COVID-19 and Mesenchymal Stem Cell Treatment; Mystery or Not

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Abstract

On December 31, 2019, novel SARS-CoV2 spread from Wuhan China to more than 200 territories around world and the World Health Organization declared a COVID-19 pandemic on January 30, 2020. At this time there is no particular therapy, drug or vaccine available to deal with COVID-19. Today actual data indicates that about 17% of closed COVID-19 cases died. Health care professionals, ministry of health in countries and the public are trying to read the runes to see when the COVID-19 pandemic will be over. Although mild cases of COVID-19 can be controlled with antiviral, anti-inflammatory and immunomodulatory treatment, severe cases may need intensive care unit support and ventilation. Cytokine storms cause high inflammatory responses and pneumonia in severe cases. Mesenchymal stem cells are immunomodulatory and they have regenerative capacity. In this sense, mesenchymal stem cells may improve the patient's clinical and immunological response to COVID-19.

Keywords

COVID-19 · Cytokine storm · Mesenchymal stem cells · Multiorgan failure · SARS CoV-2

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Abbreviations

ACE2	angiotensin-converting enzyme 2
ARDS	acute respiratory distress syndrome
CLR	C-type lectin receptor
CoV	Corona viruses
COVID-19	Coronavirus Disease 2019
CP	convalescent plasma
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	Chest computerized tomography
GGOs	ground glass opacities
HCQ	Hydroxychloroquine
HIV	human immunodeficient virus
Ig	Immunoglobulin
IL	Interleukin
IP-10 or CXCL10	human interferon-inducible protein 10
MCP-1	monocyte chemoattractant protein-1
MERS-CoV	middle East respiratory syndrome-coronavirus
MIP-1α	macrophage inflammatory protein-1 alpha
MOD	multiorgan dysfunction
N	nucleocapsid protein
NOD	Nod-like receptor
PAMPs	pathogen associated molecular patterns
Rt-PCR	reverse transcriptase-polymerase chain reaction

S	spike protein
SARS-CoV	severe acute respiratory syn- drome coronavirus
TNF- α	tumor necrosis factor alpha

1 Introduction

As of May 9, 2020, 4,032,763 million cases of Coronavirus disease 2019 (COVID-19) have been reported worldwide. A total of 212 countries and territories are affected around the world. Within closed cases, about 1,399,718 patients recovered (83%) and 276,677 died (17%) (worldometers.info). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, is the responsible causative virus for the infection and it spread worldwide dramatically in a short time. On January 30, 2020, the World Health Organization (WHO) declared the outbreak to be a Public Health Emergency of International Concern (PHEIC). Subsequently, on March 11th, it was declared a pandemic as it had spread to 113 countries (who.int).

COVID-19 shows complexity with different clinical outcomes. Patients may remain asymptomatic or show mild to severe symptoms up to pneumonia or not. The most important symptoms are fever, fatigue and dry cough. Other accompanying symptoms include vomiting, nausea, dyspnea, chest tightness, myalgia and diarrhea (Dong et al. 2020). With findings of viral pneumonia images and multiple bilateral ground-glass opacities on chest computerized tomography (CT) scans, mechanical ventilation and intensive care unit (ICU) support may be needed. In the advanced stage with cytokine storm and lymphopenia, multiorgan and systemic clinical manifestations such as sepsis, septic shock, and multiorgan dysfunction (MOD) syndrome and acute respiratory distress syndrome (ARDS) are an inevitable ending (Wu and McGoogan 2020; Wang et al. 2020a). Still there is no specialized therapeutic options for SARS-CoV-2 and new innovations are urgently required. Most of the patients benefit clinically from many known drugs which are used commonly as antiviral,

immunomodulator and anti-inflammatory agents (Kruse 2020). But we still need a way to understand the viral properties and specific target points to stop this SARS-CoV-2 s from entering tissue, replicating in cells and surviving in the human body.

Currently, there is no defined antiviral treatment option for active COVID-19 and also specific vaccine development will take more than 6 months looking on the bright side. Recent studies of cellular therapies with mesenchymal stem cells for COVID-19 indicate good prognosis for patients who are in the middle of cytokine storm and require mechanical ventilation (Bari et al. 2020). This review focuses on recent therapeutic approaches for COVID-19 and mesenchymal stem cells as an probable option.

