Perspective

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# The Cytokine Storm in COVID-19 Patients Amenable to Stem Cell Treatment: A Perspective

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COVID-19, Stem Cells, Clinical trials.

## Introduction
Coronavirus (HCoV-19) is a positive strand RNA virus originated from Wuhan China in December 2019 and is causing havoc for being pandemic with outbreak of coronavirus disease (COVID-19) that has claimed so far more than 200 000 deaths worldwide [1]. The genome of SARS-CoV-2 shares about 80% identity with that of SARS-CoV and is about 96% identical to the bat coronavirus Bat CoVRaTG13 [2]. This virus causes acute respiratory distress syndrome (ARDS) leading to severe pneumonia and death in number of cases. Currently, no specific drugs or vaccines are available to cure the patients with COVID-19 infection. Global consortia are working hard to develop vaccine against COVID-19 but that may be more than year away and may or may not work given the past experience with similar virus, SARS-CoV. Attempts are being made for repurposing the existing drugs like chloroquine albeit limited success. Alternative medicine including UV light and disinfectants are also proposed without much basis and safety data. Hence, there is a huge unmet need for developing an effective treatment for COVID-19 patients, especially the severe cases of ARDS who are on ventilators.

Current studies indicate that HCoV-19 virus specifically recognizes the angiotensin I converting enzyme 2 receptor (ACE2) by its spike protein [2-4]. ACE2-positive cells are infected by the HCoV-19, like SARS-2003 [5,6]. Also a study from Germany revealed that the cellular serine protease TMPRSS2 for HCoV-19 Spike protein priming is also essential for the host cell entry and spread [7], like the other coronavirus (i.e. SARS-2003) [8,9]. The ACE2 receptors are widely distributed on the human cells surface, predominately amongst the alveolar type II cells (AT2) and capillary endothelium [10], and the AT2 cells are also positive for TMPRSS2 [9]. However, the ACE2 receptors in the bone marrow, lymph nodes, thymus, and the spleen, immune cells, such as T and B lymphocytes, and macrophages are consistently negative [10]. These studies raise the possibility that immunological therapy perhaps may be suitable for such ARDS patients. The virus is known to stimulate a terrible cytokine storm in the lung, with influx of IL-2, IL-6, IL-7, GSCF, IP10, MCP1, MIP1A, and TNFα, followed by the edema, dysfunction of the air exchange, ARSD, acute cardiac injury and the secondary infection [11], which may lead to death. Therefore, the immunomodulatory capacity must be strong enough to combat this cytokine storm, one or two immune factors alone may not work. Therefore, any mechanism to combat cytokine storm may be the key for the treatment of HCoV-19 infected patients. The mesenchymal stem cells (MSCs), by virtue of their immunomodulatory ability have been tried recently to have beneficial effects for preventing or attenuating the cytokine storm (Figure 1).

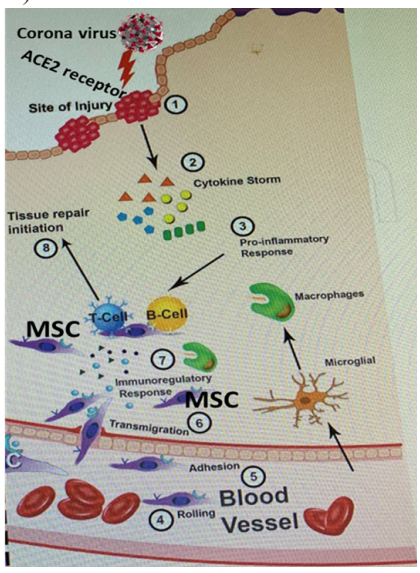


**Figure 1:** A simplistic model adapted from Rawat et al. [12] demonstrating

corona virus interaction with ACE2 receptors on the target cell and causing cytokine storm and MSCs immunoregulatory response in series of 8 steps for tissue repair.

## The Perspective

Recently MSCs have been used in cell-based therapy, from basic research to clinical trials [13, 14]. Safety and effectiveness have been clearly documented in many clinical trials, especially in the immune-mediated inflammatory diseases, such as graft versus-host disease (GVHD) [5] and systemic lupus erythematosus (SLE) [6]. MSCs play a positive role mainly in two ways, namely immunomodulatory effects and differentiation abilities [17]. MSCs can secrete many types of cytokines by paracrine secretion or make direct interactions with immune cells, leading to immunomodulation [18]. The immunomodulatory effects of MSCs are triggered further by the activation of TLR receptor in MSCs, which is stimulated by pathogen-associated molecules such as LPS or double-stranded RNA from virus [19,20], like the HCoV-19.

About 13 different clinical trials using stem cell therapy to treat COVID-19 have been registered since Jan 2020 at www.clinicaltrials.gov. In the last 2-3 months few studies already published preliminary data on MSC transplantation in pilot trials reporting therapeutic potential for HCoV-19 infected patients that are being reviewed here.

The very first coronavirus case treated with umbilical cord stem cells was reported from China [21] leading to more interest in other clinical studies. This study investigated whether MSC transplantation improves the outcome of 7 enrolled patients with COVID-19 pneumonia in Beijing Youan Hospital, China, from Jan 23, 2020 to Feb 16, 2020. The clinical outcomes, as well as changes of inflammatory and immune function levels and adverse effects of 7 enrolled patients were assessed for 14 days after MSC injection. MSCs could cure or significantly improve the functional outcomes of seven patients without observed adverse effects. The pulmonary function and symptoms of these seven patients were significantly improved in 2 days after MSC transplantation. Among them, two common and one severe patient were recovered and discharged in 10 days after treatment.

