Cell Therapy-based SARS-CoV 2-2019 Managements: A Literature Review

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In early December 2019, an outbreak of coronavirus disease 2019 (COVID-19) in Wuhan City, Hubei Province, China, affirmed to be the result of a novel coronavirus (later named Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)). Coronavirus disease-19, a kind of viral pneumonia, is caused by SARS-CoV2. This virus infects angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) positive cells and causes influenza like symptoms ranging from mild disease to severe type with multi-organ involvement. In patients with more sever conditions, dysregulation of immune system, due to either virus activity or immune-based issues, leads to cytokine storm and unwanted inflammatory changes further followed by tissue damage. COVID-19 has spread rapidly by human-to-human transmission, caused an outbreak worldwide with considerable morbidity rates and mortality, which forced WHO to officially classified it as pandemic and a global concern on March 11. Without any signs of amelioration and with confirmed cases that are expected to increase further as they are updated daily as of May 8, the outbreak has stressed global socioeconomic and health systems and posed governments to clinical management challenges. Finding appropriate clinical strategy to control and even prevent is nowadays top priority issues globally. Recent studies and investigation considerably improve our understanding of disease pattern of distribution, pathology and immune-related changes in both mild and sever cases. Thus, many promising therapeutic approaches for clinical intervention and treatment of the disease are now under further investigations and their safety and efficiency are yet to be proved in clinical trials. One of these therapeutic approaches is cell therapy-based interventions. Mesenchymal stem cells (MSCs) have commonly applied clinical trials and possess two positive roles, immunomodulatory effect and differentiation ability. MSCs immunomodulatory effects which mediated by anti-inflammatory cytokine release prevent or reduce the overactivation of the immune system and cytokine storm. So, MSCs therapy and other immune-based cell therapies can be promising in severe COVID-19 management and treatment. In this review the aim is investigation the impact of these kind of interventions in treatment of COVID-19 patients.

Keywords: SARS-CoV2; MSCs Therapy; Stem Cell Products; Immunomodulatory Effect; Immune Cell Therapy

Introduction

In the end of 2019, several cases of an acute pneumonia-like respiratory disease of unknown origin characterized by series of symptoms including fever, cough and shortness of breath were reported in Wuhan, Hubei province of China (1). The etiological agent was characterized as a novel coronavirus due to Whole-genome analysis studies results (2), shown to be transmitted from human-to-human by either droplets or direct contact (3). International Committee on Taxonomy of Viruses (ICTV) officially named the virus SARS-CoV-2 (4). This respiratory disease, which meanwhile was termed as coronavirus disease 2019 (COVID19), has spread rapidly by human-to-human transmission (2, 3), caused an outbreak worldwide with considerable morbidity rates and mortality, which forced WHO to officially classified it as pandemic on March 11.

Phylogeny and Virology

Coronaviruses (CoVs) are large enveloped viruses with positive-sense and have single-stranded RNA genomes (5, 6) and are further divided into four genera: alpha, beta, delta and gamma subfamilies (7-9).

Diseases caused by human coronaviruses include wide range of clinical conditions, from mild seasonal cold-like symptoms (10-13), to sever respiratory failure and life-threatening conditions

with pandemic potential, which can lead to death especially in older individuals and patients with other co-morbidities. As zoonotic pathogens, coronaviruses originate from animals and transmit to other mammalian and avian hosts. Therefore, responsible viruses for past outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are also classified as zoonotic pathogens. MERS and SARS original natural reservoir are bats and the responsible reservoir hosts for MERS and SARS transmission to humans were dromedary camels (14-16) and civet cats (17, 18), respectively.

Newly emerged SARS-CoV-2 is the seventh coronavirus that is capable of causing infection in humans and is classified in the Coronaviridae family and lineage B of betacoronavirus genus (19, 20).

Genetic analyses implicate bats as a natural reservoir of coronaviruses and other animals as potential intermediate hosts in the emergence of SARS-CoV-2 (21). Most probable candidate for intermediate host maybe is pangolins of an animal market due to a 99% match between genetic sequences of the extracted virus from both infected human and animals (1, 22). Genomic analysis suggested 79.6% similarity between SARS-CoV and SARS-CoV-2 (4, 23, 24).

