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Review Article

Immunomodulatory effect of Mesenchymal stem cells: A blessing to combat cytokine storm appeared during COVID-19 infection

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ABSTRACT

Whilst the manufacture of a safe and potent vaccine for SARS-CoV-2 is the ultimate goal of the COVID-19 response, research is also in progress to develop novel treatments that could facilitate infected patients in the meantime. Casualty in COVID-19 patients are connected with onset of acute respiratory distress syndrome (ARDS) due to its cytokine storm phenomenon resulting in abandoned systemic inflammatory response from the release of pro-inflammatory chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL-10) and cytokines (TNF-α, TGF-β, IFN-α, IFNγ, IL-1β, IL-6, IL-12, IL-8, IL-33). This implies immune system is not capable to turn itself off once it has generated enough of a defense against the virus. An extended cytokine storm will finally shut down breathing completely, which may lead to death. In the context of COVID19, there is a likelihood possibility of treatment of patients by transplanting Mesenchymal Stem Cells (MSCs). MSCs are known to have an immune-regulatory role and MSCs have used in patients that have been affected by the cytokine storm may fine balance the immune system in order to stop the overreaction, without switching it completely off, so that the immune system can carry on to fight the infection. In this review, we have considered the research studies which have used MSCs for the treatment of COVID-19. The cohort study is needed to approve MSCs as therapy, although many clinical trials have been registered to apply MSCs as therapy for severely affected COVID-19 patients.

1. Introduction

Recently in December 2019, a novel and highly pathogenic coronavirus named SARS-CoV-2 causing COVID-19 have been emerged in Hubei Province of the People's Republic of China. This has been recognized as a zoonotic virus which is similar to severe acute respiratory syndrome coronavirus (SARS-CoV) [Liu et al., 2020].[1] The newly emerged SARS-CoV-2 falls under the B lineage of the beta-coronaviruses and closely related to SARS-CoV virus. Therefore, World Health Organization (WHO)[2] has named this novel virus as SARS-CoV-2 and the assigned disease as COVID-19 [Ray et al., 2020].[3] At very initial stage in China, 41 patients were diagnosed with novel coronavirus SARS-CoV-2 ranges from 8^{th} December 2019 to 2nd January 2020. The symptoms of infection included fever in >90% cases, dry cough in 80%, shortness of breath in 20% and respiratory distress in 15% of the total patients [Hui et al., 2020].[4] It was confirmed as global health emergency by the WHO Emergency Committee on 30^{th} January, 2020 based on the growing infectious cases in China and other countries such as USA, Spain, Germany, Italy, UK, France, Turkey, Russia including India [Velavan and Meyer, 2020].[5] Even though taking of painful global restraint and confinement efforts, the prevalence of COVID-19 is increasing with new cases and mortality day-by-day all around the world. Since year's coronaviruses have been commonly found in various animals and humans,

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however SARS-CoV-2 is such a virus that has transmitted from animals to humans and is spreading human to human rapidly. Its symptom are reported mild to severe including dry cough, loss of smell or taste, fatigue, fever and short breathing where some severe cases have been resulted into death of the patient [Ashok Shetty, 2020].[6]

Primarily, the COVID-19 patients have developed symptoms of fever, cough, fatigue, myalgia, shortness of breath and later on developed lymphopenia, pneumonia, dyspnea have taken place which gradually turned out into acute respiratory distress syndrome (ARDS) with multiple organ failure (MOF) [Huang et al., 2020].[7] Recently, a study has reported that the severe patients of COVID-19 have shown elevated level of interleukin (IL) -6 in compare to mild patients; and decreased level of CD4+ T cells, CD8+ T cells and natural killer (NK) cells suggesting an immunosuppression in severely affected patients [Xu et al., 2020].[8] A virus induced cytokine storm with divergent pattern was playing major role in shift of mild to severe COVID-19 patients. Cytokine storm syndrome is a phenomenon where level of the pro-inflammatory cytokines rises after stimulated by microorganisms or drugs which causes from fever, headache, fatigue to diffuse intravascular coagulation, shock, MOF and death [Tanusha et al., 2018].[9] Presently, there is no significant cure available for COVID-19. Hence, lack of effective therapies and insufficient immunological treatments for severely ill COVID-19 patients, stem cell therapy has been recommended. However, because of their multiple modes of action mesenchymal stem cells (MSCs) have been considered as the most promising candidates to deal with diverse symptoms of COVID-19. Although, MSCs have shown favorable outputs in the treatment of ARDS and sepsis disease, their efficacy is still under investigations particularly for human trials [Moll et al., 2020].[10]

