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Chapter

Cellular Therapy as Promising Choice of Treatment for COVID-19

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Abstract

In the pandemic of COVID-19, while living normals have been changing, there have been a huge effort globally to find out effective and safe treatment agents and vaccines. As of now, the advances show the progress in vaccine development, however the treatment of the COVID-19 is yet not fully specified. The drugs, i.e. antibiotics, antivirals, antimalarians, even anti-HIV agents which have been known already were taken out of the shelves and brought into use in different combinations. On the other hand, the cellular treatment, more specifically the mesenchymal stem cell therapy has been encouraged, resulting in various evidence published all over the world. This chapter aims to compile the published information, in means of methods, disease manifestations, results and limitations, about the stem cell treatment of the COVID-19 and to provide a source of harmonized reference for scientific society.

Keywords: mesenchymal stem cell, cellular therapy, regenerative, restorative, personalised medicine

1. Introduction

Since the global living routine have been dramatically changed by a novel virus called SARS-CoV-2, scientific community has been working hard on the understanding of the pathophysiology of the COVID-19 infection caused by this virus, and the methods of preventing and treating the disease. The spectrum of clinical manifestations of COVID-19 varies from asymptomatic or somewhat mild-disease (81%) to severe clinical conditions characterized by respiratory failure requiring mechanical ventilation (14%) and to critical systemic presentations with multiple organ dysfunction syndromes or failures (5%) [1, 2].

There is a huge effort to develop vaccines, some are developed and received the accelerated access at the moment, however, there is no specific antiviral treatment recommended or appreved for COVID-19, yet. Current therapeutic strategies are only supportive and oxygen therapy represents the primary treatment intervention for patients with severe pneumonia. The medications that have already been known such as anti-viral, anti-malarial, and anti-inflammatory agents have been taken from the shelves and began to be used as the emergency state action to improve the recovery of the patients and increase the survival. Whilst these treatments can improve patient's recovery and survival to some extend, these therapeutic strategies do not lead to unequivocal restoration of the lung damage inflicted by this disease. [3]. The outcome so far shows that the antibiotics are ineffective; although systemic

corticosteroids seem be effective, they also reduce the immune system activity and thus its ability to fight against the infection. It is of crucial importance to save the patients with severe COVID-19 pneumonia, to prevent and even reverse the cytokine storm along with inhibiting the viral replication [4].

The cellular therapies with mesenchymal stem cells (MSCs) are attracting attention as they could offer a new therapeutic approach in this context. These stem cells have broad pharmacological effects, including anti-inflammatory, immunomodulatory, regenerative, pro-angiogenic and even anti-fibrotic properties [5].

Stem cells, in particular MSCs, exert their immunomodulatory, anti-oxidant, and reparative therapeutic effects likely through secreted extracellular vesicles (EVs), and therefore, could be beneficial, alone or in combination with other therapeutic agents, in patients diagnosed with COVID-19. [3, 6] They are are emerging as new promising treatments, since they could not only attenuate the inflammation but also regenerate the lung damage caused by COVID-19 [7, 8].

In this chapter, we outline the information about this novel virus, and the pathophysiology of the COVID-19 infection, the mechanisms of cytokine storm and lung damage caused by SARS-CoV-2 virus and how mesenchymal stem cells (MSCs) can be utilized to hamper this damage by harnessing their regenerative properties. The potential of these ancestor cells in the enhanced clinical utility in treating the COVID-19 patients along with the opportunuties major roadblocks to progressing these promising curative therapies toward mainstream treatment for COVID-19 have also been evaluated.

2. SARS-CoV-2 infection: what to focus

2.1 SARS-CoV-2 virus

Belonging to the β Coronavirus family, SARS-CoV2 is a single-stranded RNA, enveloped virus of 50-200 nm diameter [9]. Spike Glycoprotein (S) is the vital protein consisting of three S1-S2 heterodimers that bind to angiotensin-converting enzyme 2 (ACE2) receptor on type II pneumocyte in the lung tissue [3, 9, 10]. Besides S protein, enetically SARS-CoV-2 is constructed on structural proteins of membrane (M), envelope (E), and nucleocapsid (N) proteins. Spread of the virus is managed by the high affinity of S proteins to ACE2 receptors that are expressed in human organs, principally in lung alveolar epithelial cells and enterocytes of the small intestine [11, 12].

Once the SARS-CoV-2 virus enters into the type II pneumocyte and capillary endothelium by endocytosis, it increases in the cytoplasm. Apoptosis is induced by yhe stress in the pneumocytes. Besides, the viral RNA acts as a pathogen-associated molecular pattern and is recognized by the pattern recognition receptor or toll-like receptors. Subsequent chemokine attraction causes neutrophil migration and activation. Then the destruction of the alveolar-capillary walls occur. This leads to the lost interface between the intra-alveolar space and the stroma. Therefore, fluid leaks through and fills into the alveolar spaces [13, 14].

One of the prominent features of SARS-CoV-2 is its being more inclinable to infect the human lung and higher, 3.20-fold faster, duplication time than SARS-CoV [15].

2.2 The development of the SARS-CoV-2 infection

2.2.1 In the society

Modes of transmission occurs through droplet transmission, fecal-oral route, conjunctiva and fomites [13, 14]. Also, the local transmission can be traced back to

the patient's body fluids such as respiratory droplets, saliva, feces, and urine [15]. The virion is stabilized at lower temperatures, i.e., 4 °C has higher survival than 22 °C [16, 17].

Before the clinical symptoms presentation, during the symptomatic stage and even during the recovery period, the patients with COVID-19 can spread the infection, because SARS-CoV-2 virions are shed throughout the clinical course.

When it comes to the residence time of the SARS-CoV-2 virion on surfaces, it has been known that the viable residence time of SARS-CoV-1 in aerosols, copper, cardboard, stainless steel, and plastic are 3 h, 4 h, 24 h, 48 h, and 72 h, respectively [18].

2.2.2 In the clinics

2.2.2.1 Clinical presentation of COVID-19

The symptoms and relevant clinical presentations of COVID-19 was deeply elaborated in WHO-China joint report [19]. Cases of 85%, present with pyrexia in but only 45% are febrile on early presentation [20]. Cough is seen in 67.7% of patients and sputum is seen in 33.4%. Cases show respiratory symptoms such as dyspnea (18.6%), sore throat (13.9%), and nasal congestion (4.8%) [20]. General symptoms such as muscle or bone aches (14.8%), chills (11.4%), and headache (13.6%) are also seen [20]. Gastrointestinal symptoms including nausea/vomiting and diarrhea are observed in 5% and 3.7% of the cases, respectively. These clinical presentations of COVID-19 were consistent in similar studies on COVID-19 cases in China [21–24].

In SARSCoV- 2 infected severe cases, fatal acute respiratory distress syndrome (ARDS), associated with monocyte and macrophage infiltration, diffuse alveolar damage, and cellular fibromyxoid exudates have been confirmed [25, 26] with mortality reported as high as 52.4% [27]. At the 7th–10th days of the manifestations of immune dysregulation, including cytokine release syndrome with elevated cytokine levels (IL-6, IL-8, IL-1, IL2R, IL-10, and TNF-α), lymphopenia (in CD4+ and CD8+ T cells), and decreases in IFN-γ expression in $CD4^+$ T cells [26–28]. It is suggested that the cytokine storm or response may weaken the adaptive immunity against COVID-19 infection, [29] which is associated with atrophy of the secondary lymphoid tissues [25]. The risk of the success of the anti-inflammatory treatment comes from the secondary infections [30].