SARS-CoV-2/host interaction and pathogenesis mechanism

Initiation of a viral infection and its tendency to special individual cell types (tissue tropism) are highly depend on the receptor recognition. Envelope-embedded surface-located spike glycoprotein (S) reported as responsible agent for entry process in CoVs (8) and form homotrimers protruding from the viral surface (25). Nevertheless, different members of coronavirus family interact with distinct host surface molecules (26, 27) (e.g. MERS-CoV interacts with human dipeptidyl peptidase 4 (hDPP4 or hCD26)(28) and SARS-CoV interacts with ACE2(29)). Novel coronavirus interacts with ACE2 as its receptor, similar to SARS-CoV (2, 30).

ACE2 is a homologue of angiotensin converting enzyme-1 (ACE1), which converts angiotensin I to angiotensin II. It was reported that ACE2 through degrading the pro-fibrotic peptide angiotensin (Ang) II protects against non-viral lung injury (31). Injecting SARS-CoV spike proteins into mice leads to ACE2 expression levels reduction (maybe because virus entry occur mainly via endocytosis, thus results in ACE2 loss (32)) and cause exacerbated lung injury (32). Thus, ACE2 acts both as the entry receptor of novel coronavirus and to protect respiratory tissues (specially lungs) from tissue injury. ACE2 is primarily expressed in type II pneumocytes and this can explain why novel coronavirus has respiratory system tropism (2). In another study, it was found that two clusters of nasal epithelial cells (goblet and ciliated cells) shows the highest expression of virus entry factors (fully discussed later in next paragraphs) relative to other investigated cells in the respiratory tree (33). However, recent studies revealed that ACE2 expression also occur in other extra-pulmonary tissues such as heart, kidney, blood vessels and intestine suggesting that SARS-CoV-2 can also infect these organs (34, 35), which can partially explain multi-organ failure observed in patients (36, 37). ACE2 is not expressed differently between male and female or young and aged individuals in any tissues (35), indicating that SARS-CoV-2 may infect persons with different age, sex and even race equally (35). However, due to testis involvement in infected male individuals, men are more susceptible to further tissue involvement effects of SARS-CoV-2 infection than women. It is also shown that (38), COVID-19 fatality rate for female patients is lesser (1.7%) relative to male individuals (2.8%). There are two suggested reasons for explaining this difference: 1)ACE2 is located on the X chromosome ,therefore there may be alleles conferring resistance to the disease and 2) difference in male and female sex hormones immunomodulatory functions, which can influence on immune system and disease severity and outcome (39). Wild range of animal species (except rat and mouse) express ACE2 and as a result, likelihood of inter-species transmission exists which is a feature of zoonotic pathogens like CoVs (8, 40).

Usually, spike proteins undergo proteolysis due to host proteases activities and cleave into S1, that is responsible for receptor recognition, and S2 that is responsible for membrane fusion process either after endocytosis or before it(5). Alongside with receptor recognition, proteolysis of S proteins is essential for CoVs successful infection. The serine protease TMPRSS2 has been shown to be responsible for spike proteolysis in SARS-CoV-2, therefore a TMPRSS2 inhibitor may be a promising therapeutic by blocking virus entry process (30). Cathepsin B/L activity may also be able to substitute for TMPRSS2(30). S1 subunit can be further divided into an N-terminal domain (NTD) and a C-terminal domain (CTD), both of which can function as a receptor-binding entity in different CoVs (in some literatures NTD and CTD are called S^A and S^B respectively). S1 CTD is responsible for receptor recognition in both SARS-CoV and SARS-CoV-2 as shown in multiple studies (8, 26, 41).

Although the two receptor binding domains (RBD) are structurally unique and distinct, the study has shown that majority of SARS-CoV-2 S1 CTD binding sites in hACE2 overlap with the SARS-CoV binding sites. It seems that these CoVs have evolved and become capable to recognize a "hotspot" region in hACE2 for receptor binding (41). further Crystallographic assessments have indicated that although the

hACE2 binding site for SARS-CoV-2 is almost similar to that of SARS-CoV, atomic details reveal more interactions at the binding interface in SARS-CoV-2-CTD due to presence of key residue substitutions that lead to stronger interaction and consequently, higher receptor binding affinity in comparison to SARS-RBD (4-fold stronger affinity) (41, 42). Therefore, it can be partially explained why SARS-CoV-2 has higher transmission efficiency and disease severity in humans in comparison with SARS-CoV (41, 42). Another possible factor making SARS-CoV-2 more contagious among humans with altered pathogenicity, is postulated to be a furin cleavage site at the S1/S2 boundary (42), making SARS-CoV-2 different from other CoVs. The third suggested reason for highly contagious nature of SARS-CoV-2, seems to be the virus spreading via infected individuals with no symptoms (43).