2 Coronaviruses

The coronavirus family belongs to Nidovirales and involves positive sense, enveloped, extraordinarily large single-stranded RNA viruses 26–32 kilobases in length and they are characterized by club-like spikes that project from their surface (Fehr and Perlman 2015). The origin of CoVs displays differences such as birds, livestock, and also mammals like camels, bats, palm civets, mice, dogs and cats. Phylogenetically, the Coronaviridae family further divides into two subfamilies of Letovirinae and Orthocoronavirinae.

There are four *Orthocoronavirinae* genera including alpha-, beta-, gamma- and delta-coronaviruses. Alpha- and betacoronaviruses transmit disease only in mammals, whereas gamma- and deltacoronaviruses infect avian species and sometimes mammals (Cui et al. 2019). There are seven coronavirus species that cause disease in humans. Alphacoronaviruses (229E and NL63) and betacoronaviruses (OC43 and HKU1) infect humans and cause the common cold with mild symptoms (Corman et al. 2018). Other CoVs (SARS-CoV, Middle East Respiratory Syndrome (MERS) CoV and SARS-CoV2) are all betacoronaviruses and a major threat for human health. SARS-CoV was responsible for

the first CoVs outbreak in China from November 2002 to January 2004 (Zhong et al. 2003). SARS-CoV first originated in bats and intermediate transmission was suggested to occur via bats to palm civet (Guan et al. 2003). Although viral transmission from animals to humans is still debated, direct contact with the intermediary host might be a possible route. Once SARS-CoV is transmitted to humans then nosocomial transmission is defined from person to person (Guan et al. 2003). MERS-CoV was responsible for the second outbreak of CoVs in 2012 in Saudi Arabia and remained regional. The origin of MERS-CoV is bats and the intermediate host was the dromedary camel in the Arabian Peninsula (Chowell et al. 2015). Nosocomial transmission is main transmission route for this virus. SARS-CoV and MERS-CoV induce life-threatening severe pneumonia in patients (Wang et al. 2018).

SARS-CoV-2 was described recently as the seventh Coronavirus that infects human and is globally referred as novel-HCoV-19 (Zhou et al. 2020). The first data about human infection caused by SARS-CoV-2 emerged in Wuhan, Hubei province, China in December 2019. HCoV-19 was isolated and the genomic structure was identified in China between 7 and 10 Jan (who.int) (Virological.org.). The clinical picture of patients infected with SARS-CoV-2 substantially resembles viral pneumonia and the disease was named as Coronavirus Disease 2019 (COVID-19) (Virological.org.). Although viral transmission history from animals to human is still a mystery, early cases were reported around Hunan Seafood market where several wild animals such as bats are on sale as well as aquatic animals. After first transmission of the virus into humans, rapid transmission occurred between humans via droplets, contact and fomites which further leads to pneumonia diagnosed with CT scan or chest X-ray (Chan et al. 2020). The most common symptoms of COVID-19 include fever, cough, and fatigue. The incubation period is approximately 3–7 days. One of the prominent features of SARS-CoV-2 is more efficient tendency to infect the human lung and higher duplication time than SARS-CoV. Indeed SARS-CoV-

2 replicates 3.20-fold faster than SARS-CoV in infected lung tissue (Chu et al. 2020). Genetically SARS-CoV-2 is constructed on four structural proteins as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Spread of the virus is accomplished by high affinity of S proteins to angiotensin-converting enzyme 2 (ACE2) receptors that are expressed in human organs, principally in lung alveolar epithelial cells and enterocytes of the small intestine (Peiris et al. 2003).

