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Therapeutic use of Mesenchymal Stem Cells against SARS-Cov-2: Present and Future prospects

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ABSTRACT

The Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) outbreak, also known as COVID-19, from the seafood market in Wuhan, China, has the world on its knees within a short time, impacting health infrastructure, economy, science, and most importantly human existence. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. Since the first encounter with COVID-19, the medical fraternity has been exploring various ways to counter the disease and related complications. Attempts have also been made to prevent infection by developing vaccines to reduce the severity of the disease and mortality post-infection. However, even as the first peak of the epidemic (also known as the "first wave") has flattened, the second peak (second wave) has been even more detrimental, with a rapid rise leading to an unprecedented burden on healthcare infrastructure and resulting in high mortality. The second wave has been predicted to be triggered by a double mutant strain, which resulted in a higher incidence of pneumonia, faster progression of the disease, increased oxygen requirements, and higher mortality. In contrast to the current treatment options available, which include antivirals, antimalarial, and anti-inflammatory agents, MSC can be proved to be a better treatment modality for COVID-19. In this article, we focus on the role and use of mesenchymal stem cells (MSC) as a potential therapeutic measure to win the battle against the SARS-CoV-2 virus.

Keywords: Mesenchymal stem cells, SARS CoV-2, MSC Therapy, ACE-2

1. INTRODUCTION

After the first outbreak of the atypical virus was detected in China in November 2019, WHO was alerted, and in March 2020, the disease has declared a pandemic. According to official data, as of April 1, 2022, India has the second-highest number of confirmed cases in the world with 43,031,958 reported cases of COVID-19 infection and the third-highest number of COVID-19 deaths at 521,530 deaths.

Further, owing to the respiratory syndrome caused by the virus, the International Committee on Taxonomy of Viruses named the causative agent severe acute respiratory syndrome-2 (SARS-CoV-2) [1]. COVID-19 infections are characterized by a broad spectrum of presentations ranging from asymptomatic infection to symptoms of respiratory distress, including breathlessness, cough, high-grade fever, and headache. The respiratory symptoms typically proceed to viral pneumonia in a segment of patients, with an estimated case fatality rate of 3.4% [2].

In most cases, the mortality is attributed to a phenomenon of immune dysregulation called a cytokine storm, which is an activation cascade of auto amplifying cytokine production due to an unregulated host immune response to different triggers. When associated with COVID-19, this phenomenon has been termed cytokine storm syndrome [3].

A cytokine storm in COVID-19 is supposed to be contributed by interleukin-1β (IL-1β), IL-2, IL-6, IL-10, IL-12, IL-13, tumor necrosis factor-alpha (TNF-α), IFN-α/β, IFN-γ, monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory protein-1A (MIP-1A), and granulocyte-macrophage colony-stimulating factor (GM-CSF) released from the host cells [4]. High mortality is caused by pulmonary hyperinflammation, edema, acute respiratory distress syndrome (ARDS), acute renal injury, acute cardiac injury, and multiple organ failure [4], shown schematically in Figure 1.