In addition, Although SARS-CoV and SARS-CoV-2 are similar in more than 70% sequence identity in the S protein (2), and both interaction with hACE2 via the S1-CTD; recent studies have shown the antigenicity of SARS-CoV and SARS-CoV-2 CTDs are different from each other (41). While spike proteins are surface-exposed and regulate virus entry into host cells, it has become the main target of therapeutic and vaccine designs (e.g. neutralizing Ab). Despite of striking structural similarity and sequence conservation among the SARS-CoV-2 S and SARS-CoV S proteins, there have been contradictory evidences about efficiency of SARS-CoV polyclonal and monoclonal neutralizing antibodies and vaccines targeting spike proteins in SARS-CoV-2 entry inhibition (41, 42, 44). Therefore, further investigations are needed for efficiency assessments and evaluations. Another novel strategy to block virus entry is focused on ACE2 function as virus main host receptor. In this effort, Monteil *et al.*, utilized a clinical-grade human recombinant soluble ACE2 (hrsACE2) to avoid SARS-CoV-2 infection (45). Nevertheless, because of ACE2 crucial role in natural renin-angiotensin system (RAS) physiologic system (46), precautionary actions should be taken in ACE2 manipulation protocols. Therefore, further studies are needed to illuminate the effect of hrsACE2 at both infection process and RAS system.

After SARS-CoV-2 enters ACE2-positive cells, the 30 kb genome, encoding proteases and an RNA-dependent RNA polymerase (RdRp) as well as several structural proteins, undergoes replication and translation into structural viral proteins including a helical capsid formed by nucleocapsid (N) proteins which binds to the RNA genome and membrane/envelope proteins like envelope (E) proteins, matrix glycoprotein (M) and trimeric spike (S) proteins (2). Next, new virions after assembly would release (2). There is no approved anti-viral treatment/prophylaxis for SARS-CoV-2 infection as of May 8 to the best of our knowledge, therefore, it is of utmost importance to define and evaluate potential roles for novel recommended antiviral agents and specific immunomodulators in order to control the rising number of infected individuals and deaths.

Current promising antiviral agents include inhibitors endosome maturation (hydroxychloroquine), inhibitors of viral RNA-dependent RNA polymerase (remdesivir, favipiravir) and inhibitors of viral protein synthesis and maturation (lopinavir/ritonavir); however, their exact efficiency and clinical benefits in disease management are yet to be proved (47). It is noteworthy to mention that temporality of treatment should be considered during evaluations, because some therapeutic strategies may have greater efficiency at different disease stages.

Immune system role in COVID-19

Against viral infections innate and adoptive immunity countermeasures are of utmost importance for pathogen control and clearance. In order for SARS-CoV-2 to overcome these obstacles and cause infection and progression of the disease, virus needs to interfere with complex networks of immune system. Understanding pathogen-host immune interactions and dysfunctional immune response effects on disease initiation and progression may lead to treatment and management of the disease, including identification of new therapeutic strategies with clinical benefits. Due to SARS-CoV-2 high genetic similarity with SARS-CoV, insights learned from other two coronavirus outbreaks may help us to predict and simulate who SARS-CoV-2 may react and interfere with host immune system (40, 48). COVID-19 shows a median incubation period of approximately 4–5 days before symptom onset. 97.5% of symptomatic patients show symptoms within 11.5 days (36, 49, 50). Majority of patients (about 80%) are asymptomatic or manifest some mild symptoms (fever, cough, *etc*) while remainder encounter with sever or critical stage of the disease. ARSD and multi-organ failure are common complications in sever stages of COVID-19, which later may result in death (36, 49). In addition, increased total neutrophils, reduced total lymphocytes, increased serum IL-6 and increased c-reactive protein are observed in sever, not mild, patients (2). It is speculated that as the disease progress the lymphocytes count in peripheral blood gradually decrease due to either direct infection with virus and bone marrow suppression or lymphocyte infiltration in afflicted tissues such as lower respiratory tract to fight against virus (48, 51). Patients who have recovered or are convalescent show normal amount of CD4+T cells, CD8+T cells, B cells and NK cells and the markers of exhaustion on cytotoxic lymphocyte (52, 53). Inflammatory factors, specially IL-6, are shown to be significantly increased, which also contributed to the