In severely damaged the lung tissue the ARDS develops which can further turns to septic shock. These two complications are the major issues in intensive care unit (ICU) care. The mortality from COVID-19 in patients older than 60 years, with smoking history, and comorbid medical conditions including but not limited to hypertension, cardiovascular and cerebrovascular disease, and diabetes also occurs from these complications. Notably, smoking and older age group patients tend to have a higher density of ACE2 receptors [13].

Asymptomatic or presymptomatic infection takes its naming from the patients which are the most majority of the all cases have no symptoms although they test positive for SARS-Cov-2 by reverse-transcriptase polymerase chain reaction (RT-PCR). The rest of the cases demonstrate the symptoms of fever (98%), cough (76%), dyspnoea (55%) and myalgia or fatigue (44%). Other signs, such as sputum production (28%), headache (8%), haemoptysis (5%) and diarrhoea (3%), may also be present [31]. On the other hand, the severe cases are seen in the clinics and are typically characterised by pneumonia and usually accompanied by the complications of ARDS [31, 32], acute cardiac injury [33], and secondary infections [34].

ARDS is the most significant complication in severe cases of COVID-19, and it affects 20–41% of hospitalized patients [31, 35] besides, heart failure, renal failure, liver damage, shock and multi-organ failure have also been observed as complications.

Clinical manifestation severity has been seen in a stratification which depends on symptomatology [36] (**Figure 1**). Adult COVID-19 cases may be grouped as follows [37, 38]:

1. Mild: The cases with any of the various signs and symptoms of COVID-19 (e.g. muscle pain, fever, malaise, headache, cough, sore throat) but the absence of breath shortness, dyspnoea or abnormal chest imaging.

2. Moderate: The cases with showing signs of lower respiratory illness by clinical assessment or imaging and peripheral oxygen saturation (SpO^2) ≥ 94% (room air at sea level).

3. Severe: The cases characterized by breathing rates ≥30 breaths/min, SpO^2 < 94% (room air at sea level); a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO^2/FiO^2) less than 300 mmHg, or lung infiltrates greater than 50%.

4. Critical: The patients presenting with respiratory failure requiring mechanical ventilation, septic shock and/or multiple organ dysfunctions [36].

As the RNA expression is detectable across a wide range of human tissues [39],it is thought that the multi-organ dysfunction is probably linked to the expression pattern of ACE2 gene. The cells, tissues and organs most affected are those with high ACE2 expression, the entry receptor or opening doors for SARS-Cov-2. The research has shown that ACE2 is abundantly expressed in the epithelia of the lung and small intestine in humans, for possible routes of the SARS-Cov-2 [40]. Since the recent data suggest that cell-surface expression on the lungs is below the detection limit [41], it has been proposed that the COVID-19 disease pathology would not be directly correlate with ACE2 cell-surface protein expression [41]. As reported for the heart and kidneys, the said disparity may be linked to the selective, transient expression of ACE2 [42, 43].

Health condition of the patients suddenly detoriates in the later stages of diseases progression. Death comes right after the fast multiple organs' failure and ARDS. Cytokine storm has been indicated as the causal factor for ARDS and multiple organ failure [44, 45]. WHO has announced the case fatality rate of

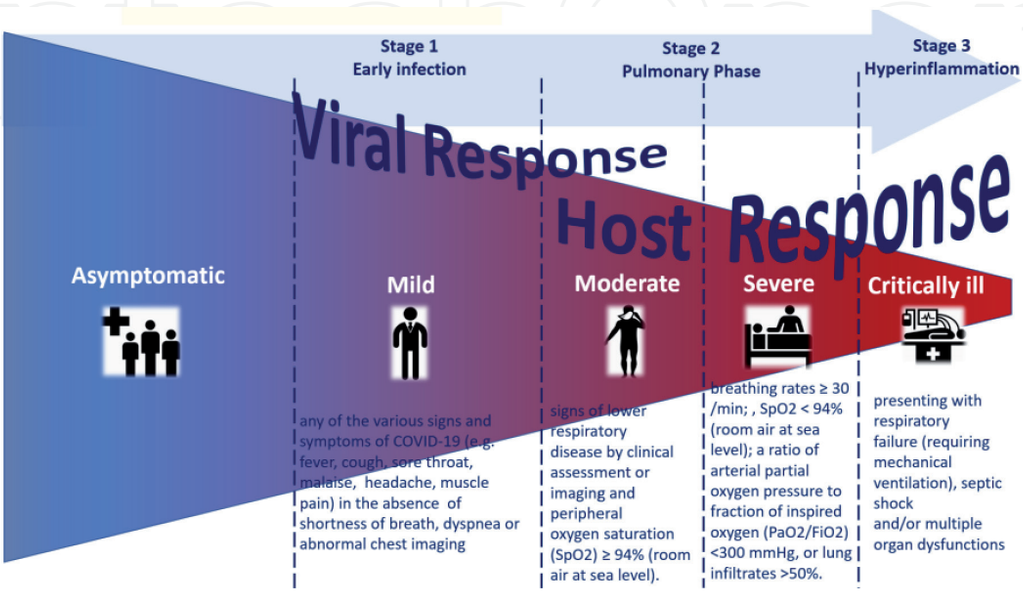

Figure 1.
Clinical stages and the manifestations of COVID-19 disease.

COVID-19 as ranging from 0.3 to 1%, higher than that of influenza A which is 0.1%. The epidemiological studies reported from the countries implementing COVID-19 mitigation strategies revealed that almost 80% of patients of COVID-19 had no symptoms or mild disease, whereas 14% of the patients had severe symptoms, and 6% of them were in critical condition [46].

2.2.2.2 COVID-19 disease management

The management of viral pneumonia is supportive in absence of specific treatment. The most dominating symptoms are fever and dry cough, therefore the first-line antipyretic agent antitussive medications [47]. Oxygen supplementation at 5 L/min must be administered for patients requiring ARDS treatment and the oxygen saturation target must be ≥92–95% in pregnant cases, ≥90% in other cases [48].

Conventionally, the complications of septic shock and acute kidney injury should be managed with relevant sepsis and renal replacement therapies [49]. In the middle to later course of COVID-19, some of the cases may develop overlapping bacterial and/or fungal infection. In these cases, the empiric antimicrobial treatment should be provided.

The WHO has been recommending the usage of extracorporeal membrane oxygenation in the patients who sustain hypoxia refractory to supplementary oxygen [49]. Or else, the convalescent plasma and IgG are used as rescue therapy in critical cases, without any solid evidence for the benefit of this practice. Most of the cases demonstrate vital health measures to control COVID-19 spreading. If the public health measures are not taken properly, there will be a patient burden that exceeding the volume of ICU beds and mechanical ventilation, as seen in the crisis in Italy. Hence, the objective of the COVID-19 management lies on the maintenance of social distancing to suppress the rapid emergence inflow of new cases. This epidemiological approach is called as flattening of the curve. The public health interest should be for identifying and isolating the infective cases, attain and maintain contact tracing and isolation [50].