MSCs are multipotent cells which can be derived from various parts in the human body including adipose tissue, bone marrow, placenta and umbilical cord tissue. MSCs can be easily harvested, isolated, cultured and used in therapy, from basic research to clinical trials [Shimabukaro-Vornhagen et al., 2018].[11] MSCs play positive role typically in two ways, namely immunomodulatory effects and differentiation abilities. MSCs can secrete many types of cytokines by paracrine secretion or can make direct interactions with immune cells, leading to the immunomodulation. We also know that the immunomodulatory effects of MSCs are triggered further by the activation of toll-like receptors (TLRs) in MSCs, which is trigger by the pathogen-associated molecules such as porins, peptidoglycan, lipopolysaccharides or viral genomes, such as SARS-CoV-2. The immunomodulatory effects of MSCs have capability to defeat the cytokine storm and can reduce morbidity and mortality of the COVID-19 associated diseased [Atluri et al., 2020].[12] MSCs have properties to secrete many macro and micro molecules involved in immunosuppression, immunoregulation and immunomodulation for the tissue repair. Furthermore MSCs growth factors help to generate extracellular matrix, reduces the progression of inflammation and encourages differentiation of in situ progenitor cells to replace damage cells and promote angiogenesis [Vieira Paladino et al., 2019].[13] MSCs secrete substances such as prostaglandin E2 (PGE2) and indoleamine 2,3-dioxygenase (IDO) and inhibit programmed deathligand 1 (PD-L1) to suppress the proliferation of stimulated T cells. Also, they activated regulatory T cells by secreting cytokines such as IL-6, IL-10, and hepatocyte growth factor (HGF) and hinder the development of TH-17 proinflammatory cells [Kim et al., 2018].[14] In this review, we have briefed that MSCs would be better therapeutic treatment to overcome the problem arose due to release of cytokine storm.

2. Human Coronaviruses

Coronaviruses (CoVs), a genus of the Coronaviridae family, is a group of a large positive strand RNA virus. Its genomic RNA strand is 27-32 kb in size, 5' capped and 3' polyadenylated. Their structure resemble to the corona of the sun as they characterized by globular, enveloped particle varying from 80 to 160 nm in width with conspicuous projections up to 20 nm in length on their whole virion surface. These viruses have both medical and veterinary importance as they infect multiple animal species such as mouse, rabbit, dog, cats, horse, porcine, turkey, bovine and others causing cardiovascular, neurological, gastrointestinal and respiratory diseases whereas in humans they are allied with diarrhea, common colds, and possibly multiple sclerosis [Lai et al., 1990].[15]

At very first in 1966, Tyrrell and Bynoe had cultivated human coronaviruses from patients with common cough and cold [Tyrell and Bynoe, 1966].[16] Human coronaviruses such as HCoV-OC43, SARS-CoV, HCoV-229E, and MERS-CoV have been studied well. Where HCoV-OC43 and HCoV-229E were known to cause regular cold, however SARS-CoV and MERS-CoV were more pathogenic causing life-threatening pneumonia [Peiris et al., 2003].[17] Both of the pathogenic coronaviruses were expected to inhabit in animal reservoir but they infected humans through zoonotic transmission responsible of the epidemic [de Groot et al., 2013].[18] Only after epidemic of SARS-CoV in 2003 at China, human coronaviruses were turned out to be more documented [Peiris et al., 2003].[17] In 2012, a new human coronavirus MERS-CoV was originated in Jeddah, Saudi Arabia causing renal failure and acute pneumonia in contaminated patients [de Groot et al., 2013].[18]