aggravation of the disease around 7–14 days after onset (2). Besides, high-levels of pro-inflammatory cytokines including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα, the so called "cytokine storm", were observed in the COVID-19 severe cases as well (37). It seems cytokine storm can initiate viral sepsis and inflammatory-induced lung injury, multiple-organ failure and potentially death. Based on a hypothesis (48), if the patient is old or have co-morbidities which influence and hinder efficient immune responses, the virus can not be controlled effectively in acute phase of the disease, thus disease can further progress into more sever and critical stage which is characterized by further decrease in B cells and T cells and by continued increase of inflammatory cytokines and coagulant parameters (such as D-Dimer) (48). These clinical features suggest that disease severity in patients is because of both the viral infection and the host response. Thus, although SARS-CoV-2 infection can activate innate and adaptive immune responses, dysregulated inflammatory innate responses and impaired adaptive immune responses result in aggressive tissue damage, both locally and systemically.

The first step in infection is virus entry. Virus entry to host cells results in loss of ACE2 and because of ACE2 protection against acute lung injury and its participation in RAS system, a reduction in ACE2 function due to viral infection could interfere RAS and as a result increased inflammation and vascular permeability in the airways occur (51).

Type I IFN is one of the most important parts of innate immune system in mediating effective response against viral pathogen replication. Invasion of the virus is recognized by TLR3, TLR7 and TLR9 during viral genome replication process. This recognition finally leads to expression of IFN I and other pro-inflammatory cytokines as first line defense against viral infection at the entry site (54). In the case of SARS-CoV-2 it is speculated that the response to viral infection by type I IFN is suppressed which results in freely replication of the virus (40). Thus, during SARS-CoV-2 infection and replicative cycle, virus-infected cells and tissues undergo a highly inflammatory form of programmed cell death called pyroptosis (55, 56). By releasing IL-1β, which is also elevated in SARS-CoV-2 infection, pyroptosis mediate recruitments of monocytes and macrophages to injured area and then, as major sources of pro-inflammatory cytokines and chemokines, monocytes and macrophages secrete IL-6, IFN γ, MCP1 and IP-10 into blood of afflicted individuals (37, 57). These cytokines are indicative of a T helper 1 dominant response which is responsible for an adaptive immunity to viral infections (58). In most individuals, in a healthy immune response recruited virus-specific T cells alongside with other immune cells clear the infection in the lung, Neutralizing antibodies in these individuals can block viral infection, the immune response finally leads to patient recovery (51). However, in some patients, a dysfunctional immune response occurs, most likely because of virus-induced interferon antagonism and dysregulated interferon system (40, 59-61), which results in a cytokine storm that attract monocytes, macrophages and T cells to the site of infection (62, 63).

As a result, further infiltration of immune cells in the respiratory tract leads to overproduction of mentioned cytokines, thus, tissue damage is inevitable. By circulation to other organs via blood, cytokine storm can cause multi-organ damage (37, 64). Putting together, the way virus interacts with host immune system and the immune response to the virus, play an important role in disease pathology, severity and clinical outcome. Now this can be explained why individuals with underlying diseases such as diabetes, hypertension, and cardiovascular disease are more susceptible to COVID-19 and, on the other hand, why there are too few reported severe cases in young children. These facts strongly indicate that immune response is a critical factor and of utmost importance for disease management and treatment and controlling unwanted inflammatory response is as important as targeting the virus. Thus, several promising immunomodulation and immunosuppressive strategies, in order to reduce virus/immune system-induced tissue damage in COVID-19, are under evaluation and investigation at various phases of development(65). Some of these suggested therapies includes: IL-6 receptor or IL-6 antagonists (e.g. tocilizumab, siltuximab, sarilumab) (47), factors that target (GM-CSF) (gimsilumab, lenzilumab, namilumab) (51), Passive immunization with convalescent plasma and active immunization strategies involving live-attenuated virus and chimeric virus (51). Other novel strategies are immunomodulation via cell therapy (*e.g.* MSC therapy) and immune cell therapy that are discussed in next section.