After treatment, the peripheral lymphocytes were increased, the C-reactive protein decreased, and the overactivated cytokine-secreting immune cells CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells disappeared in 3-6 days. In addition, a group of CD14+CD11c+CD11bmid regulatory DC cell population dramatically increased. Meanwhile, the level of TNF-α was significantly decreased, while IL-10 increased in MSC treatment group compared to the placebo control group. Furthermore, the gene expression profile showed MSCs were ACE2- and TMPRSS2- which indicated MSCs are free from COVID-19 infection. Thus, the intravenous transplantation of MSCs was safe and effective for treatment in patients with COVID-19 pneumonia, especially for the patients in critically severe condition. Limitations of this study include the small sample size and short-term follow-up.

The second trial [22] phase I, was registered on Feb 5th 2020 by Beijing 302 Hospital to inspect the safety of UC-MSCs therapy in pneumonia patients infected with HCoV-19. This multi-centre trial is expected to recruit 20 patients. 10 patients will receive 3 IV transfusions of stem cells in the treated group, along with the conventional treatment. In addition, 10 patients receiving conventional treatment will be used as controls. The clinical symptoms, pulmonary imaging, side effects, 28-days mortality, immunological characteristics (immune cells, inflammatory factors, etc.) will be evaluated during the 180 days follow up. Authors felt that these findings seem to suggest the potential beneficial effect of MSC based treatment could be principally due by the immunomodulation and regenerative potential of these cells.

The third trial [23], Phase II was registered on 13th Feb 2020 by Zhong nan Hospital and is being conducted to assess the role of umbilical cord stem cells in treating the HCoV-19 infection pneumonia. The fourth trial [24] was registered on 18th Feb 2020 by Wuhan Union Hospital They want to exploit the anti-inflammatory effects of MSCs to reduce virus induced lung injury and mortality in mice. The purpose of this study is to investigate effectiveness and safety of UC-MSCs in treating severe pneumonia patients infected with HCoV-19. This trial is expected to recruit 48 patients, with 24 patients receiving 4 IV transfusion of 5.0 x106 cells/kg of UC-MSCs in the treatment group. All of them also will receive conventional treatment. In addition, another 24 patients receiving conventional treatment will serve as a control group. Based on the study protocol, "The respiratory function, pulmonary inflammation, clinical symptoms, pulmonary imaging, side effects, 28-days mortality, immunological characteristics (immune cells, inflammatory factors, etc.) will be evaluated during the 90 days to 96 weeks follow up.

The fifth trial [25] was registered on 3rd March 2020 by the Puren Hospital Affiliated to Wuhan University of Science and Technology. Per the investigators, this clinical trial will be performed to explore the safety and efficacy of UC-MSCs therapy for coronavirus pneumonia patients. The investigators planned to recruit 48 patients aged from 18 to 75 years old and had no severe underlying diseases. In the cell treatment group, 24 patients will receive 0.5 x 106 UC-MSCs /kg body weight intravenous treatment 4 times every other day besides conventional treatment. In the control group, other 24 patients will receive conventional treatment plus 4 times of placebo intravenously. The lung CT, blood biochemical examination, lymphocyte subsets, inflammatory factors, 28-days mortality, etc will be evaluated within 24h and 1, 2, 4, 8 weeks after UC-MSCs treatment.

Based on these studies, some biotech companies are also involved in carrying out FDA-approved pilot studies with their proprietary stem cells for ARDS patients.

## Discussion

Based on previous and recent published data, intravenous infusion of expanded MSCs from different sources (allogeneic) seem to be

safe and possibly efficacious based on the early and preliminary reports from China. Therefore, it is pertinent to consider the compassionate use of these cells for treatment of critically ill COVID-19 patients, before in depth details studies are undertaken to understand the mechanism and mode of delivery of MSCs to patients. The cell therapy has been under the microscope for some time and it's the right opportunity to ascertain their use in critical ill patients with COVID-19 and the followings may be considered to make it happen:

- The regulatory agencies should treat stem cells therapy under orphan drug development paradigm and minimize the regulatory burden as was done for developing blood transfusion during the world wars so that properly informed, critically ill COVID-19 patients/proxies will have access to expanded MSC therapy
- Cell source should be from legitimate laboratories under some sort of regulatory manufacturing licencing ensuring safety of patients and they do not suffer any negative consequences from this treatment from unscrupulous sources.
- Stem cells-derived products such as conditioned media and exosomes trials be encouraged as these have been shown to be affective in other diseases and would be less controversial and more acceptable.
- Proper data be collected and published for future development.

Currently most of the regulatory agencies in the world have placed autologous use of stem cells for patients outside their regulatory regime such as for their use in musculoskeletal diseases and related. There is a strong need to promote the use of allogeneic, off the shelve approach so that large number of patients can be treated from different sources given the fact that such paradigm does not evoke any immune response in the most of the studies reported in literature and is safe. The source of such stem cells be such that it is easy to extract and less intrusive for donors, i.e. dental (deciduous), bone, fat, umbilical cords and/or be derived from induced pluripotent stem cells. And establishment of allogeneic stem cells biobanks may be encouraged for easy accessibility of stem cells.

In summary, the data from these studies indicate that intravenous infusion of MSCs is a safe approach for treating patients with COVID-19 severe pneumonia in elderly patients. Alternately use of stem cells-derived products such as conditioned media and exosomes delivered as an aerosol to the lungs may offer respite to such patients. Additional systematic studies in a larger cohort of patients are needed to validate this therapeutic intervention further.

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