Human coronaviruses are separated into four sub-families explicitly alpha (α), beta (β), gamma (γ) and delta (δ) coronaviruses whereas α and β viruses were originated from mammals; and γ and δ viruses come out

from pigs and birds. Among these alpha coronaviruses cause asymptomatic or mild symptomatic infections whereas beta coronaviruses can cause severe disease and mortality. Human coronaviruses are divided into seven sub-types: four common coronaviruses, which cause mild to moderate symptoms of cough and cold, are 229E-CoV, NL63-CoV, OC43-CoV and HKU1-CoV; while other three hCoV which cause acute respiratory syndrome in humans are SARS-CoV, MERS-CoV and SARS-CoV-2 [Weiss and Navas-Martin, 2005].[19] Majorly, there be four structural genes encoding the a small membrane protein (SM), membrane glycoprotein (M), nucleocapsid protein (N), and the spike protein (S) with additional membrane glycoprotein (HE) present in the beta-coronaviruses such as HOC43-CoV and HKU1-CoV [Astuti et al., 2020]. On complete phylogenetic analysis of the SARS-CoV-2, it was found that the viral genome is consisting of 29,903 nucleotides, where it was having 89.1% similar genome to a class of Severe Acute Respiratory Syndrome (SARS) coronavirus (Figure 1). Moreover, this novel virus belonged to the genus β-coronavirus with subgenus Sarbecovirus and subfamily orthocoronavirinae [Ray et al., 2020].[3]

The globally clinicians and scientists have learned much of the pathogenesis of the disease COVID-19. The study reveals that not all people who have exposed to the SARS-CoV-2 have got infected and not all patients infected with SARS-CoV-2 have developed the symptoms of it. As per the resent studies, the pattern of infection of SARS-CoV-2 has divided into three stages: (i) an asymptomatic stage where during incubation period virus can be detectable or not; (ii) a symptomatic stage where virus is present with mild effects and (iii) a severe respiratory symptomatic stage where viral load is high with other complications [Bai et al., 2020].[20] In general, COVID-19 is a curable disease however patients with comorbid conditions had much higher fatality rates. Those with no comorbidites had a fatality rate of 0.9%. Critical cases had a fatality rate of 49%, no deaths occurred among those with mild or even severe symptoms [Jason et al., 2020]. The reasons have been suspected the severe onset of the disease which extremely damage alveolar cells in lungs causing progressive respiratory failure. However in primary phase none of the pathology has been reported due to lack of access of autopsy and biopsy of the infected patients [Huang et al., 2020].[7] Afterward pathological investigations have been initiated to study the characteristics of the syndrome from the postmortem biopsies of dead SARS-CoV-2 patients [Xu et al., 2020].[8]

3. Pathogenesis of SARS-CoV-2

On 17 May 2023 the reported confirmed cases of COVID-19 were 765,903,278 including 6,927,378 deaths, reported by WHO. The leading reason for high mortality rate in COVID-19 was occurrence of ADRS in approximately 50% of the patients [Mehta et al., 2020].[21] It has been reported that the S protein of the SARS-CoV-2 present on the surface recognizes the angiotensin I converting enzyme 2- receptor (ACE2) protein of human cells. After exposure, they bind to the ACE2 protein and enter to the cell by infecting it. On completion of incubation period, the SARS-CoV-2 evokes protective immune response with mild symptoms. The successful eradication of the virus depends on the infected person's physical condition and HLA haplotype. During this, if health of the infected person is normal then it could get enter to the severe stage where strong damage of lung tissues would be induced by elevated inflammatory response [Shi et al., 2020].[22]

Regrettably, most of the human endothelial cells and smooth muscle cells such as Angiotensin II receptor type 2 (AT2) of the lungs, heart, liver, digestive organs and kidneys. Hence, the coronavirus can widely spread once it gets able to enter the blood circulatory system. Therefore, this is the reason that COVID-19 patients also develop the complications of acute myocardial injury, acute kidney injury, arrhythmia, shock and ultimately multiple organ dysfunctions which lead them to the death. Along with receptor ACE2, the study from Germany has revealed that the cellular transmembrane protease serine 2 (TMPRSS2) is essential for priming of SARS-CoV-2 to enter and spread into the host cells [Leng et al., 2020; Huang et al., 2020].[7,23] The influx of neutrophils and macrophages on viral infection increases the release of chemokines and pro-inflammatory cytokines in lungs causing cytokine storm; where B cells are involved in production of antibodies to neutralize viruses. Here, Figure 2 shows the proposed mechanism of action of SARS-CoV-2 coronavirus developing pneumonia by infecting human lungs [Prompetchara et al., 2020].[24]