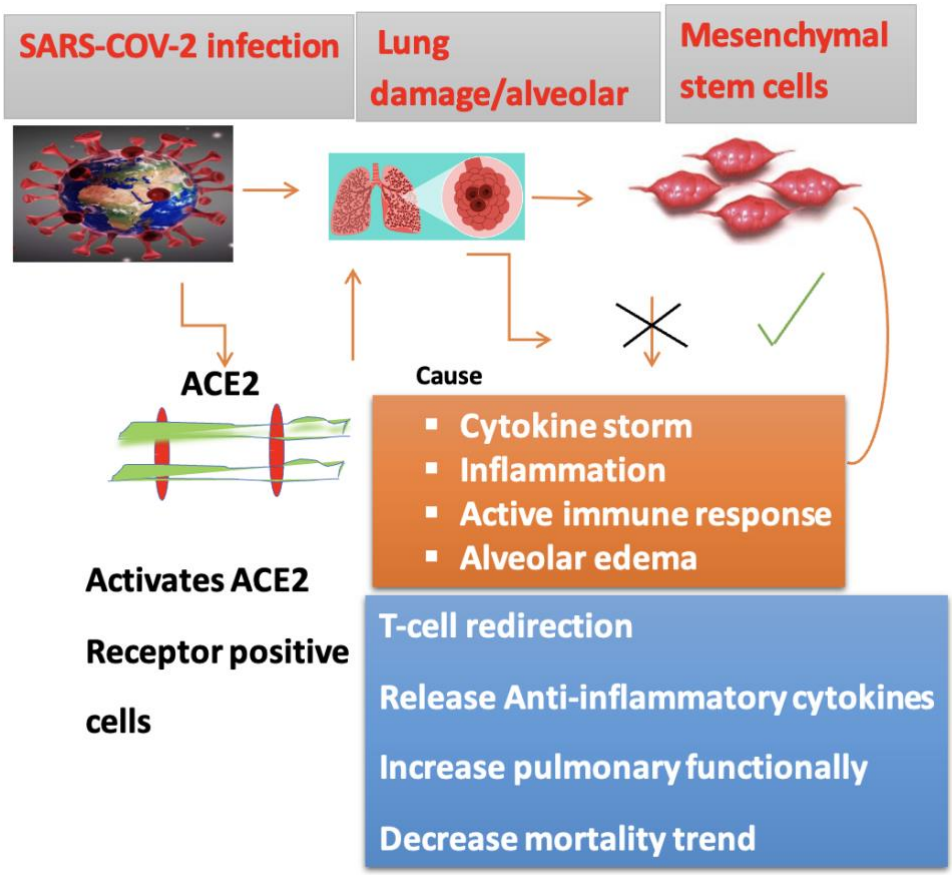

Figure 1- Graphical representation of disease spreading pathway

The current treatment options available are a number of antivirals, antimalarial, and anti-inflammatory agents to combat COVID-19 infection [14]. On the other hand, COVID-19 has no specific treatment, even after a year. Vaccines targeting different aspects of virus structure have been produced, and their efficiency varies. Patient management includes infection prevention or control and supportive care, such as increased oxygen. These treatment approaches have demonstrated efficacy in some patients, resulting in a reduction in disease severity and, as a result, a better chance of survival. Despite this, they could not restore the substantial lung tissue damage caused by COVID-19 infection in most individuals. [2]. Because of their immunomodulatory and regenerative capabilities, mesenchymal stem cells (MSCs) have received much interest [6]. In this review paper, we will summarise several studies that have used MSCs as a therapy option for patients with COVID-19 who are fighting for their lives. In addition, we will discuss current COVID-19 infection medicines, treatment procedures, outcomes, and side effects. In addition, there are benefits of using MSCs to treat COVID-19 infection.

2. SARS-COV-2

The coronavirus disease-2019 (COVID-19) is caused by a positive-sense single-stranded RNA virus that belongs to the Pisuviricota phylum, Pisoniviricetes class, Nidovirales order, Coronaviridae family, and *Betacoronavirus* genera [7]. The virus has a circular structure embedded with various viral cell surface proteins, such as the spike protein. Its genetic material is a positive-sense single-stranded RNA [(+) ss-RNA] genome ranging in size from

27 to 32 kb, allowing for a fast growth rate in the human body [8]. Protruding nonstructural proteins play a major role in pathogenesis by helping replication, including spike protein, envelope, matrix or membrane, and nucleocapsid [9]. The spike protein found on the surface of viruses aids in virus binding to angiotensin-converting enzyme 2 (ACE2) receptors [10, 11], the nucleocapsid protein aids RNA replication, virion production, and immunological infiltration [12]. ACE2 receptors are located in a range of mammalian bodily tissues, primarily in lung epithelial cells, kidneys, gastrointestinal tract, heart, liver, blood vessels, and some immune cells [13]. ACE2 receptors are critical components in regulating the renin–angiotensin–aldosterone system pathway. Based on structural tests and biochemical analyses, SARS-CoV-2 appears to have a receptor-binding domain RBD that strongly binds to ACE2 receptors in humans, cats, ferrets, and other species with similar receptors [14].

3. MESENCHYMAL STEM CELLS

MSCs are multipotent stem cells that can differentiate to regenerate tissue and repair nearly all cell types in the body [15]. These cells can be obtained from plant and animal sources and are compatible with source organisms. In humans, they can have been successfully isolated from bone marrow, amniotic fluid, placenta endometrium, dental tissue, and menses blood [16], as shown in Figure 2.