3. The pathophysiology of the SARS-CoV-2 infection: what we know

3.1 Cytokine storm

The story of the cytokine 'breeze' transformation to the 'storm' starts with the infection of the cell through receptor–ligand interactions which activates massive numbers of leucocytes, particularly B cells, T cells, natural killer cells, monocytes, dendritic cells and macrophages. The release of inflammatory cytokines from these cells attract and activate more white blood cells. Cytokine breeze starts locally post-primary infection with appearing classical signs of inflammation including, calour (heat), dolour (pain), rubor (redness), tumour (swelling or oedema) and loss of function. At the beginning, the localized response works for eliminating the trigger. The host response involving the increase in blood flow, facilitation of leucocyte extravasation and delivery of plasma proteins to the site of injury, increase in body temperature and pain triggering spreads throughout the body via systemic circulation. These responses along with the host repair processes results in either gradually restored organ function or recovery happening by fibrosis which may lead organ dysfunction [51, 52].

Fibroblasts proliferate and invade the intra-alveolar zone constructing fibroblast foci. This seems as the beginning of the pulmonary fibrosis pathogenesis [53]. Lung sections from two patients with early-phase COVID-19 pneumonia demonstrated the characteristics similar to this initiation step of fibrosis [54]. Fibroblast foci were observed in the airways, besides the edema, type II pneumocyte hyperplasia with

infiltration of inflammatory cellular and multinucleated cells. Some reactive epithelial hyperplasia areas are also abundant alveolar macrophages [54]. The SARS-CoV-2 caused progressing injury of the alveolar zone, apears to establish a pro-inflammatory microenvironment triggering this aberrant response with partial replacement of normal tissue by fibrous tissue. Since the severe and critical COVID-19 presentations show strong involvement of inflammatory components and possibly loss of resident stem cell stocks, the research is focused in investigating the role of cellular therapy using immune response-suppressing MSCs for COVID-19 therapy [55].

In COVID-19, the extend of the cytokine release can be the ground for the diversity of the clinical manifestations. The term 'cytokine breeze' meaning a mild/nonlethal cytokine release response to infection includes the symptoms of increased local temperature (heat), myalgia, arthralgia, nausea, rash, depression, and other mild flu-like symptoms. The compensatory repair process in the body is launched for the reparation of the organs and tissues affected. The term 'cytokine strom' is used to describe the similar sudden and uncontrolled cytokine releases observed in autoimmune, hemophagocytic lymphohistiocytosis, sepsis, cancers, acute immunotherapy responses, and infectious diseases [56, 57].

All these cytokine strom ailments were not only observed in SARS-Cov-2, but also previously reported in SARS-Cov-1 and MERS-Cov cohorts [58, 59]. Hyperinflammation, though, is characteristic for SARS-Cov-2 which is a unique immunological feature of COVID-19. The data reported from recovered and seriously ill patients suggests that there is a significant relationship between severe inflammation and mortality. The main components of the cytokine strom are the critical pro-inflammatory immune elements in the inflammation site [51]. Once the immune system is activated by infection, drug or any stimulus, the cytokines (IFN, IL, chemokines, CSF, TNF, etc.) are released in high levels into the circulation leading to deleterious and diffuse impact on multiple organs..

At the moment, the factors responsible for triggering the inflammatory sequence resulting in cytokine strom are still ambiguous. It is attributed to an imbalance in immune-system regulation resulting from increasing immune cell activation via TLR or other mechanism and decreasing in anti-inflammatory response.

Altough the local and systemic cytokine responses of host to theinfection are essential parts of the host's initial response to infection, a cytokine strom, due to the harmful effects on the host, almost always is a pathological process [31]. Normally, to keep the pathogen under control, the cytokines released from natural killer (NK) cells and macrophages, activated T cells, and humoral immunity work to resolve the inflammation, along with the antibody-dependent cell-mediated cytotoxicity [60]. When looked in some more detail, epithelial cells produce local cytokines like IFN-α/β and IL-1β which can protect neighbouring cells by stimulating IFN-stimulated gene expression. This also activates the immune competent cells such as NK cells. In turn, the lytic potential of NK cells increased and IFN-γ secretion is potentiated [61]. IFN-γ actives the resident macrophages which amplifies TLR-mediated stimulation, specifically induce the high NK cells release [62]. On one side, the IL-12 acts to increase NK IFN-γ secretion, on the other side, increased levels of IL-6 also may limit the immune response by its effects on the cytotoxic activity of NK cells via the down-regulation of intracellular perforin and granzyme B levels [63]. The disease does not regress but progress further, the activities of the T cells and humoral responses causes additional cytokine responses. This process, like pouring petrol on fire, results in greater or sustained antigen release and added TLR ligands from viral-induced cytotoxicity [64]. Concurrently, an insufficient negative feedback mechanism by IL-10 and IL-4 would be expected to increase the severity of cytokine responses toward a cytokine storm. The exacerbated fire of the lethal cytokine storm reveals widespread alveolar damage characterized by

hyaline membrane formation and infiltration of interstitial lymphocytes [65, 66]. In COVID-19 disease, a cytokine storm is demonstrated frequently in patients with severe-to-critical symptoms; concurrently the lymphocytes and NK cell counts are sharply reduced with elevations in levels of D-dimer, C-reactive protein (CRP), ferritin, and procalcitonin which are the inflammation biomarkers [67].

As the reported evidence regarding the immunological response to SARS-CoV-2 is quite limited, we are able to compile and interpret the relevant information from the published information. After the host is invaded by the virus, host innate immune system through pattern recognition receptors (PRRs) including C-type lectin-like receptors, Toll-like receptor (TLR), NOD-like receptor (NLR), and RIG-I like receptor (RLR), is the first to pick out [68]. The inflammatory factors' expression, dendritic cells' maturation, and type I interferons (IFNs) synthesis are promoted by the virus for basically two main purposes: limiting the spread of the virus, and phagocytosis of the viral antigens [68]. Whilst the escape of the virus from the immune responses is facilitated by the N protein of the virus [69], a strong troop of the adaptive immune response joins the combat against the virus, with its elements of T lymphocytes including CD4+ and CD8+ T cells. CD4+ T cells stimulate B cells to produce virus-specific antibodies, and CD8+ T cells directly kill virus-infected cells. T helper cells produce proinflammatory cytokines to enhance the antiinflammatory process. Paradoxically, SARS-CoV-2 induces the apoptosis of the T cells, hence inhibit their function. The major role of humoral immunity over its complements such as C3a and C5a and antibodies cannot be overlooked in the fight against the virus [70, 71]. Here comes another paradox where the immune system overreaction of the generates a large amount of free radicals locally causing severe damages to the lungs and other organs, even multi-organ failure and even death [62, 72].

In severe cases, it has been reported that SARS-CoV-2 affects heart, kidney, liver, GI-system, resulting in multiple organ dysfunction and in some cases even death [73]. One study supports that the novel virus also could potentially infect the enterocytes through a ACE2 enzyme; as ACE2 is highly expressed on enterocytes may help to explain why diarrhea occurs with acute infection as well as the fecal shedding observed [74]. Since the ACE-2 receptors are also expressed on other tissues like kidney, liver, heart and digestive system organs; thus, explaining the rapid progression towards systemic inflammatory conditions as observed in critically ill patients [75]. Hence, it is worth to consider that the infection spreading in broader scale would have impact the inflammatory cascade sources in a number of tissues in several organs, besides the lung.

4. The treatment options in SARS-CoV-2: what to use

Based on evidence from laboratory, animal, and clinical studies, the WHO recommends the drugs for treatment of COVID-19 includes Remdesivir, Lopinavir/Ritonavir, Lopinavir/Ritonavir with interferon beta-1a, chloroquine, and hydroxychloroquine [76].