Secondary factors associated with COVID-19 are haemophagocytic lymphohistiocytosis (sHLH), hyper-inflammatory syndrome and hypercytokinaemia with multiorgan failure [Lima et al., 2020].[25] In adults, sHLH is usually activated by viral infections and happens in 3.7-4.3% of sepsis cases. Basic features of sHLH involve cytopenias, unremitting fever and hyperferritinaemia [Ramos-Casals et al., 2014].[26] Along with sHLH, a similar cytokine profile; characterized by augmented monocyte chemoattractant protein 1, granulocyte colony stimulating factor, interferon-γ inducible protein 10, macrophage inflammatory protein 1-α, tumor necrosis factor-α and interlukin (IL)-2, IL-7 [Huang et al., 2020];[7] also associated with severity of the disease with enhancing the mortality rate. A retrospective study in Wuhan, China 150 confirmed COVID-19 cases has shown the elevated level of IL-6 and ferritin suggested the death rate might be due to hyper-inflammation driven by viral infection [Shi et al., 2020].[22] Many pathologists have observed that severely affected COVID-19 patients were showing an uncontrolled ramping up of the immune response, which

have also observed in sepsis, where there was acute release of cytokines such as TNFα, TNFβ, MCP1, MIP1A, GSCF, IP10, IL-7, IL-6, IL-2 and chemokines such as CXCL9, CXCL-10, CXCL8, CCL5, CCL3, CCL2 combined known as cytokine storm (Figure 3).

This elevated cytokine storm induces ADRS, pulmonary oedema, defective of air-exchange, acute myocardial infarction and secondary infection leading to the fatality [Jeyaraman et al., 2020].[27] Currently, only supportive therapeutic options are available for the patients with severe pneumonia while for patients with respiratory failure mechanical ventilation support is obligatory. The way out to save severely affected COVID-19 patients may be in inhibition of viral replication, prevention and neutralization of cytokine storm [Mehta et al., 2020].[21]

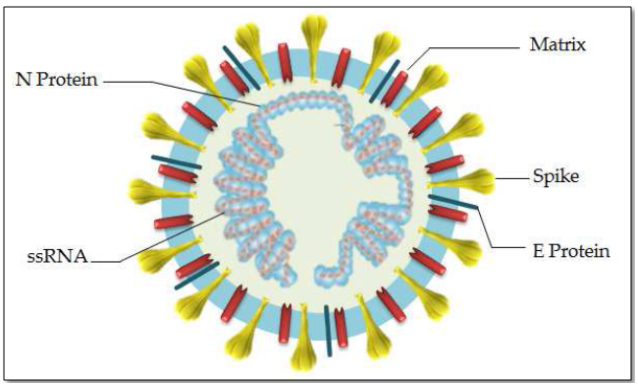

Fig. 1: Structure of Severe Acute Respiratory Syndrome Coronavirus-2 [Ray et al, 2020][3]

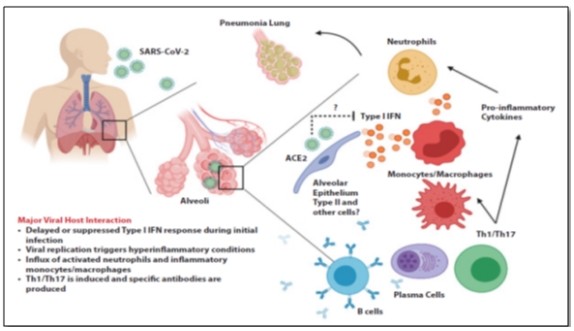

Fig. 2: Proposed host immune responses during SARS-CoV-2 infection [Prompetchara et al, 2020][24]

4. Obtainable Treatments Against COVID-19

After many clinical observations and investigations the medical professionals has able to recognize the pathogenicity of SARS-CoV-2, still there are new emerging challenges of understanding variable strain of SARS-CoV-2 infecting to the others parts of the world. Therefore, there is no concrete treatment existing to cure the COVID-19.