Potential mechanisms MSCs in treatment of severe patients COVID-19

Stem cells are unspecialized cells with the self-renewal and differentiation potential; these features could able them to maintain their stemness properties or differentiate into specialized cells. Their Safety and efficacy have been obviously documented in several clinical trials. MSCs as a type of stem cell obtained from different sources including Bone marrow, peripheral Blood, dental pulp, adipose tissue, umbilical cord. MSCs

Table.1. Clinical trials study for treatment of SARS-CoV 2-2019 patient by transplantation of MSCs; Data obtained from https://clinicaltrials.gov/

Clinical trial no	Location	Title of clinical study
NCT04273646	Tongji Hospital, Wuhan, China	Clinical Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19
NCT04288102	Multiple sites in China	Treatment with Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)
NCT04346368	Guangzhou Institute of Respiratory Health, Guangdong, China	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)
NCT04371601	Fuzhou General Hospital, Fujian, China	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019
NCT04345601	Houston Methodist Hospital, Texas, United States	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)
NCT04339660	Puren Hospital, Wuhan, China	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia
NCT04361942	Hospital Universitario Rio Hortega, Spain	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV)
NCT04331613	Beijing Hospital, China	Safety and Efficacy of CAStem for Severe COVID-19 Associated With/ Without ARDS
NCT04252118	Beijing Hospital, China	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19
NCT04313322	Stem Cells Arabia, Amman, Jordan	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells
NCT04349631	Hope Biosciences Stem Cell Research Foundation, Texas, United States	A Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Autologous Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19
NCT04348435	Hope Biosciences Stem Cell Research Foundation, Texas, United States	A Randomized, Double-Blind, Placebo- Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogeneic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19
NCT04333368	Hôpital Pitié-Salpêtrière & Hôpital Européen Georges Pompidou - APHP, Paris, France	Cell Therapy Using Umbilical Cord derived Mesenchymal Stromal Cells in SARS-CoV-2-related ARDS
NCT04366063	Royan Institute, Tehran, Iran	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome
Data obtained from https://www.irct.ir/		
IRCT20200413047063N1	Masih Daneshvari Hospital & Shariati Hospital, Tehran, Iran	Placental Mesenchymal Stem cells for treatment of ARDS in Coronavirus infection, Phase 1 and 2 Clinical Trials

COVID-19: coronavirus disease 2019, CAStem: Human embryonic stem cell-derived M cells, ARDS: Acute Respiratory Distress Syndrome, SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2

have been commonly applied in pre-clinical and clinical cell-based therapies (66-68), due to their less ethical concerns, easily isolation method (easily accessible), and abundant sources (69-71).

MSCs mainly have two positive roles, one of them is the immunomodulatory effect and another one is differentiation ability. A variety of cytokines were secreted by MSCs via paracrine secretion or interactions with immune cells (i.e. T cells, B cells, dendritic cells, macrophages and natural killer cells); this can lead to MSCs immunomodulatory effect. These cells are able to regulate the inflammatory reaction and promote repair and regeneration (72). MSCs can upregulate the expression of MHC-I, MHC-II, CD112, CD155, CD54, CD106, CD200, PDL-1, and Jagged-1 but not upregulate of costimulatory molecules like CD80 and CD86 (73, 74). The MSCs therapeutic effects on several inflammatory and autoimmune diseases have been widely considered (75). The interactions between MSCs and immune cells have been displayed to contribute to remodeling and healing of tissue (76-78).

It has reported that the majority of MSCs are entrapped in the lung following their systemic administration through an intravenous infusion. Tracking investigations using labeled MSCs show that the most are cleared in 24-48 hours while there can be longer perseverance in injured or inflamed lungs (79). The lodged MSCs in the lungs are capable to release soluble mediators such as anti-inflammatory cytokines,(80) antimicrobial peptides and proteins (AMPs),(81) angiogenic growth factors, and extracellular vesicles (EVs) (82). Pattern of released anti-inflammatory

Table.2. Clinical trials study for treatment of SARS-CoV 2-2019 patients by immune cell therapy; Data obtained from https://clinicaltrials.gov/

Clinical trial no	Location	Title of clinical trial
NCT04280224	The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China	NK Cells Treatment for COVID-19
NCT04324996	Chongqing Public Health Medical Center, Chongqing, China	A Phase I/II Study of Universal Off-theshelf NKG2D-ACE2 CAR-NK Cells for Therapy of COVID-19
NCT04351659	National University Hospital & Singapore General Hospital, Singapore	Novel Adoptive Cellular Therapy With SARS-CoV-2 Specific T Cells in Patients With Severe COVID-19