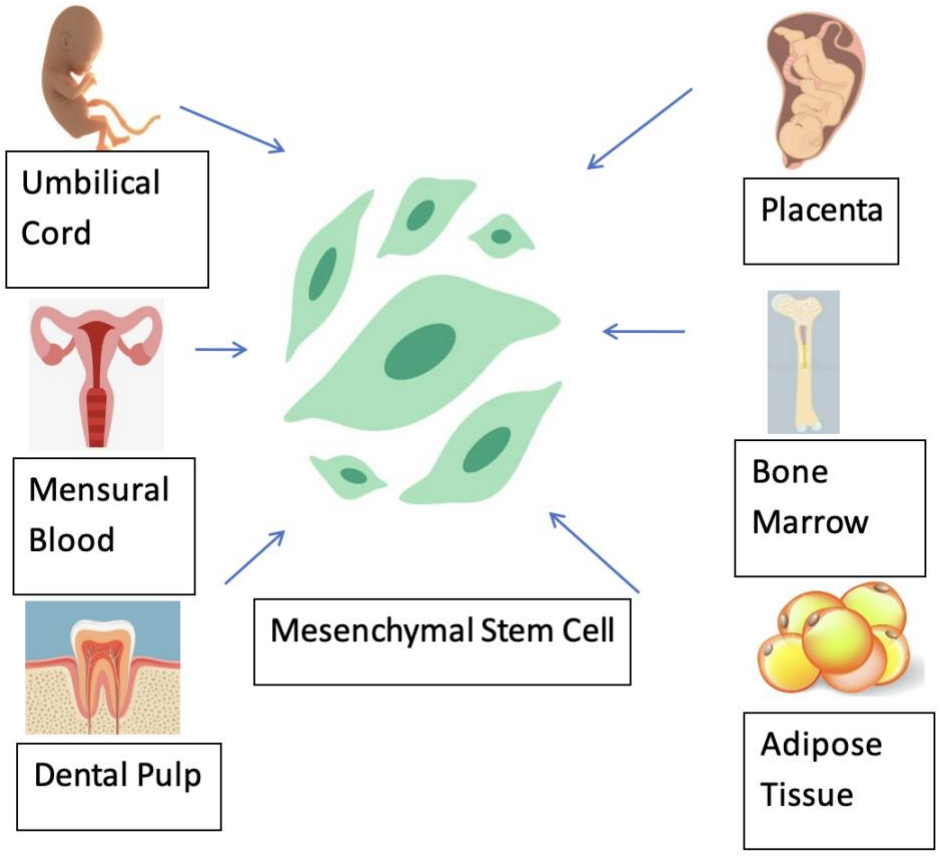

Figure 2: Source of mesenchymal stem cells for COVID-19 treatment.

The immunomodulatory functions, including secretion of cytokines and immune receptors on the surface of MSCs, may help produce a substantial immune response against the virus. Based on the notion that MSCs can moderate the overactive immune system [17], a few benefits of MSCs therapy in COVID-19 infections can be predicted. Because MSCs have a considerable multiplication potential, they can quickly scale up to meet the demands. MSCs are being studied to treat patients with COVID 19 with cytokine storm due to the above features [15, 16]. Autologous MSC transfusion is a generally non-invasive treatment with a well-established safety profile and a long list of documented advantages [18]. SARS-CoV-2 infection results in severe pneumonia-like symptoms in the lungs, which are linked to increased levels of proinflammatory cytokines like C-reactive proteins, fibrinogen, LDH, and D-dimer, as well as immune reactive cell invasion [19]. Following events such as ARDS, macrophage activation syndrome (MAS), and alveolar and endothelial damage, cytokines storms may occur, resulting in patient mortality [20]. One of the significant objectives in managing uncomplicated SARS-CoV-2 infection is to avoid cytokine storms. For the reasons

stated above, MSC therapy has the potential to significantly reduce the serious consequences of COVID-19 infection. When administered intravenously, 90% of MSCs are trapped in the lungs. Depending on the environmental surroundings, these MSCs have been shown to generate an abundance of anti-inflammatory cytokines and angiogenic growth factors, which stimulate tissue repair and improve pulmonary function [21]. MSCs can modulate dendritic cell maturation, activate M2 macrophages, and thus inhibit tissue damage by inducing Th1 to Th2 conversion or directly interacting with immune cells such as T cells and B cells [22]. They can also modulate dendritic cell maturation, activate M2 macrophages, and thus inhibit tissue damage, as depicted in Figure 3.