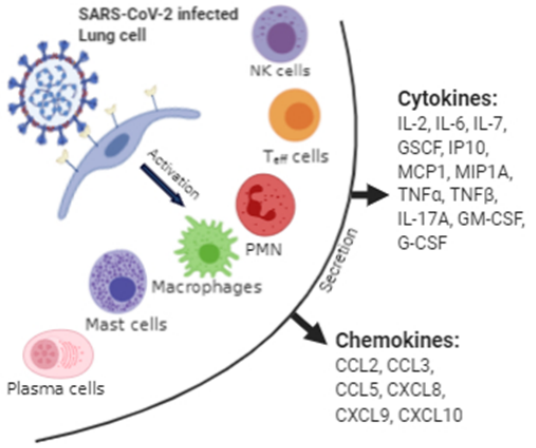

Fig. 3: Release of cytokine storm: The infection of SARS-CoV-2 coronavirus to lung cells activates multiple immune cells which releases numerous cytokines and chemokines which cumulatively known as cytokine storm that leads to hyperinflammation and various health issues.

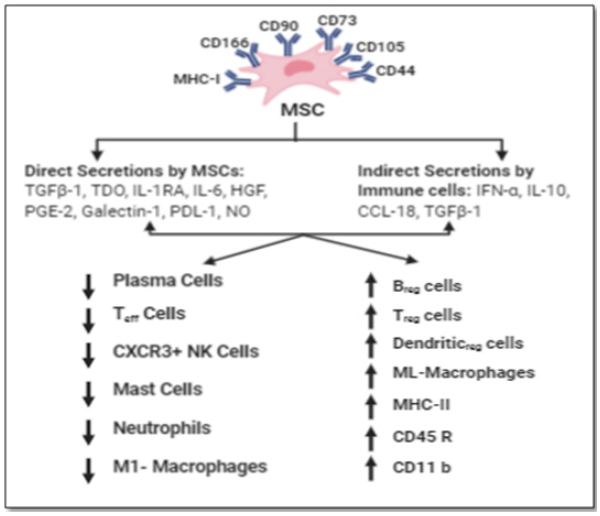

Fig. 4: Regulation of cytokine storm by MSC secretome: MSCs secretes various macro- and micro- molecules which up-regulates and down-regulates the SARS-CoV-2 activated immune cells

The global emergency has left an unfulfilled requirement of a protected and effective treatment majorly for the severe patients of COVID-19 [Jeyaraman et al., 2020].[27] Up till now, multiple treatment strategies have been selected by medical professionals to combat and overcome the symptoms of COVID-19. These include antiviral therapy, hydroxychloroquine and combinations, neutralizing antibodies, passive antibody by convalescent plasma therapy and cellular therapy [Leng et al., 2020].[23]

According to studies, ACE2 positive cells; such as the alveolar type-II cells and capillary endothelium; are highly susceptible to the S protein of the virus, a new therapy

Table 1: List of registered MSCs based clinical trials for treating COVID-19

S.No.	Clinical Trial No.	Cell Source	
1	ChiCTR2000031319	Allogeneic Human Dental Pulp MSC	http://www.chictr.org.cn
2	ChiCTR2000030944	human NK cells and MSCs transplantation	
3	ChiCTR2000030300	human umbilical cord-MSCs (huc-MSCs)	
4	ChiCTR2000030224	MSCs	
5	ChiCTR2000030173	hUC-MSCs	
6	ChiCTR2000031319	Human MSCs	
7	ChiCTR2000030088	Umbilical cord Wharton's Jelly derived-MSC	
8	ChiCTR2000030020	MSCs	
9	ChiCTR2000029816	hUCB-MSCs	
10	ChiCTR2000029580	Ruxolitinib in combination with MSCs	
11	CTR2000030116	hUC-MSCs	
12	ChiCTR2000030484	HU-MSCs and Exosomes	
13	ChiCTR2000030866	hUC-MSCs	
14	ChiCTR2000030835	hUC-MSCs	
15	ChiCTR2000030138	hUC-MSCs	
16	NCT04313322	Wharton's Jelly derived-MSC	https://clinicaltrials.gov
17	NCT04302519	Dental Pulp- MSCs	
18	NCT04288102	MSCs	
19	NCT04273646	UC-MSC	
20	NCT04252118	MSCs	
21	NCT04299152	MSCs	
22	NCT04269525	UC-MSCs	
23	NCT04276987	MSCs-derived exosomes	
24	NCT04313647	MSCs-derived exosomes	