NK: Natural killer, COVID-19: coronavirus disease 2019, NKG2D: Natural killer group 2 member D, ACE2: angiotensin-converting enzyme 2, CAR: chimeric antigen receptor, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

mediators is unique for encountered the inflammatory lung environment and is mediated via different activation of injury and pathogen-associated molecular pathogen receptors expressed on cell surfaces of MSC (83) .Toll-like receptors (TLRs) are activated by viral RNA (TLR3) (like in COVID-19) and viral unmethylated CpG-DNA (TLR9), lead to downstream cell signaling pathways resulting in MSC activation (84).

MScs secrete paracrine soluble factors including angiopoietin-1 (Ang-1) and keratinocyte growth factor (KGF) that can restorate alveolar-capillary barriers disrupted as part of ARDS pathogenesis (85). Ultimately, MSCs therapy can improve the pulmonary microenvironment, protect the alveolar epithelial cells, inhibit the pulmonary fibrosis and recover the lung function (72).

In a clinical trial study, Zhao *et al.*, have evaluated the effect of intravenous MSC transplantation for COVID-19 infected patients. The results showed that the peripheral lymphocytes were elevated, the C-reactive protein reduced, and the overactivated Cytokine secretion by immune cells CXCR3 NK cells, CXCR3 CD8 T cells, and CXCR3 CD4 T cells cleared in one week. Additionally, regulatory DC cell population (i.e. CD14, CD11c, and CD11bmid) significantly increased. Since the level of TNF-α was dramatically decreased, IL-10 increased in treatment group compared to placebo. The findings showed that the MSCs immunosuppressive activities are started by cell-to-cell contact and the immuno-regulatory molecules release. Thus, MSCs can prohibit the proliferation and function of T cells, natural killer cells, B cells, and dendritic cells, and increase the proliferation of regulatory T cells. Chest CT imaging has indicated reduced pneumonia infiltration and the ground-glass opacity. but other organs were not examined or it was not reported (71). In addition, the gene expression profile revealed MSCs were $ACE2^-$ and $TMPRSS2^-$ which demonstrated that MSCs are safe from COVID-19 infection. Therefore, the safety and efficacy of the intravenous transplantation of MSCs for the treatment of patients with COVID-19 pneumonia is confirmed (86).

In another clinical study, the effect of systemic administration of allogenic human umbilical cord mesenchymal stem cells (hUCMSCs) has evaluated in patients with COVID-19; in this study, antibiotics and thymosin α1 were also given to patients. It has reported that the neutrophil count and white blood cell count as well as lymphocyte count reached to the normal level. Additionally, the CD4+T cell-, CD3+T cell- and CD8+T cell counts were significantly improved to normal levels. The outcome revealed that hUCMSCs or combined with thymosin α1 could significantly decrease the inflammation response and facilitate the recovery of antiviral immune cells and tissues (87).

Currently, our research group are conducting a clinical trial study (IRCT20200413047063N1) with the aim to investigation the safety and efficacy of cell therapy for treatment of ARDS in coronavirus infection using placental MSCs. The study is ongoing at Masih Daneshvari Hospital and Shariati Hospital in Iran. In this research three doses of MSCs are infused in patients aged 18 to 65 years with a definitive diagnosis of COVID-19. Main outcome variables are including safety, blood oxygen saturation, reduced intensity of pneumonia and improvement of ARDS.

Several clinical trials for treatment of COVID-19 patients are being conducted by transplantation of different types of MSCs such as Wharton's Jelly-MSCs, Human Dental Pulp MSCs, Umbilical Cord derived Mesenchymal Stromal Cells (Table 1). The beneficial effect of MSCs mainly is due to the immunomodulation and regenerative potential of these cells. MSCs able to significantly decrease the pathological changes of lung and prohibit dysregulated cell-mediated immune inflammatory response. Therefore, MSC therapy in the treatment of COVID-19 patients is taken into consideration.