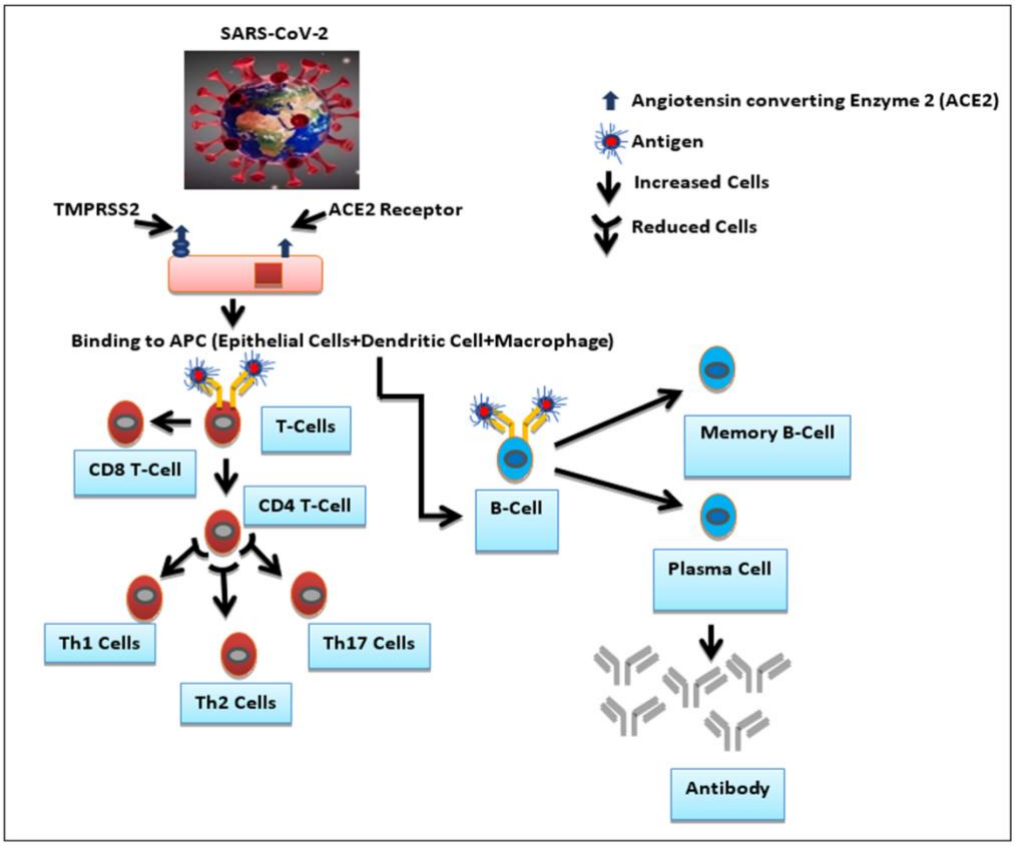

Figure 3: Putative mechanism of COVID-19 infection and host immune response.

Patients with COVID-19 and associated comorbidities poorly respond poorly to preapproved antiviral and anti-inflammatory treatments and frequently require intensive care [23].

We have seen a significant shortage of beds, medical oxygen, and ventilatory support facilities in the ongoing pandemic, which is expected to worsen in the so-called third wave. To reduce the pressure on intensive care units, the Italian College of Anaesthesia, Analgesia, Resuscitation, and Intensive Care has developed recommendations for using stem cells to treat patients with COVID-19 [24]. In severely ill patients infected with COVID-19, MSCs have been shown to reduce the need for mechanical ventilation and enhance recovery rates. In a proof-of-concept study, 13 critically ill patients on mechanical ventilators with severe SARS-CoV-2 pneumonia did not respond well to previous antiviral and anti-inflammatory drugs. Still, when adipose-derived MSCs (median number of cells per dose: 0.98 × 106 AT-MSC/kg of recipient's body weight) were given intravenously, nine patients showed clinical improvement, with seven being extubated after a median follow-up of 16 days.

The endothelial thrombo-inflammatory syndrome (with elevated D-dimer) associated with poor prognosis is a distinguishing feature of COVID-19 infection [22]. There was a significant improvement in the biochemical parameters of patients with a substantial decrease in D-dimer, C-reactive protein, LDH, and ferritin levels. The potential of MSCs in treating patients with infected COVID-19 was studied by Leng et al. [25, 26], in which seven patients with proven COVID-19 infection were transplanted with 1 × 106 per kg body weight MSCs in normal saline. With a decrease in C-reaction protein levels, inflammation levels were reduced in a short time. Furthermore, with a rise in oxygen saturation, all of the patients' pulmonary function improved.