is targeting to develop blocking agents connected with AP2-associated protein kinase 1 (AAK1) that binds to the proteins to inhibit the entry of the SARS-CoV-2 into the host cells [Hoffmann et al., 2020].[28] Studies have also suggested the use of two anti-viral drugs such as Baricitinib to control the SARS-CoV-2 genome replication, as it is a Janus kinase and AAK1 inhibitor [Richardson et al., 2020];[29] and other is Remdesivir, an adenosine analogue which act as viral protein inhibitor. Chloroquine has seen to affect the replication of the viral genome of HCoV-229E by activation of p38 mitogen-activated protein kinase [Wang et al., 2020].[30]

There was an official publication from Chinese government on 11^{th} January, 2020 stating the achievement of the sequencing of the genome of SARS-CoV-2 causing COVID-19 which has triggered the global R&D activity to build up an impactful vaccine against the virus. These currently available therapeutic options are involved in reduction of viral load, other secondary bacterial infections and inflammations. Whereas the hallmark effect of the SARS-CoV-2 is the induction of cytokine storm in the lungs of the COVID-19 patients. Blocking of these cytokines and chemokines may be a key treatment to recover patients from the cytokine storm of COVID-19. Human MSCs have powerful immunomodulatory properties to prevent the cytokine storm [Metcalfe, 2020].[31] MSCs restrain the proliferation of activated T cells by secretion of IDO and PGE2; and also suppress pro-inflammatory Th17 cells. They enhance the increase regulatory T cells by releasing immunosuppressive cytokines [Kim et al., 2018].[14] In consideration of these benefits, several medical location in China have announced the application of human MSCs in severely affected persons with COVID-19 infection. Many trail studies has been already and many are in under investigations. Presently, many clinical trials has been registered on several therapeutic considerations such as effectiveness of remdesivir, arbidol hydrochloride, immunoglobulins combined with hydroxychloroquine, methylprednisolone, ASC09F plus Oseltamivir, interferon atomisation, lopinavir plus ritonavir, ritonavir plus, oseltamivirdarunavir plus and washed microbiota transplantation plus human mesenchymal stem cell treatment [Bari et al., 2020].[32]

5. Application of MSCs in COVID-19

MSCs are self-renewal; multipotent, non-hematopoietic, heterogenic plastic adherent cells which have high

proliferation, multi-lineage differentiation and in vitro expansion capabilities [Chamberlain et al., 2007].[33] They can be majorly retrieved from adipose tissue (AT), placenta, umbilical cord tissue (UCT) and bone-marrow (BM) [Vieira Paladino et al., 2019].[13] Among these UCT is the best source for MSCs as they have numerous numbers of cells, easy to obtain by noninvasive technique, less ethical issue and easy to extract and expand MSCs by in vitro explant culture method [Urvi et al., 2021a].[34] MSCs can be differentiate into mesodermal lineage cells such adipocytes, osteocytes, chondrocytes, muscle cells; also they can transdifferentiate into nerve cells, cardiac cells, etc [Urvi et al., 2021b].[35] Irrespective of the source MSCs commonly express CD90, CD73, CD90 and HLA-ABC; and lack the expression of and HLA-DR and CD19, CD11b or CD14, CD79a and or CD34, CD45, [Thanunchai et al., 2015].[36]

Presently, MSCs have grabbed major attention by clinicians and scientific research communities for basic research and their clinical approach in incurable diseases due to their properties of Immunomodulation, anti-inflammatory and differentiation potentials. The Toll-like receptors (TLR) receptor proteins present in MSCs are activated by pathogen associated molecules such as lipopolysaccharides (LPS) or double/single stranded RNA of virus like SARS-CoV-2; which triggers the immunomodulatory effects of MSCs [Vieira Paladino et al., 2019].[13] By owing to the immense immunomodulatory ability, MSCs have natural immunity to fight against coronavirus such as SARS-CoV-2 by preventing or attenuating the virus induced cytokine storm by secreting anti-inflammatory factors. During stem cell based therapy for COVID-19, a part of the administered MSCs accumulates in the lungs where they progress pulmonary microenvironment, stop pulmonary fibrosis, guard alveolar epithelial cells and improve lung function [Ashok Shetty, 2020].[6] One of the studies has shown that MSCs activated with gamma-Interferon (IFNγ) exert anti-inflammatory effects which may be missing in COVID-19 patients as T cells are not highly activated by SARS-CoV-2 infection. To boost its effect IFNγ-MSCs can be pre-treat with or without TNF or IL-15 [Shi et al., 2020].[22] These cytokine conjugated MSCs could be further effective in repression of agitated immune response and also promote tissue repair in LPS stimulated acute lung damage. Though, the tissue or other cells are virus infected, the viral activated MSCs could remain functional because they release antimicrobial peptides (AMPs) which fight against the virus [Atluri et al., 2020].[12]