MSC products in treatment of severe COVID-19 patients

Besides therapeutic effects of MSC, they can also secret multiple critical factors such as extensive spectrum of cytokines, growth factors, chemokines and extracellular vesicles (EVs) (88, 89). MSCs act via a paracrine mechanism; MSC-secretome interact with the target cells and modulate cellular responses. Indeed, secretome could activate endogenous stem cells and progenitor cells, suppress apoptosis, adjust the inflammatory response, cause the extracellular matrix remodeling and angiogenesis, mediate the chemoattraction and reduce fibrosis (90, 91).

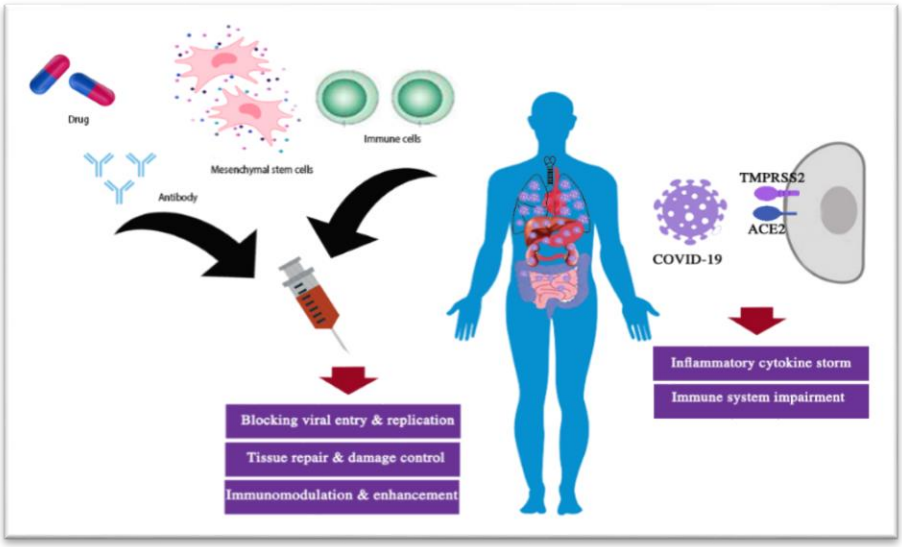

Figure 1. Schematic of ACE2 and TMPRSS2 positive cells infected by COVID-19. In this condition, inflammatory cytokine storm occurs and immune system is impaired. Thus, administration of mesenchymal stem cells, immune cell, drug and antibody could be effective in treatment of severe patients. Mechanisms including blocking entry viral replication, regulating inflammatory response and enhancing immune system can lead to promoting tissue repair and regeneration. (Figure is made by PhotoshopCs6)

MSC-secretome appears as a novel cell-free therapeutic option for the treatment of severe and mild lung diseases, because of its immunomodulatory, anti-inflammatory, pro-angiogenic, anti-protease and regenerative properties equivalent parental MSCs (92). In the Acute respiratory distress syndrome (ARDS), the efficacy of MSC-secretome in vivo and ex vivo studies are approved (93). Following intravenous injection, the secretome persisted extremely stable in the blood flow and distributed over the lungs. Here, secretome spread into the tissues which can modulate immune system, eradicate inflammation, restore the capillary barrier function and improve bacterial clearance (94, 95). Remarkably, the use of cell-free therapies such as MSCs secretome have several advantages compared to MSCs. Secretome is commonly considered safer than cells: it is not associated with the risk of endogenous tumor formation, as it is unable to self-replicate, it has low immunogenicity and after intravenously injection it leads to less emboli formation (96-98). It has reported by van Asten's research group that the fibroblast growth factor (FGF), isolated in adipose derived- MSCs (Ad-MSC) secretome inhibited viral replication (97, 99).

The application of MSC-secretome in therapy also involves technological advantages as follow: they can be manipulated and stored simpler than cells, it costs lesser, and it results in a ready to use product appropriate for emergency treatment (99). The possibility of pharmaceuticalizing MSC-secretome into permanent powder products via freeze-drying technology would make it as more available treatment approach (100-102). Moreover, experimental studies have showed that MSCs or their extracellular vesicles (MSCs-EVs) notably decrease lung inflammation and pathological impairment caused by different types of lung damage. As well as, bacterial killing, macrophage phagocytosis, and the results are improved (103).

There are ongoing clinical trials using MSC-secretome in treatment of COVID-19 patients. However, the final results have not yet been reported.

