Jarek Kobiela. "Estimating case fatality rates of COVID-19." *The Lancet. Infectious Diseases* (2020).
- [15] Backer, Jantien A., Don Klinkenberg, and Jacco Wallinga. "Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20–28 January 2020." *Eurosurveillance* 25.5 (2020): 2000062.
- [16] AL, BİLGİ. "Kök Hücreyle Covid 19 Tedavisi Mümkün."

- [17] Russell, Clark D., Jonathan E. Millar, and J. Kenneth Baillie. "Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury." *The Lancet* 395.10223 (2020): 473-475.
- [18] Vickers, Neil J. "Animal communication: when i'm calling you, will you answer too?" *Current biology* 27.14 (2017): R713-R715.
- [19] Hamming, Inge, et al. "Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis." *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland* 203.2 (2004): 631-637.
- [20] Baruah, Vargab, and Sujoy Bose. "Immunoinformatics-aided identification of T cell and B cell epitopes in the surface glycoprotein of 2019-nCoV." *Journal of medical virology* 92.5 (2020): 495-500.
- [21] Bhattacharya, Manojit, et al. "Development of epitope-based peptide vaccine against novel coronavirus 2019 (SARS-COV-2): Immunoinformatics approach." *Journal of medical virology* 92.6 (2020): 618-631.
- [22] Golchin, Ali, and Tahereh Zarnoosheh Farahany. "Biological products: cellular therapy and FDA approved products." *Stem cell reviews and reports* 15.2 (2019): 166-175.
- [23] Golchin, Ali, et al. "The clinical trials of mesenchymal stem cell therapy in skin diseases: an update and concise review." *Current stem cell research & therapy* 14.1 (2019): 22-33.
- [24] Mehta, P., et al. "Across Speciality (2020)." *COVID-19: Consider cytokine storm syndromes and immunosuppression. The Lancet (London, England)* 395.10229: 1033.
- [25] Leng, Zikuan, et al. "Transplantation of ACE2-mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia." *Aging and disease* 11.2 (2020): 216.
- [26] Golchin, Ali, Forough Shams, and Farshid Karami. "Advancing Mesenchymal stem cell therapy with CRISPR/Cas9 for clinical trial studies." *Cell Biology and Translational Medicine, Volume 8: Stem Cells in Regenerative Medicine* (2020): 89-100.
- [27] Novello, Solen, et al. "Clinical application of mesenchymal stem cells in periodontal regeneration: A systematic review and meta-analysis." *Journal of periodontal research* 55.1 (2020): 1-12.
- [28] Zhao, Ke, and Qifa Liu. "The clinical application of mesenchymal stromal cells in hematopoietic stem cell transplantation." *Journal of hematology & oncology* 9.1 (2016): 1-9.
- [29] Chen, Jiajia, 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* 6.10 (2020): 1153-1161.
- [30] Liang, Bing, et al. "Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report." *Medicine* 99.31 (2020).