COVID-19 patients show diversity in clinical manifestations from asymptomatic to mild and severe symptoms accompanied with or without pneumonia. This wide range of clinical tableau may be related to viral load, advanced age, immune response of individuals and comorbid diseases such as hypertension, coronary disease, diabetes and renal disease (Zhang 2020). Based on recent research, varying laboratory results such as negative or positive SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction (RT-PCR), total cell blood count, C-reactive protein (CRP), serum amyloid A (SAA), and procalcitonin (PCT) and radiological images such as CT are present. Also, clinical and demographic data such as symptoms (fever, cough, sore throat, chest tightness, shortness of breath, loss of appetite, myalgia, fatigue, diarrhea, dizziness), age and gender show diversity within patients (Dong et al. 2020).

3 Immune Response to SARS-CoV-2

Actually, we have limited data about SARS-CoV-2 and the immune response of the COVID-19 patients so far. To understand the mechanism of the disease and immune reaction against SARS-CoV-2, it is better to analyze the pathway which the virus follows. Briefly, after reaching the airway epithelium, SARS-CoV-2 binds to epithelial ACE-2 with high tendency via its S protein. Viral entrance is the first step and this is followed by replication of virus with the help of the host genome. Then the virus is released from the host cell leaving damage. So, it continues to spread to

other cells that express ACE-2. During all these stages, the innate and adaptive immune responses are active against the virus. Some data basically reported increased total neutrophils, reduced lymphocyte count, enhanced serum IL-6 levels and increased CRP levels in the disease state (Wu et al. 2020; Huang et al. 2020). COVID-19 severity seems to be correlated with increased leucocytes, neutrophils, procalcitonin, serum ferritin and CRP and decreased lymphocyte and monocyte numbers (Qin et al. 2020). Although most of those values are in the normal range except for lymphocytes, serum ferritin, CRP, and procalcitonin they tend to increase compared to non-severe conditions. For lymphocytes, while the number of total $CD3^+CD4^+$ T cell decreases in severe cases under normal range, the percent ratio of naïve Th cells ($CD3^+CD4^+CD45RA^+$) to Th cells increases in severe cases and percent ratio of $CD28^+$ Ts cells ($CD3^+CD8^+CD28^+$) to Th cells decreases in severe cases compared to non-severe subjects. Also, T reg levels are under normal range in severe cases (Qin et al. 2020). A healthy and coordinated immune response is essential to SARS-CoV-2 as for all viral infections, we have some limited input to understand the immune recovery process to this special virus. This data clearly shows the need for more studies in order to speculate further.

The innate immune response to RNA viruses such as SARS-CoV-2 starts with recognition of pathogen-associated molecular patterns (PAMPs) as viral genomic RNAs by pathogen recognition receptors (PRR) such as TLR8, TLR7, RIG-I-like receptors (RLR), NOD-like receptors (NOD), and C-type lectin-like receptor (CLRs) (Li et al. 2020). Activation of innate immune system with PAMP-PRR stimulates production of inflammatory cytokines such as tumor necrosis factor (TNF- α and IL-1) and chemokines like CCL2 and CXCL8. Besides these, the preventive type I IFNs response is suppressed in SARS-CoV-2 (Rokni et al. 2020).

Anti-viral immunoglobulin M (IgM), IgG, and IgA antibodies neutralize antibodies. Detection of SARS-CoV-2 specific neutralizing antibodies is helpful to confirm developed immune response against COVID-19. Indeed, sometimes the

RT-PCR results for SARS-CoV-2 fall on the negative side, so it is important to clarify the virus has affected patients with antibody levels for epidemiological and surveillance studies. Recent data also declare that the first antibody specific to SARS-CoV-2 is IgA and it increases up into 3 weeks and persists about 38 days while IgM is still at moderate levels (Padoan et al. 2020). So mucosal immune responses, characterized first by the production of secretory IgA, are established, then systemic antibodies occur later (Zhao et al. 2020).

4 Current Therapeutic Approach

Many protocols have been recommended to cure COVID-19 from countries that are globally affected. Up to now, there is no conductive therapies available or protective vaccines. But nowadays therapies focus on treatments that already exist in the medical agenda which is specific to viral infections and pneumonia. So antiviral agents, immunomodulatory and anti-inflammatory agents are taken off the shelf. Also, other approaches like vaccines specific for SARS-CoV-2 for active immunization (Amanat and Krammer 2020), convalescent plasma (CP) for neutralizing the virus for passive immunization (Roback and Guarner 2020) and mesenchymal stem cell therapies to suppress cytokine storm and to prevent tissue damage and enhance alveolar tissue regeneration (Golchin et al. 2020) are still current issues.