Recently, MSCs have been clinically used to treat the viral infection of H5N1 where they have shown the expected and positive recovery results. A case study in China reported that a female patient, with critically ill of acute COVID-19, was treated with three infusions of 5×10^7 hUC-MSCs at the period of three days where needed parameters like T-cell counts of the patient were restored back to usual levels after 21 days which was confirmed with laboratory tests and CT images and also patient displayed not noticeable side effects [Liang et al., 2020].[37] An outstanding study has been carried out in China with collaboration to United States on use of MSCs in severely ill COVID-19 patients, it was approved by the ethical committee of the Beijing YouAn hospital (LL-2020-013-K) [Leng et al., 2020],[23] a total ten patients were taken as subjects, and MSCs were administered intravenously to seven patients and three patients severe as placebo controls. The patients were treated with 1×10^6 MSCs/kilogram body weight although their condition was worsening severely. They were monitored for 14 days of post treatment. The study has proved that majority of the symptoms displayed by the patients prior to infusion fall down within 2 to 4 days subsequent to they received the infusion. The oxygen diffusion, with or without oxygen uptake (around 5 L/minute), rose to $\geq$ 95 % at rest. Their inflammation was assessed within 14 days of the treatment. Additionally, before MSC transplantation the patient's PBMC were releasing higher percentage of CXCR3+ NK cells, CXCR3+CD4+ T cells and CXCR3+CD8+ T cells causing cytokine storm in comparison to the healthy controls. On 6^{th} day of the treatment, the results showed restored normal levels of peripheral lymphocytes and the extra-activated cytokine-secreting immune cells such as CXCR3+ NK cells, CXCR3+ CD8+ T cells and CXCR3+ CD4+ T cells were disappeared. It was also observed regularize level of CD11b+ CD14+ CD11c middle regulatory DC cell populations along with IL-10 and significant decrease in levels of TNF-α in the patients have taken with MSCs treatment in compared to the patients treated with conventional therapy [Leng et al., 2020].[23] The results have proved that MSCs have inhibited the over-activation of the immune system and also improved lung microenvironment leading to the tissue repair which was damaged due to striking of SARS-CoV-2 infection [Leng et al., 2020].[23] Although, there are studies supporting the MSC therapy for treatment of COVID-19 patients, a large cohort study of COVID-19 affected patients with different criteria are need to be done to validate this therapeutic intervention.

Till date, along with many completed clinical studies, more 90 trials have been recorded on https://clinicaltrials.gov reporting encouraging results in treating respiratory disorders with MSCs [Golchin et al., 2021; Sharma et al., 2022].[38–40] It was showed that the infusion of the MSCs was harmless as well as there were no any treatment-related adverse events or infusion-linked events were reported [Wilson et al., 2015].[41] However, many questions are unanswered, like best possible source for MSCs, how many cells need to be used and the dosing strategies ranging from

a single administration to multiple doses. The majority MSC studies in various indications have assessed solo infusions, but it is not clear whether single, high-dose infusion would be better than frequent, lower-dose infusions. Also, the ideal turnaround time for administration is not clear.