Another clinical measure that increased was lymphocyte count and the CD14+CD11c+CD11bmid regulatory DC cell population. Proinflammatory cytokines secreting cells CXCR3+CD4+ T cells, CXCR3+CD8+ T cells, and CXCR3+ NK cells were

reduced due to the immunomodulatory function of MSCs. According to this study, the immune regulation and tissue healing characteristics of MSCs enhanced the result of patients with COVID-19. According to another case report, a patient with COVID-19 with severe COVID-19 pneumonia and a history of diabetes was treated with human umbilical cord Wharton's jelly-derived MSCs (hWJCs, 1 × 106cells/Kg wt.) from a healthy donor. The patient's pulmonary function and symptoms greatly improved after treatment. Inflammatory markers significantly dropped, such as IL-6, TNF-α, and C-reactive protein, whereas lymphocyte count increased (CD3+, CD4+, and CD8+T cell). Another case report from China claimed that MSC therapy could prevent a patient's condition from worsening. A 72-year-old COVID-19 patient with diabetic nephropathy, high blood pressure, lymphopenia, increased C-reactive protein, and renal insufficiency was given UC-MSCs (1.5 × 106 cells per kg of the patient's body weight) intravenously five times [27]. The patient's antiviral medication, which included recombinant human interferon and lopinavir/ritonavir, was ineffective. As a result, the patient was placed on mechanical ventilation. However, after receiving MSCs, lymphocyte levels were elevated, renal function improved, and the patient later had lung transplantation. This case report implies that MSC transfusion can help prevent severe deterioration of the patient's condition and give doctors more time to figure out the best way to save the patient. Similarly, a 65-year-old woman in China with severe multiorgan injury caused by an inflammatory response, acute respiratory distress, multiorgan injury (liver, respiratory system, and haematological complication), hypertension, type 2 diabetes, electrolyte disturbance, immune suppression, acute gastrointestinal bleeding, and allergy on corticosteroid therapy was transfused with allogeneic human umbilical cord MSCs (hUCMSCs) (5 × 107 each time). The patient's neutrophil and lymphocyte count improved after receiving the second dose, as evidenced by chest CT scans, and the patient was successfully weaned off invasive ventilation. This case report indicated a favourable clinical effect of hUCMSCs therapy in a patient with substantial lung inflammation [28]. Similarly, another study found that giving patients with COVID-19 ARDS allogeneic clinical-grade human prenatal MSCs from the placenta (PL-MSC) alleviated respiratory distress and reduced inflammation. Five patients got three doses of 200 × 106 PL-MSCs cells every other day via an infusion. Each patient received a total dose of 600 × 106 allogeneic MSCs via intravenous infusions. Although the study's patient population was smaller, it demonstrated the efficacy and safety of allogeneic clinical-grade human prenatal MSCs in critically ill COVID-19 patients with lung injury and disproved MSC therapy in patients with sepsis and organ failure. [29].

Similar to COVID-19 infection, H7N9 infection has a few overlapping clinical symptoms. In severe cases, the H7N9 influenza virus infection causes ARDS, pneumonia, and lung collapse. During the 2013 H7N9 outbreak, MSCs obtained from menstrual blood were given to 17 patients with H7N9-induced ARDS. In total, 44 individuals with H7N9 ARDS were treated with routine antiviral therapy in the control group. The experimental group had a 54% mortality rate, while the test group had a 17% mortality rate. No adverse effects were recorded in the test group, including the four patients who participated in a 5-year follow-up research. This research lays the groundwork for evaluating the efficacy of MSCs produced from menstrual blood in treating COVID-19 [30]. Regarding safety, scalability, and regulatory concerns, exosomes produced from MSCs have an advantage over direct MSC transfusion. Intravenous injection of bone marrow-derived exosomes reduced cytokine production and alveolar inflammation and restored damaged epithelial lining in animal models of inflammation, ARDS, and acute lung injury. Sengupta et al. [28] conducted a study where ExoFlo, a bmMSC-derived exosome agent, was studied in 24 COVID-19 patients with moderate-to-severe ARDS to see if it was effective.