Antiviral agents which are specific normally to treatment of human immunodeficient virus (HIV), hepatitis and flu symptoms are in the treatment protocol for COVID-19 patients. Among antivirals; lopinavir/ritonavir (Cao et al. 2020a), remdesivir (Wang et al. 2020b) and favipiravir (Khambholja and Asudani 2020) ameliorate the clinical circumstances of patients.

Clinical and laboratory observations of COVID-19 patients clearly show disturbed immune activity and increased inflammatory process, especially in the lungs. Current immunomodulatory and anti-inflammatory treatment approaches are also medicinal. Many trials have

been carried out about hydroxychloroquine (HCQ) as a treatment option for COVID-19 patients. A recent systemic review and meta-analysis (Sarma et al. 2020) showed some benefits like body temperature and cough days with HCQ but less improvement per case was observed for radiological progression of the lung. Also, days spent in hospital reduce with HCQ treatment (Gautret et al. 2020). The combination therapy of HCQ with azithromycin turned PCR positivity to negative and looks helpful and safe (Saleh et al. 2020). Many COVID-19 patients are highly affected by the cytokine storm and their progression worsens. Anticytokine therapy seems to be effective to control the inflammatory response by controlling the cytokine release syndrome (CRS). For this purpose, tocilizumab, an interleukin-6 (IL-6) receptor antagonist, was used for COVID-19 patients. Although some conflicting results were found (Radbel et al. 2020), tocilizumab will be useful in the early stages of COVID-19 and prevents the hyperactivation pathway, oxygen requirements, CT lesions, alleviates CRP levels and average hospitalization days (Xu et al. 2020).

5 Convalescent Plasma Therapy

German scientists in 1893 described serotherapy to treat patients who suffered from diphtheria. This is the first declared trial with plasma from animals immunized against diphtheria to cure patients stricken with diphtheria (Dunmire). Plasma therapy contains plasma from early actively immunized or convalescent patients. First person to person transfer of convalescent plasma therapy was used around 1917–1918 during the A/H1N1 Spanish flu (Luke et al. 2006) and about 100 years later from 2005–2015 during the A/H5N1 flu epidemics (Zhou et al. 2007), the 2009–2010 A/H1N12009p flu epidemics (Hung et al. 2011) and around 2013–2015 during the Ebola virus outbreak in West Africa (Burnouf and Seghatchian 2014). Since the outbreak of COVID-19 has rapidly spread globally, viral specific therapy protocols or medications cannot be found. But old-fashioned CP therapy turned the

light on for severe COVID-19 patients. Until now there are numerous practices which have been performed and are encouraging. One of these is CP derived from convalescent patients and transfused to 10 severe patients who need maximal supportive in intensive care and also receive antiviral treatment. The results of therapy with CP indicates that it is well tolerated, clinical symptoms improved with increased oxyhemoglobin saturation within 3 days, increased absolute lymphocyte counts, normalized CRP levels and neutralized viremia (Duan et al. 2020). Another descriptive study also supports the effectiveness of CP therapy for COVID-19 (Ye et al. 2020). They transfused CP to 6 patients and 5 of them had obviated ground glass opacities (GGOs). Additionally, CP purified intravenous globulin (IVIg) also assists COVID-19. At the time of initiation of respiratory distress syndrome, high-dose intravenous globulin (IVIg) was used intravenously for 3 COVID-19 patients in China and resulted in convincing clinical and radiographic recovery (Cao et al. 2020b). In order to transfer CP infusion into practice, some important limitations should be considered. Both antibody and neutralization activity should be tested in convalescent patients' plasma. Previous to CP collection, host eligibility and donor qualifications must be debated. For safe use of CP in the SARS-CoV2 pandemic, we still need time to determine optimal dose and intervals for infusion with controlled clinical trials.