Immune cell therapy in treatment of severe COVID-19 patients

A successful immune response against viral infections relies on cytotoxic T cells activation that can clear infection via killing of virus-infected cells (103). Promoting the counts and function of T cells in patients with COVID-19 is important for effective recovery. It has reported that the 82.1% of COVID-19 patients showed low circulating lymphocyte counts (104). T cells are critical for mediating viral clearance; CD8+ cytotoxic T cells (CTCs) secrete molecules such as perforin, IFN-γ, and granzymes to eliminate viruses from the host (105). Simultaneously, CD4+ helper T cells (Th) can help CTCs and B cells by intensifying their ability to clear pathogen (106).

Huang *et al.*, have demonstrated that the levels of TNF-α, G-CSF, IP-10, IL-2, IL-7, IL-10, MCP-1 and MIP-1A were remarkably higher in COVID-19 patients (37). TNF-α, as a pro-inflammatory cytokine, can raise T cell apoptosis by interacting with its receptor (37).

T cell exhaustion is a type of T cell dysfunction that occurs during cancer and many chronic infections. Persistent stimulation via the virus can lead to T cell exhaustion, cytokine production, loss of T cell capability and reduced functions (104, 107). It causes weak effector function, sustained expression of inhibitory receptors, and a transcriptional state different from that of memory T cells or functional effector (108) . In conclusion, T cells reduces and exhausts in COVID-19 patients. Cytokines including IL-10, IL-6 and TNF-α might lead to reducing T cell (104).

Helper T (Th) cells and suppressor T cells in COVID-19 patients were reduced. In addition, the percentage of memory Th cells decreased and naive Th cells increased in severe cases. Moro-Garcia *et al.*, showed that severe patients with COVID-19 had low level of CD3+ cells and CD4+ cells. The differentiation of naive CD4+ T cells into effector and memory subsets is the critical factor for T-cell–mediated immunity (109). Therefore, the balance between the Naive and memory CD4+ T cells population is important for preserving an effective immune response. In severe cases, the higher level of naive CD4+ T-cell, the lower level of memory cells, and the higher ratio of naive-to-memory CD4+ T-cell immune system was observed (110). In addition, the lower levels of regulatory T cells was detected, which has an important role in maintaining immune homeostasis and self-tolerance immunity(111, 112).

Natural killer (NK) cells are innate lymphoid cells (ILC) that may act as helpful effectors against danger infection. NK cell-based immunotherapies are important for treating diseases due to their recognition and killing characteristic; they have a role of the early defense against infectious pathogens and MHC class-I-negative and are able to lyse target via the release of granzymes/ perforin and using antibody-dependent cell-mediated cytotoxicity (112-114) .

The new coronavirus might mostly act on lymphocytes, particularly T lymphocytes. Cytotoxic lymphocytes including cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells are essential for the control of viral infection, and the functional exhaustion of cytotoxic lymphocytes is associated with disease progression (115).

A researcher group showed that the total count of NK and CD8+ T cells were significantly decreased in patients with SARS-CoV-2 infection. The function of NK and CD8+ T cells was exhausted with the increases expression of NKG2A in COVID-19 cases. Results showed that the functional exhaustion of cytotoxic lymphocytes is dependent on SRAS-CoV-2 infection (115).

As regard to clinical results, the function of T-cells are exhausted with imbalanced activity in sever COVID-19 patients. Additionally, a reduction in the percentage of NK cells has observed in severe COVID-19 cases. Taken together, transplanting T-cell and NK may be helpful in the treatment of COVID-19. In this regard, there are ongoing clinical trials that are aimed at evaluating the safety and efficiency of the transplantation of the special T-cell and NK for patients infected with SARS-CoV-2 (Table 2).

Conclusion

In severe COVID-19 patients, inflammatory cytokine storm occurs and immune system is impaired. Cell therapy as a promising treatment approach is taken into consideration. MSCs transplantation could be efficient because of the immunomodulatory effects which inhibit the over activation of the immune system and cytokine storm. Therefore, the transplantation of MSCs and their secretome improve COVID-19 patient's symptoms due to anti-inflammatory effect and promoting tissue repair and regeneration. The T-cells are exhausted with imbalanced activity in sever COVID-19 patients, and also T-cells and NK cell population are reduced. Thus, immune cell-based therapies with the aim of enhancement of immune system could be an efficient therapeutic option. Currently, several clinical trials study are conducting using cell transplantation for COVID-19 management.

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