Remdesivir is a monophosphoramide prodrug that causes premature termination of viral RNA replication. It was developed against Ebola, MERS-CoV, and SARS-CoV, before the COVID-19 pandemic shook the globe. Potent interference of remdesivir with the NSP12 polymeras3e of SARS-CoV-2 was shown in vitro despite intact ExoN proofreading activity [73, 77]. It is suggested that when the baricitinib which is an inflammatory drug used in combination with anti-viral drugs like Remidesivir, increases the potential of the drug to reduce viral infection [78, 79].

The Lopinavir/Ritonavir drugis a protease inhibitors combination. It is usually used to treat HIV infection; from the laboratory experiments, it is evident that

these drugs could be used to treat the COVID-19 infections [80]. The lopinavir and ritonavir are used as a regimen single-agent or combination with either ribavirin or interferon-α [81]. It is also reported that the interferon beta-1a, which is used to treat multiple sclerosis, can also be used as a remedial approach for COVID-19 disease [73].

A randomised controlled trial (ChiCTR 2000029308) aimed to evaluate the efficiency and safety of lopinavir and ritonavir in severe COVID-19 patients, comparing lopinavir-ritonavir (n: 99) to standard care (n: 100). There was a significant difference in the time to clinical improvement between the two groups on day 14, whereas this difference was not statistically significant on day 28. The decrease of 5.8% in mortality at 28 days and the length of stay in the ICU reduced as five days in the lopinavir-ritonavir treatment [82].

Spike protein from virus binds to ACE2 or CD147 on the host cell, mediating viral invasion and dissemination of virus among other cells [55, 83]. In addition to ACE2, it has recently been demonstrated that S protein of novel virus also binds to CD147. Meplazumab which is an anti-CD147 humanized antibody, co-immunoprecipitation, ELISA, and immuno-electron microscope were handled to demonstrate the new CD147 path of viral invasion. This importanty evidence has been providing a key target for the development and administration of specific anti-SARS-CoV-2 medicines [84].

ACE Inhibitor and Angiotensin Receptor-1 Blocker are also medications used for the curative purposes of COVID-19. As already mentioned, SARS-CoV-2 enters the type II pneumocytes via the ACE2 receptor. Functionally ACE2 receptor has a mutual physiological action to ACE1, it converts the angiotensin II back into angiotensin I. Thus, patients taking receptor blocker will have an increased plasma angiotensin II. On the contrary, patients taking inhibitor will have low angiotensin II levels [85, 86]. Its effect in the alveolar tissue is still unknown. Discontinuation of ACEi or ARBs is not recommended yet as hypertension is an acute risk of discontinuation and can exacerbate the clinical course and increase mortality of COVID-19 if infected by SARS-CoV-2. Although chloroquine is an anti-malarial medication, it can inhibit pH-dependent stages of replication in viruses, as well as having immunomodulation which is dependent on the suppression of cytokines (IL-6 and TNF-α) production and dissemination. Secondary COVID-19 rates can be minimized with pre- and post-exposure prophylaxis in an individual with document exposure to SARS-CoV-2. Therefore, hydroxychloroquine has been hypothesized to be an adequate chemoprophylaxis candidate to reduce secondary COVID-19 [87].

WHO recommends to continue the use of ibuprofen as antipyretic agent, yet the first-line antipyretic remains to be acetaminophen.

The use of systemic corticosteroids in the management of ARDS secondary to viral pneumonia is debatable. The rationale behind this that the corticosteroids prolong the viral shedding time and maintain a systemic anti-inflammatory condition. This will minimize the precipitation of ARDS, dyspnea, and severe pneumonia.

The systemic corticosteroid usage in the management of ARDS developed due to viral pneumonia is still under discussion. The aim of this medication use is that corticosteroids prolong the viral shedding time and maintain a systemic anti-inflammatory state that will minimize the precipitation of ARDS, dyspnea, and severe pneumonia [76].

Considerable amount of protection is provided by the convalescent plasma collected from donors who have survived an infectious disease by developing antibodies is considered to provide a great degree of protection for recipients affected by the emerging virus [88]. Convalescent plasma is an old tool that has been successfully used to treat numerous infectious diseases, including the 2003 SARS-CoV-1 epidemic, 2009–2010 H1N1 influenza virus pandemic, and 2012 MERS-CoV epidemic [88–91] for which there is no effective treatment.

Based on the clinical effectiveness of convalescent plasma, such as signs of improvement approximately 1 week after convalescent plasma transfusion, effectively neutralizing SARS-CoV-2, leading to impeded inflammatory responses and improved symptom conditions without severe adverse events the FDA has granted clinical permission for applying convalescent plasma to the treatment of critically ill COVID-19 patients [92]. Antibiotics with immunomodulatory actions are used in therapy with antiviral drugs and to avoid secondary infections, such as bacterial and fungal infections in patients. Besides their antimicrobial function, antibiotics such as Azithromycin show immunomodulatory properties, which can reduce inflammatory macrophage polarization and inhibit NF-κB signaling pathways, minimizing the hyperinflammation damage. Since the beginning, antibiotics have been used with good results in mortality reduction and shortening of intubation time in COVID-19 disease [93, 94].

The expressive number of deaths and confirmed cases of SARS-CoV-2 call for an urgent demand of effective and available drugs for COVID-19 treatment. Currently, multiple avenues for therapies are being explored.

5. The mesenchymal stem cells or medicinal signalling cells

Human mesenchymal stromal cells are also recognised as mesenchymal stem cells and medicinal signaling cells (MSCs). The reason of why the MSCs are named as 'mesenchymal' is their residence in the mesodermal niche, and their multipotency. They are also termed as mesenchymal stromal cells, if they fulfill the minimum criteria of adherence, expression of CD105, CD73, and CD90, absence of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR cell surface markers as well as gives rise to descendant lineages including myocytes, adipocytes, chondrocytes, and osteocytes [95, 96] as characterized by International Society of Stromal Therapy (ISCT) in 2005 [97].

Since initial isolation from the bone marrow (BM), MSCs have been found in numerous adult and fetal-derived organs/tissues such as adipose tissue, dental pulp, umbilical cord, and placenta [98]. For translational research, MSCs are categorized into different generations according to their preparation strategy as minimally manipulated, culture-expanded, lineage induced, or genetically modified [99].

Another recommendation of naming is "medicinal signaling cells", as inspired by the fact that these cells possess the properties of homing and secrete bioactive factors that possess the immunomodulatory and regenerative potential. These features give these cells the ability to act as drugs in situ and they have shown site-specific therapeutic outcomes. The infused exogenous MSCs were shown to signal resident stem cells of the patient to repair the damage via their bioactive factors instead of undergoing their differentiation [100]. For both research and clinical purposes, large amounts of MSCs can be isolated from the embryo, fetus as well as adult stem cell sources, including bone marrow, umbilical cord blood, adipose tissue, menstrual blood, Wharton's jelly, amniotic fluid and human deciduous teeth [101, 102].