6 Vaccine

More than 100 centers around the world are focused on the urgent need for a vaccine against COVID-19 as a prophylactic and preventive approach (Gao et al. 2020) (Eyal et al. 2020). With the sequencing of SARS-CoV-2, different approaches have been used including small molecules targeting RNA polymerase, 3C-like protease, and RNA endonuclease. Among them, mRNA-127 (NCT04283461) is a synthetic strand of mRNA which encodes the viral spike protein was developed by Moderna and phase I trials are ongoing. The University of Oxford created a

non-replicating adenovirus vector and the genetic sequence of the S protein of SARS-CoV-2 in a vaccine named ChAdOx nCoV-19. This non-replicating adenoviral virus may also be safe for children and has also entered phase I/II clinical trials ([NCT04324606](#)). Other trials are about stabilizing subunit vaccines and nanoparticle-based vaccines. It is believed that a vaccine target for COVID-19 would save many lives in this current pandemic. But indeed, we need time to develop a safe and effective vaccine based on bioethical issues and clinical trials and also risks and benefits should be considered.

7 Mesenchymal Stem Cells

It is now well known that SARS-CoV-2 induces a scary cytokine storm especially in the lungs with the early response of proinflammatory cytokines such as TNF- α , IL-6 and IL1 β . Also, other inflammatory cytokines like IL-2, IL-7, GSCF, IP10, MCP1 and MIP1 α are involved in the process. Those cytokines lead to dramatic edema, air exchange dysfunction, acute respiratory distress syndrome, acute cardiac injury, secondary infection and catastrophic effects on tissues and organs which may lead to death ([Huang et al. 2020](#)).

MSCs are non-specialized multipotent cells that have self-renewal and differentiation capacity into diverse cell types such as adipose, chondrocyte and osteocyte cells. Mesenchymal stem cells (MSCs) are multipotent cells and can be isolated from several sources mainly from bone marrow, peripheral blood, adipose tissue (abdominal fat, buccal fat and infrapatellar fat pad), human placental tissue, umbilical cord, Wharton's jelly and dental tissues and further they have the ability to differentiate into various lineages of cell types ([Al-Nbaheen et al. 2013](#)). MSCs have high capacity to modulate immune responses. Basically, they suppress T cell proliferation and regulate the balance of Th1 (autoimmunity related)/Th2 (allergic disease related). On the other hand, they regulate the immune response with T regulatory cells and control antigen presentation of dendritic cells ([Akkoc 2019](#); [Duman et al. 2019](#);

[Genc et al. 2019](#)). All of these modulatory effects are important to control cytokine storm disease. Further MSCs are involved in regenerative processes for damaged tissues and organs. Patients with COVID-19 pneumonia are faced with severely destroyed alveolar lung tissue and this leads to dysfunction of the lung which will end in death. After the intravenous transplantation of MSCs, cells accumulate in the lung and are activated because of the proinflammatory stimulus of the environment. Once MSCs are stimulated with proinflammatory cytokines, they become immunomodulatory cells and are further programmed to protect alveolar epithelial cells, prevent pulmonary fibrosis, and reverse lung dysfunction. However, currently, there are no approved MSC-based therapies for COVID-19 patients but there are some trials about MSC and COVID-19 ongoing.

Pathogenesis and current therapeutic approach. The role of MSCs are summarized

Prostaglandin E2 (PGE2), transforming growth factor (TGF)- β , indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), hepatocyte growth factor (HGF)

[ClinicalTrials.gov](#) Search Results 05/05/2020. Clinical trials conducted with MSC therapy for COVID-19

The Asian lineage avian influenza A (H7N9) virus, with outbreak reported between 2013–2017 in China, shares similar clinical outcomes like ARDS, lung failure, pneumonia and further multi-organ dysfunction in severe cases. The first clinical study related to MSC transplantation for H7N9 infected patients with ARDS ended up with lower mortality compared to the control group. In that study allogenic menstrual blood-derived MSCs were transplanted to 17 patients with H7N9-induced ARDS, while 44 patients with the same criteria were included as a control group. MSC therapy reduced CRP, procalcitonin, serum creatinine, and creatine kinase levels. Mortality seemed to be lower in the MSC treated group (17.6%) compared to controls (54.5%) ([Chen et al. 2020](#)). Regarding clinical observations, there are high similarities for ARDS and lung failure and further multi-organ dysfunctions between H7N9 and COVID-19.