6. Mechanism of Action

It has been confirmed from various literatures that MSCs act by a paracrine mechanism. MSCs have ability to secrete multiple biological active molecules such as growth factors, cytokines, chemokines, and micro- and nano-size extracellular vesicles (EVs) which collectively known as MSC-secretome. This secretome released through paracrine secretion otherwise direct communication to immune cells together with dendritic cells, natural killer cells, macrophages and T cells, B cells by ligand-receptor interaction which lead to the immunomodulation [Golchin et al., 2020].[38] In fig.4 a proposed mechanism of regulation of cytokine storm by administered MSCs has been shown. The MSC-secretome activates progenitor cells and endogenous stem cells to encourage tissue repair and regeneration, suppress apoptosis, stimulate remodeling of the extracellular matrix and angiogenesis, regulate inflammatory response, decrease fibrosis, and mediate chemo-attraction along with improvement in cardiovascular, renal, hepatic functions and other multiple disorders [Kim et al., 2020].[14] Therefore, MSC-secretome is considered as powerful therapeutic tool to treat acute as well as chronic lung diseases since it exhibits the immunomodulatory, regenerative, pro-angiogenic and anti-protease and anti-inflammatory, properties of parental MSCs.

In the condition of ARDS, following intravenous injection the secretome remains highly constant in blood stream and distributes in to the lungs where it raises in tissues and provide immune modulation, control inflammation, restoration of capillary barrier function and enhance microbial clearance [Shah et al., 2020].[42] With the properties of immunomodulatory and differentiation capacity, MSCs can be used to fight against COVID-19 by neutralizing the cytokine storm along with rejuvenation of damaged lung tissues [Golchin et al., 2020].[38]

Based on these various studies, MSCs and their secretome have emerged as potential therapies to combat against COVID-19. Various clinical trials have been already done and numerous of clinical examinations have been registered for application of MSCs in COVID-19 depending upon their sources and cellular products (Table.1). Also a formulated freeze-dried MSC-secretome powder, administered through the intravenous injection or inhalation, might be an appropriate approach to treat severely affected patients with COVID-19 [Bari et al., 2020].[32] The ultimate purpose of these clinical trials are to investigate safety and efficacy of MSCs to treat severely affected COVID-19 patients with pneumonia along with advanced ARDS, shock and DIC.

7. Conclusions

The novel coronavirus SARS-CoV-2 causing a rapidly progressing infectious disease such as COVID-19 is becoming a threat day by day not because of pathogenicity of the virus but due to not have of effective treatment for the disease. It has made the worldwide population to be under lockdown just break the chain of infection though this is not the way to stop the virus effect. We must have to find an absolute and effective cure against COVID-19. The critical stage of COVID-19 is to have patient in ICU struggling to breathe and the only option to make them survive is to keep them on ventilator. The actual difficulty for critically sick patients with the COVID-19 is an acute inflammation of the lung tissues, due to emergence of cytokine storm in affected patients' which doesn't allow enough oxygen to enter the blood circulation, finally leading to death in 50% of COVID-19 cases. MSCs having anti-inflammatory and immunomodulatory properties which prevent the over-activation of the immune system which could help to reduce the inflammation caused due to the cytokine storm elicited by the pateint's immune cells in response to SARS-CoV-2 virus infection. MSCs have been proven as an anti-inflammatory therapy and have been shown to alleviate ARDS, even in Wuhan, China, during the first wave of the spread of SARS-CoV-2 in January, 2020. Thus published results suggested that MSCs could be an ideal treatment choice either alone or in combination with other immune modulators for the acute COVID-19 patients, moreover MSCs can diminish the cytokine storm produced by COVID-19 infection. Furthermore, MSCs might be able to recover pulmonary fibrosis along with the lung function. However many concerns related to the relevance of MSCs, including the ideal dose along with optimal timing of MSC delivery, should be further explored.

8. Highlights

1. SARS-CoV-2 infection is initiated by virus binding to ACE2 cell surface receptors, followed by fusion of virus and cell membranes to release the virus genome into the cell.
2. This viral infection within the lungs results in a cytokine storm, thus elevating the level of many pro-inflammatory cytokines. The increased level of these cytokines leads to oedema, dysfunction in exchange of air, and acute respiratory distress, which may eventually cause death.
3. Till date no dedicated therapeutic strategies have been implemented or confirmed to prevent COVID-19.
4. MSCs are multipotential stem cells and have remarkable immunomodulatory capacity, since COVID-19 is noted for cytokine storm and high

inflammation in lungs, MSC seems to be a treatment option.

5. This review "Immunomodulatory effect of Mesenchymal stem cells: A blessing to combat cytokine storm appeared during COVID-19 infection" articles can prove valuable for the future design of more effective MSCs for COVID-19 therapy.

9. Conflicts of Interests

None.

10. Source of Funding

None.

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None.

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