Our age is the time of MSCs, thanks to the self-renewal and differentiation properties, have already demonstrated a promising role in treating numerous life-threatening diseases as part of the modern research and regenerative medicine [103]. Depending on their origin, stem cells can be divided into three categories of embryonic, fetal and adult stem cells [104]. Indeed, fetal and embryonic stem cells have a higher potential than adult stem cells. The adults stem cells are more used in the research and development because they have the availability and less ethical issues. Bone marrow, fat tissue, human dental pulp and umbilical cord blood are amongs the numerous sources of adult stem cells, which are of crucial importance in regenerative medicine. The technology, moreover, allow these stem cells to be isolated and protected in stem cell banks

under low temperature for many years without losing their potential. Particularly, the umbilical cord blood and bone marrow are the reservoirs of both hematopoietic stem cells and MSCs. It has been known that the MSCs are the most explored and exploited categories of stem cells in treating various disorders [102].

MSCs have the differentiation capacity toward trilineage paraxial mesodermal derivates such as bone, cartilage, and fat. Besides, immunomodulatory properties of MSCs allow for expansion of therapeutic use of them in regenerative medicine in inflammatory diseases, in addition to the allogeneic allogeneic use [105–108]. Interestingly, the first published evidence in the allogeneic MSCs use in inflammatory disease is a pediatric case with acute refractory graft-vs-host-disease (GVHD) in 2004 in which MSCs derived form bone marrow were given. In this study, the patient transplanted MSCs survived in well condition 1 year after MSC treatment, while other 24 patients having severe GVHD showed the median survival rate as 2 months [109]. After this pioneering evidence, MSC immunomodulation has shown to be broad-based, best detailed for CD4 lymphocytes but also for dendritic cells and natural killer cells [110, 111]. As evident by the increasing MSC trials focusing on immune/inflammatory diseases in recent years which are accounted for almost one-third of the trials, the clinical importance of the immunomodulatory properties is compromised [112–114] .General charateristics of the MSCs is their being fibroblast shaped cells which are plastic adherent; fulfilling the criteria of stem cells and MSC as well as stromal cell types [109, 115]. The immunomodulatory activities are suggested to include:

a. inhibition of the proliferation and function of dendritic cells, T and B cells, as well as NK cells.

b. polarization of monocyte to anti-inflammatory macrophages called M2 cells.

c. production of IL-10 and decreased production of TNF-α and IL-12. [116, 117].

In addition, MSCs have powerful antifibrotic effects which may alleviate lung fibrosis. [118, 119].

Lately, there have been increasing reports revealing that the MSCs induce therapeutic characteristics by releasing bioactive substances known as secretomes in a paracrine path [120] .The soluable proteins such as chemokines, growth factors, cytokines, and extracellular vesicles (EVs) including microvesicles and exosomes present in the MSC-secretomes. [121]. MSCs, like all other stem cells, when the culture medium or secretome are injected into the patients, show paracrine signalling to take in these molecules to the cells in vicinity [122]. The exosomes contain bioactive molecules, including microRNAs (miRNA), transfer RNAs (tRNA), long noncoding RNAs (lncRNA), growth factors, proteins, and lipids. Of note, the lipid content of the exosomes is an added value by facilitating the infusion of the exosomes attracted to the plasma membrane of the neighboring cells [123]. Once the molecules content of the secretome is internalized, the neighboring cells modulate various downstream pathways, including immunomodulation, suppression of apoptosis, prevention of fibrosis, and remodelling or repair of the damaged tissues [120, 124].

Several studies with drugs targeting GM-CSF, IL-6, IL-1, IL-2 and TNF-α is already in the pipeline which aims to calm down the inflammatory response in COVID-19 patients. MSCs are well-known for their immuno-modulatory properties including the anti-inflammatory cytokines/chemokines secretion, anti-apoptotic effect and their reparative ability for the damaged epithelial cells. Their inherent nature to migrate towards injured lungs and secretion of paracrine factors which protects and repair alveolar cells; make MSCs a potential therapeutic option for COVID-19 treatment. Recently, MSCs have been widely studied from basic research

to clinical trials particularly for immune-mediated inflammatory diseases such as systemic lupus erythematous (SLE) and GVHD [125–127].

6. The mesenchymal stem cell treatment in COVID-19: what to prove

The therapy using MSCs usually covers the processes of isolation, culture, subculture, proliferation, and differentiation of exogenously obtained stem cells, which are then transplanted into patients for immune regulation and microenvironment repair. The therapy success determinants are the safety and efficacy for any treatment. Hence the safety and effectiveness of MSCs are important as shown in a number of clinical trials besides fundamental studies.

MSCs have been widely used in the treatment of inflammatory diseases, such as in graft vs. host disease [128] and lupus erythematosus [129]. Some studies have shown that MSCs have definite efficacy in improvement in cardiovascular, kidney, liver, and other diseases. [130, 131].

MSCs are able to regulate the immune response by controlling the function and proliferation of various immune cells. They alsocan inhibit monocyte differentiation into dendritic cells (DCs) which results in upregulation of regulatory cytokines and downregulation of inflammatory cytokines [132]. It was suggested that systemic administration of MSC resulted in reduction of H5N1 influenza virus-induced mortality in older patients with severe pulmonary illness [133]. Also, in patients with H7N9 induced ARDS, a significant improvement in survival rate was observed [134]. So far, MSC transplantation in human subjects with diverse disease conditions has not showed any severe adverse events [135]. Therefore, it is plausible that MSC-therapy can be used to treat COVID-19 patients.

MSCs are evaluated as one of the most promising candidates for SARS-CoV-2 infection treatment. Since the key target for the treatment of SARS-CoV-2 infection resides in the cytokine storm management in lungs, MSCs are well-suited considering their main mechanism of action is through their immunomodulatory and anti-inflammatory properties [129].

MSCs have immunomodulatory effects and they:

1. prevent uncontrolled cytokine or inflammatory factors production,

2. inhibit excessive immune responses, and.

3. reduce immune damage to tissues and organs.

Having the immunemodulatory properties, MSCs not only take part in suppressing immune injury, but also replace and repair damaged tissue and inhibit lung fibrosis. Treating COVID-19 with MSCs has presented considerably good results [136]. Stem cell therapy can suppress the storm of cytokine release, promote endogenous repair by improving the microenvironment, slow the progression of acute lung inflammation down and relieve the symptoms of respiratory distress [137]. The reports suggested that the potentially COVID-19 can be successfully treated with MSCs therapy by the MSC regulation mechanism of the immune system. Studies revealed that when the MSCs are exposed to an inflammatory microenvironment, they can regulate immune cells and inflammatory factors, such as cytokines, leading the alterations in the specific or nonspecific immune responses in vivo. The said modulation is shown to be related to exosomes or the cytokines secreted by MSCs, such as transforming growth factor (TGF)-b, prostaglandin (PG)E-2, and interleukin (IL)-10 [138, 139].

The regulation of the T and B lymphocytes' functions is of special interest as it has been done in several ways. One of these is the T cell proliferation, which is controlled by inflammatory stimulation. A study on cell cycle analysis revealed that T cell subsets can be blocked at the G0/G1 phase. Another way of modulation is that the MSCs can control T cell function via cytokines, by releasing TGF-β, inhibiting the immune activity of Th17 cells, inducing their altering to form T regulatory cell Treg cells, or secreting hepatocyte growth factor to regulate the Th17/Treg cell balance [140]. The modulation of the B cells' proliferation, differentiation, and antibody secretion by the MSCs is also important, since MSCs can affect the G0/G1 phase transition of B cells and regulate the antibody secretion ability of B cells through various transcription pathways [141]. MSCs help to regulatory B cells to multiply; these B cells express IL-10. MSCs activate T cells to release interferons, as well. Suppression of activated B cells regulates the immune function of B cells, and MSCs can also affect innate immune cells, including macrophages and dendritic cells, to realize immune regulation. Under inflammatory conditions, MSCs regulate macrophage function, as well [142]. Once the proinflammatory macrophages (M1) secrete the inflammatory agents, activated MSCs can up-regulate the cyclooxygenase (COX)-2 signal and increase PGE2 secretion. This thereby promotes the transformation of macrophages from activated proinflammatory type to selectively activated anti-inflammatory type (M2).