Thereby, MSC-based cellular therapy may be an encouraging alternative for COVID-19 in severe cases.

It was shown that the administration of ACE-2 negative MSCs (free from COVID-19) improved functional outcomes in COVID-19 patients. Regarding that study, patients enrolled with COVID-19 pneumonia (Seven SARS-CoV-2⁺ patients) and received 1×10^6 MSC cells per kilogram of weight in 100 ml saline intravenously. Two days after MSC transplantation they observed improved pulmonary functions and symptoms. MSC therapy lead to increased peripheral lymphocytes which normally decreased in severe cases. TNF- α and CRP are other signature markers of inflammation and they increased dramatically especially in severe COVID-19 cases. They showed clearly that MSCs reversed this and decreased TNF- α and CRP levels to the normal range. IL-10 is an important cytokine for immunomodulatory activity and suppresses the inflammatory response. MSC transplantation also enhances IL-10 levels and controls the cytokine storm. One of the attractive results is disappearance of overactivated cytokine-secreting immune cells of CXCR3⁺ CD4⁺ T cells, CXCR3⁺ CD8⁺ T cells and NK CXCR3⁺. Additionally, CD14⁺ CD11c⁺ CD11b^{mid} regulatory DC cell populations also increased dramatically (Leng et al. 2020). Similarly, Liang and colleagues transplanted 5×10^7 umbilical cord MSCs three times (every 3 days) intravenously to a 65-year-old female with COVID-19 pneumonia. After the second infusion, vital signs were improved, the trachea cannula was removed and serum bilirubin, C-reactive protein (CRP) and alanine transaminase/aspartate transaminase (ALT/AST) gradually reduced. Also, CT images improved (Bing et al. 2020). All these results indicate the safety and treatment options for MSC in COVID-19. Beside MSCs themselves, MSC-secretomes may also function in immunomodulation and silence the cytokine storm in COVID-19 disease (Bari et al. 2020). In this regard, two Chinese clinical trials recently appeared on <http://www.clinicaltrials.gov> (last access: 01/04/2020) investigating inhaled secretome for the treatment of COVID-19

pneumonia (NCT04276987) and its tolerance in healthy volunteers (NCT04313647).

As of May 6, 2020, 33 clinical trials are being conducted with MSCs therapy for COVID-19. All of them are summarized in. When we researched these trials, researchers chose different sources of MSCs such as Wharton's jelly, umbilical cord, adipose tissue, dental pulp and company-produced MSC. After completion of these studies, we will be able to obtain scientific results about the therapeutic intervention of MSC in COVID-19 disorder. Also, a lot of questions about therapy for COVID-19 with MSCs regarding the route of administration, dose, source of stem cells, safety of use and clinical outcomes, as well as ethical issues, will be clarified.

8 Conclusion

SARS CoV2 has spread to more than two hundred countries and territories. It has become a pandemic and affects people mostly with chronic disease, comorbidities and older age. Patients suffer from pneumonia which leads to ARDS and sepsis with multi organ dysfunction in severe cases. Although there are no confirmed treatment protocols, mild patients benefit from antiviral, immunomodulatory and anti-inflammatory therapies. But in severe cases, the situation worsens. Severe pneumonia and ARDS are real clinical pictures because of the inflammatory cytokine storm. After this, patients need intensive care unit support and ventilation. Recently, the literature showed that convalescent plasma infusion helps to control viremia. We also need remarkable time to develop a vaccine that is specific to COVID-19. Studies in recent years clearly showed the beneficial effect of mesenchymal stem cells for autoimmune and allergic disease, as well as regenerative and immunomodulatory impact. Since COVID-19 is noted for cytokine storm and high inflammation in lungs, MSC seems to be a treatment option. Although there are limited studies to that end, clinical and laboratory improvements with MSCs were declared. There are about 33 clinical trials ongoing to date. Additional studies about stem cell-based

therapies in larger groups of COVID-19 patients are needed to further validate this therapeutic intervention.

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