The MSCs releasing the anti-inflammatory factor TSG-6 and the CD44 macrophages act collectively to destroy the interaction between CD44 and toll-like receptor-2, inhibit the nuclear factor-jB signal downstream, and reduce the inflammatory response [143]. On the other hand, the MSCs can secrete HGF under endotoxin stimulation to induce differentiation into regulatory dendritic cells and alleviate acute lung injury [144].

As explored by research, COVID-19 patients' blood have large numbers of inflammatory factors including interferon-c, interferon-inducible protein-10, and monocyte chemoattractantprotein-1. Additionally, when the patients staying in ICU is compared with the patients in the inpatient clinics, the concentration of granulocyte colony-stimulating factor (G-CSF), MCP-1, tumor necrosis factor (TNF)-a, and other inflammatory factors were shown to be dramaticaly higher in the ICU patients, hence there is a positive correlation between the severity of the cytokine storm and the clinical manifestations of COVID-19. [145]. As discussed previously (see section 2.2.2) COVID-19 have a variety of clinical manifestations changing from a mild disease to a severe disease. This change in severity results both from complications of the viral infection and the cytokine storm. The cytokine storm damaging effects are well-known. Cytokine storm in patients with severe COVID-19 can lead to the release of nitricoxide, which affects the normal systolic and diastolic function of blood vessels, thereby causing hypotension and multi-organ hypoxia. [146]. Severe patients have IL-6 levels ten-times higher than those in non-severe patients. In addition, the IL-6 levesl are closely related to the serum SARS-CoV-2 virus load and vital signs of patients. Some study reports have now shown that tozumab (anti-IL-6 receptor) use can prevent worsening of the disease [147]. The MSCs of umblical cord origin, can also inhibit monocyte activation and IL-6 production to inhibit the development of cytokine storm, these result in the improved patient's prognosis. It has been reported that the microenvironment having high IL-6 levels, lead the MSCs to produce cytokines and exosomes enriched with mirR-455-3p, thus calming cytokine storm down and treating acute inflammatory injury. However, the effect of MSCs on cytokine storm in patients with COVID-19 still needs further confirmation [148].

MSCs may suppress ARDS exacerbation and pulmonary fibrosis. Studies have revealed that, once infused or transplanted intravenously, MSCs can reside in the lungs and help improving the microenvironment of the lungs, protecting alveolar epithelial cells, promoting neovascularization, and preventing pulmonary fibrosis

[149, 150]. So it seems that one of the most important outcome of the MSC treatment is its reparative action. The reperative function of the MSCs is managed over a variety of the cytokines, particularly keratinocyte growth factor (KGF) [151]. KGF functions through promoting alveolar fluid clearance and alleviating the acute lung injury induced by endotoxin by up-regulating ACE-2 [152]. Another up-regulation managed by KGF is that the activity of sodium potassium ATP enzyme in alveolar cells, resulting in the improvement in alveolar fluid transport, and this play a therapeutic role in ARDS and lung injury [153].

MSCs may have bacteriostatic role. There was a controversy in whether the virus could cause MSCs to lose their function when the MSCs are invaded by bacteria. Although conducted in limited number of patient size, the clinical trial reported from Beijing, showed that the COVID-19 virus could not infect umbilical cord MSCs that were infused intravenously [136]. MSCs can exert their anti-COVID-19 virus effect through direct and indirect mechanisms, according to the recent research. Direct function of the MSCs can be lined up as the direct anti-viral effect by secreting antibacterial peptides and proteins, indoleamine 2,3-dioxygenase, IL-17, and other molecules. MSCs can activate a large number of anti-virus genes independent of interferon, such as the IFITM gene, which can encode protein structures that prevent viruses from invading cells [154]. When it comes to the indirect function of the MSCs combating against COVID-19, they also exhibit an indirect antiviral effect through regulating the coordination of pro-inflammatory and anti-inflammatory actors of the patient's immune system and inducing the macrophages' functions. [155–157].

The in vitro sepsis model, ARDS model, and alveolar epithelial fibrosis model use in the research activities demonstrated the immunoregulation and antibacterial and antiviral values of MSCs [156, 157]. Studies show that MSCs secrete at least four AMPs including, antibacterial peptide LL-37, human defensin 2, hepcidin, and lipocalin-2. The function of these AMPs includes killing cells, inhibiting the synthesis of essential proteins, DNA, and RNA of infected cells, interacting with certain targets in infected cells, and playing an active regulatory role in the infection and inflammatory progress of COVID-19 patients. [158].

The therapeutic properties of the MSCs against SARS-CoV-2 infection include:

1. Apoptosis induction via activated T-cells alleviating excessive immune responses.

2. Regeneration and maintenance of the homeostasis in specific lung injuries.

3. Release of cytokines to inhibit neutrophil intravasation and enhance macrophage differentiation which helps attenuate inflammation and also promotes the release of extracellular vesicles which deliver microRNA, mRNA proteins and metabolites into host cells post lung injury which promotes repair regeneration and lung function restoration. Therefore MSCs should be considered as a potential treatment for critically ill patients with SARS-CoV-2 infection [159, 160].

6.1 MSC clinical studies

It has been observed that most of the clinical trials for COVID-19 treatment have used allogeneic stem cell source. The curative effect of MSCs in the treatment of COVID-19 has been shown by the two recent clinical trials. In one of them, human umbilical cord derived MSCs were used in three consecutive intravenous infusions administered to patients with COVID-19; it was reported from this trial that subject demonstrated the neutrophil levels decreased significantly, lymphocytes increased, $CD4^+$ T and $CD8^+$ T cells returned to normal level, and vital signs were improved, after the second intravenous infusion [161]. The other trial recruited

seven patients with COVID-19 (two mild cases, four severe cases, and one critical case) to receive one intravenous MSC transplantation each. According to the published results, The patient's regulatory dendritic cell population increased, the level of the pro-inflammatory factor TNFa decreased, and the level of antiinflammatory factor IL-10 increased, after 2–4 days after MSC transplantation [136]. This was a pilot study Clinical grade MSCs were injected intravenously (1×10^6 cells/kg body weight) and the patients were followed-up for 14 days. From clinical point of view, a significant reduction in clinical symptoms and pneumonia infiltration was observed in chest CT of critically ill COVID-19 patient within 2–4 days of MSC-therapy. An increase in peripheral lymphocyte levels, decrease in C-reactive protein (CRP), drastic disappearance of activated cytokine-secreting immune cells ($CXCR3^+CD4^+$T-cells, $CXCR3^+CD^8$ + T-cells and $CXCR^3$ + NK-cells) and restoration of regulatory DC cell population to normal levels was observed after day 6 of MSC transplantation. From cytokines point of view, the level of anti-inflammatory cytokine IL-10 was increased and the levels of serum pro-inflammatory cytokine TNF-α was significantly decreased. These were considered as the indicators of the efficient regulation of cytokine storm in COVID-19 patients on MSC transplantation. On the other hand, the absence of ACE-2 receptor and TMPRSS2 on the transfused MSCs affirmed that they cannot get infected with SARS-Cov-2, suggesting the beneficial effects of the MSC-therapy in COVID-19 infection. The authors suggested that this clinical trial showed that transplantation of MSCs can improve the prognosis of patients with COVID-19 [145]. In a case report of one critically all COVI-19 case who is 65-year-old woman with underlying with type-II diabetes and hypertension, it was reported that after receiving MSC-based treatments her health improved and she left the ICU. The authors of this case report proposed that the possible effects of hUCMSCs might be anti-inflammation and tissue repair to COVID-19 patient. They also suggested that MSCs could down regulate proinflammatory cytokines and chemokines and increase IL-10 and VEGF which could promote the lung repair [161]. The patient didn't respond to any anti-viral drug and the disease progressed to multiple organ injury. During this critical stage when the patient is ventilated, hUC-MSC was infused in 3 consecutive administrations in 50 × 106 cells/dose. After second MSC administration, ventilator was removed as the vital signs had improved with gradual decrease in serum albumin and CRP levels. CT images showed no infiltration patches of pneumonia by the end of MSC infusions. These results suggest that hUC-MSC can be beneficial for patient who showed resistantance to anti-viral drugs. The therapeutic potential of MSCs in viral infections and immunomodulation capabilities to alleviate the cytokine storm, are being tested in clinical studies that have been initiated to further evaluate their efficiency for COVID-19 treatment.

The evidence pf the published results of the clinical trials in which the MSC transplantation is used for curative purposes, shows the beneficial effect of MSCs on the treatment of severe patients. However, more clinical data are still needed to confirm its effectiveness [162].

Several anti-viral drugs such as remdesivir, favipiravir, ribavirin functioning as RNA dependent RNA polymerase inhibitors, lopinavir, ritonavir which are protease inhibitors and drugs suc as hydroxychloroquine targeting endocytic pathway are being evaluated for COVID-19 but standard therapeutics yet not available. To fight against the cytokine storm, immune-therapy targeting TNFα, IL-1, IL-2, and IL-6 and are evaluated. One of the promising immune-modulators is the MSCs administered as add-on therapy can surmount the severity of COVID-19 infections. Recent studies have shown that MSC-therapy significantly dampens the cytokine storm in critically ill COVID-19 patients [163].

The published results of MSC add-on therapy for ARDS, with focused clinical outcome measures' analysis on safety, efficacy, and related immunologic and

pulmonary responses [164]. The clinical studies have demonstrated that MSC therapy is safe and has the potential to mitigate inflammatory and physiologic damage for a variety of conditions involving the central nervous, [165] cardiac, [166] renal, [167] gastrointestinal, [168] and respiratory [169, 170] systems. The data in the literature suggests similar results for MSC therapy for treating ARDS in COVID-19.

As expected, safety is the most important matter for all new therapies, especially in patients at high risk for death from the condition being treated and was carefully evaluated for MSC-treated patients in the clinical trials published. According to the literature review, out of the 200 ARDS patients were treated with intravenously or intratracheally administered MSCs or placebo, 30patients died in the active treatment group. None of these 30 deaths were found to be related to MSC therapy. Also, no other SAEs attributed to the MSC therapy. Some transient adverse effects reported, but all of them resolved on its own in short term. This safety profile is consistent with the experience of other human clinical trials involving MSC therapy [165, 171].

The clinical trials of cell-based therapy using MSCs and their safety has been reported in several clinical trials related to GVHD and SLE [127, 172–174]. The approach of MSC transplantation has been used to treat H7N9-induced ARDS patients and the outcome showed significant reduction in mortality rates [134]. Similarly, the study of MSC-based treatment for SARS-CoV-2 suggested that MSCs lack SARS-CoV-2 infection-vital receptors (ACE2- and TMPRSS2-); so MSCs are SARS-CoV-2 infection-free. Also, the these cells' infusion in SARSCoV- 2-infected patients improved the outcomes because of their extraordinary immunosuppressant potential [136].

The potential efficacy of MSC therapy for ARDS in COVID- 19-infected patients is reported from a phase 1 trial. There were 9 patients enrolled. In-hospital mortality was reported as 33.3% (3/9), including two with septic shock and one with ventilator-induced severe pneumomediastinum and subcutaneous emphysema. No serious prespecified cell infusion-associated or treatment-related adverse events was identified in any patient. The circulating inflammatory (CD14CD33/CD11b+CD16+/CD16+MPO+/CD11b+MPO+/CD14CD33+) and MSC markers (CD26+CD45-/CD29+CD45-/CD34+CD45-/CD44+CD45-/CD73+CD45–/CD90+CD45-/CD105+CD45-/CD26+CD45-) were reported as progressively reduced and the immune cell markers such as Helper-T-cell/Cytotoxity-T-cell/Regulatory-T-cell were notably increased after cell infusion. As a result, this phase I clinical trial showed that a single-dose intravenous infusion of hUC-MSCs was safe with favourable outcome in nine ARDS patients [175]. According to the available evidence, SARS-CoV-2 affects not only the lung, but also the heart and kidney with reported cardiomyopathy and kidney injury [171, 176]. It has been reported that the improved resolution of multiple organ failure or increased organ failure-free days with MSC treatment, which further supports their consideration for clinical use.

The safety and efficacy profile of MSCs is well-constituted based on the results from several completed clinical studies conducted on the therapeutic potential of these therapies in lung diseases such as ARDS [134, 177] as well as broncho-pulmonary dysplasia cardiovascular diseases), diabetes [178, 179] and also spine injuries [180]. Although it has been still in experimental phase, the stem cell types investigated for possible cure of SARS-CoV-2 infections include human induced pluripotent stem cells. Recently, it has been reported that when iPSCs were exposed to SARS-CoV-2, it was presented a deleterious effect on the cells in vitro where the pluripotency of iPSCs was lost leading to fibroblast-like phenotype [181, 182]. Therefore, evidence-based selection of stem cell type for the treatment of COVID-19 is critical for safety and efficacy.

Wraping up, it seems the MSC-therapy, when applied as add-on treatment, suppresses the over activated immune system through its immuno-modulatory properties and promotes the tissue repair of alveolar cells in lung microenvironment

of SARS-CoV-2 infected patients. Clearly, the data of the recent studies are encouraging, however they have major limitations such as the small-sized patient recruitment. Hence, the need for larger randomized control trials to establish the effectiveness and safety of MSC-therapy in SARS-Cov-2 infection is obvious.

The immense knowledge available with reference to the mechanism of action of MSCs and their effective potencies at a specific disease stage makes MSCs as an promising and effective therapeutic candidate.

6.2 Mesenchymal stem cell treatment action of mechanism

It has been demonstrated that MSCs have broad immunomodulatory, anti-inflammatory capacity [183, 184], as well as regenerative properties [185]. MSCs can induce the repair of damaged tissue, and eventually prevent long-term lung damage resulting from COVID- 19. The stabilization of the endothelial fluid leakage and maintenance of the alveolar-capillary barrier function are also characteristics demonstrated by MSCs; obviously, these features are irrevocable to decrease lung permeability and attenuating the development of interstitial lung oedema [186]. These are the main grounds for the MSC based cellular therapy as potentially effective treatment for COVID-19 infection.

Severe cases of COVID-19 infection is characteristic with high levels of cytokines in the plasma, particularly IL-6 which is a biomarker of inflammation and immune response. From this perspective, clinical trials using the medications such as Sarilumab and Tocilizumab, the antibodies anti-IL6 receptors, has been testing such therapeutic strategy in hospitalized COVID-19 infected patients.

Azithromycin is an antibiotic with immunomodulatory effects and invasion inhibitory activity. That is why this drug has been also administrated for the therapy of chronic inflammatory conditions, such as bronchiolitis and rosacea. Although the exact mechanisms of this anti-inflammatory effect are still not fully known, some studies presented a reduction of IL-6 levels after azithromycin treatment [187, 188]. What is more, another study has demonstrated that azithromycin increases rhinovirus-induced interferons and interferon-stimulated mRNA and protein expression as well as decreases rhinovirus replication and release, resulting in induced anti-viral responses in epithelial cells of the human brochiols [189].

After administered systemically, the majority of MSCs reside in the vascular bed of lungs through the interactions with the capillary endothelial cells. When labelled MSCs are traced, it was seen that most are cleared within 24–48 h, and there can be persistence in injured or inflamed lungs for a longer period [190]. It has been suggested that the apoptosis and subsequent efferocytosis and phagocytosis by resident inflammatory and immune cells could be amongst the clearance process [191]. MSCs can secrete various soluble mediators including anti-inflammatory cytokines [192],antimicrobial peptides [193], angiogenic growth factors, as well as extracellular vesicles [194] in their vicinity.

There are evidence for cell–cell transmission of mitochondria from MSCs to respiratory epithelial and immune cells [195]. This reveals the release of anti-inflammatory mediators is specific for the inflammatory lung environment and is mediated through differential activation of damage- and pathogen-associated molecular pathogen receptors expressed on MSC surfaces [196, 197]. Amongst these receptors, Toll-like receptors are crucial; since these are activated by viral RNA in COVID-19 and viral unmethylated CpG-DNA (e.g. TLR9). This leads to modulate the pathways of cell signalling resulting in MSC activation [198]. MSCs derived angiopoietin-1 and keratinocyte growth factor (KGF) contribute to the reparation or restoration of alveolar–capillary barriers disrupted as part of ARDS pathogenesis [199]. On the other hand, the specific inhibitory microRNAs in extracellular vesicles

are also described as mediating the protective effects of MSCs in pre-clinical models of infectious or non-infectious acute lung injuries [200].

6.3 Developing the stem cells as advanced medical products for COVID-19

Currently, there are 82 clinical trials investigating the therapeutic potential of mesenchymal stem cells in COVID-19 patients that are registered on clinicaltrials.gov website; out of all these, 70 trials have (83%) the MSCs as therapeutic agent being tested. The allogeneic bone-marrow or umbilical cord-derived MSCs transplanted intravenously on three different occasions is involved in 21 studies (63%). Most of these trials are either recruiting patients or have not yet started the enrolment. MSCs have been investigated and reported in ARDS both in pre-clinical [201] and clinical settings [127]. Now that, a number of promising trials are currently underway, which could revolutionize the regenerative or MSC-based cellular treatment prospects for severe COVID- 19 patients.

Regardless of how urgent the development of MSC-based therapies for COVID-19 is, it is critically important that the manufacturing of MSCs is in compliance with good manufacturing practices (GMP) and follows strict regulations prior to being approved for the use in humans.

The current findings clearly show that there is a huge unmet need for globally coordinated approach to support to conduct multicentre clinical trials aiming to demonstrate safety and effectiveness of various types of stem cells to treat health complications of novel virus. Also, there is a need in biomedical research and development to establish the most effective stem cell types that are ideally suited for the treatment of the complications.

The development of the stem cell advanced medicinal products will also require: (a) GMP compliant technologies to enable massive stem cell production, and (b) testing platforms that mimic human pathophysiology as much as possible, such as 3D bio-printed organoids, organon- chip, to allow targeted screening and rapid testing of stem cells safety and efficacy. EVs appears as an attractive alternative to cell–based therapy, recently. EVs have several advantages compared to the whole cell therapy including lower risk of oncogenic effects, lower susceptibility to harm by hostile disease tissues and for longer-term storage. The long-term storage is fundamental to make the treatment accessible globally and it surrounds the requirement to have expensive GMP cell manufacturing facilities. The production of EVs must follow the same strict guidelines that apply to stem cells and any EV-based therapy needs to be approved by the health authorities after being tested in clinical trials to demonstrate and confirm the safety and efficacy.

6.4 Stem cells route of delivery

In most clinical trials investigating the MSC treatments of SARS-CoV-2 infection so far, MSCs are delivered via the intravenous route by infusion. The direct target of the intravenous route is not the lungs, that is why the inhalation route delivering the cells directly to lungs could be theoretically more effective. However, the inhalation route has the risk of not able to manage the uniform delivery of cells to lungs [202]. The evidence is being more and more visible to suggest that the curative potential of MSCs is attributed mostly to their secreted EVs via paracrine effects [203].

As evident from several clinically available inhaled medications for chronic lung disease, the inhalation route of delivering therapeutics to the lungs is a more direct route with lower the number of adverse effects, compared to the intravenous route. However, it must be appropriately managed for inhaled administration of a treatment in COVID-19 patients in the hospital setting. Many studies have showed the

feasibility of delivering stem cells via spray for direct pulmonary delivery with high viability [204]. Inhalation route of stem cell administration is an opportunity for efficient delivery of stem cells directly to the lungs, yet it needs further research and proof of concept.

7. Conclusion

Once the globe has suddenly got into the pandemic of COVID-19, all the scientific community has been making every effort to understand the etiology, pathophysiology, societal and clinical aspects of the SARS-CoV-2 viral infection all over the world. As of time this chapter is compiled, there are several vaccines developed in several countries. However, despite all the efforts, there is yet no specific and validated treatment for the infection. Instead, the medicinal products already available are being used in all clinical presentations, including antivirals, antibiotics, antimallarians, ans the agents aiming to take the disease under control. Here, taking the available published evidence in place, we elaborated the structure and pathophysiological aspects which are treatment targets to fight against the pandemic of our age. In this context the mesenchymal stem cells apear as advanced medicinal product of the cellular treatment option. Having the available knowledge refering the mechanism of action of MSCs and their safe and effective potencies at a specific disease stage makes MSCs as an ideal therapeutic candidate. Although still the data to be obtained from future the large scale randomised controlled clinical trials conduct remains an under-explored research area in the field, we suggest that under the light of the available evidence today, MSCs can be used as add-on therapy with promising effectiveness and safety to control, and even treat the COVID-19 infection with regenerative, anti-inflammatory, anti-fibrotic, immunomodulatory and reparative characteristics.

Conflict of interest

The authors declare that they have no conflict of interest.

Abbreviations

ACE2	angiotensin-converting enzyme 2
ARDS	acute respiratory distress syndrome
CoV	Corona viruses
COVID-19	Coronavirus Disease 2019
CP	convalescent plasma
CRP	C-reactive protein
CRS	cytokine release syndrome
CT	Chest computerized tomography
HCQ	Hydroxychloroquine
HIV	human immunodeficient virus
Ig	Immunoglobulin
IL	Interleukin
MCP-1	monocyte chemoattractant protein-1
MERS-CoV	middle East respiratory syndrome-coronavirus
MIP-lα	macrophage inflammatory protein-1 alpha
MOD	multiorgan dysfunction
TNF-α	tumor necrosis factor alpha

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