Every patient received a single intravenous dosage of 15 ml ExoFlo in 100 ml saline for 60 minutes. Until 72 hours after the transfusion, none of the patients experienced any negative effects. For two weeks, the safety and efficacy of the treatment were monitored. After a single therapy dosage, the patient's general clinical state and oxygen saturation improved. The survival rate was discovered to be 83%. The acute phase reactants, CRP (77%), ferritin (42%), and D-dimer (42%), all showed a considerable drop (43%). There was also a considerable rise in CD3+ (46%), CD4+ (45%), and CD8+ T (46%) lymphocyte counts and a decrease in neutrophil counts (32%). This study found that bone marrow-derived exosomes are more convenient and beneficial than MSCs for suppressing the cytokine storm and enhancing the body's antiviral defences against COVID-19. Improvements in neutrophilia and lymphopenia further confirmed exosome vesicles' immunomodulatory activity. Exosomes (Ex) or macrovesicles (MV) were extracted from murine hypothalamus neural stem/progenitor cells (htNSC) or subtype htNSCPGHM, as well as hippocampus NSC. Exosomes can act as a cell-free innate antiviral defence against pseudotype SARS-CoV-2 viruses, as per the study. Table 1 and Table 2 offer a list of ongoing and finished clinical trials involving MSCs, along with

details. MSCs can also demonstrate adaptive immunity-like antiviral function when stimulated with viral exposure. Induced Ex/Mv was found to be more effective than basal Ex/Mv in reducing viral infections. The synthesis of P-element-induced wimpy testis- (PIWI-) interacting RNAs (piRNAs) targeting viral genomes is linked with NSC Ex/antiviral Mv action [31]

MSCs are known to possess immune-modulatory functions and secrete cytokines and immune receptors on their surface, which help produce immune-modulatory action against viruses.

These are multipotent stem cells that can differentiate into any body cell type. These cells can be obtained from both plant and animal sources.

4. PATHOGENESIS

The pathogenesis of the virus involves the function of the spike protein and the ACE2 receptor, which is present on the epithelial cell surface. The spike protein attaches to the ACE receptor, which then facilitates the entry of the virus into the human cells and its further proliferation. It spreads to the various parts of the body. Due to the virus's great similarity to its family, efforts have been made to develop COVID-19 treatments and vaccines. Variations in the length of the spike of COVID-19 are expected to play a role in the virus's pathogenesis and treatment. On the other hand, identifying the virus's exact molecular features is essential in achieving treatment objectives [32].

5. THERAPEUTIC REGIMEN IN COVID-19 ANTIVIRALS

Antiviral medicines block viral entrance through the ACE2 receptor and TMPRSS2, viral membrane fusion, and endocytosis, as well as the function of the SARS-CoV 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase [20]. They stop viral replication in the early stages of the disease, decreasing the severity and length of the overall illness until the body can develop an immune response. Lopinavir/Ritonavir failed to show a decrease in overall mortality and was subsequently abandoned. Favipiravir had no significant benefit as proven in studies and is not recommended currently for moderate or severe illness. It may be used in mild illnesses only. Remdesivir is an antiviral with a broad spectrum of activity that inhibits viral RNA polymerase. The early termination of viral replication inhibits viral replication. FDA approved for treating hospitalized adult and pediatric patients (over the age of 12 and weighing more than 40 kilograms) [33].

6. ANTIBIOTICS

Antibiotics do not work against viruses but may be prescribed when a patient with COVID-19 is suspected of having a secondary bacterial infection and indicated in severely ill and critically ill patients on ventilators [34]. Some of the commonly used antibiotics for COVID-19 patients are as follows:

Azithromycin is used for significant antiviral and immunomodulatory effects besides antibacterial actions. Doxycycline is a highly lipophilic antibiotic that chelates the zinc component of matrix metalloproteinase, decreasing coronavirus survival and replication. In addition, broad-spectrum antibiotics are added to the treatment regimen per the local/institutional programs for prevalent bacteria [35].

7. ANTIMALARIAL

The efficacy of hydroxychloroquine is not conclusive, and it is not recommended for treatment anymore. Whether the combination of hydroxychloroquine + azithromycin has more harm than benefit is still a matter of debate [36].

8. MONOCLONAL ANTIBODIES

Tocilizumab binds to IL-6 receptors, which are involved in the inflammatory response to COVID-19 infection. It can help patients get through a cytokine storm. The exact timing and stage of infection at which this medicine should be initiated are unknown [37].

9. NONSPECIFIC ANTI-INFLAMMATORY DRUGS

Because of their anti-inflammatory and immune-suppressive properties, steroids have played a critical role in COVID-19 treatment. At 28 days, they have been shown to lower mortality, and WHO recommends them for severe and life-threatening illnesses [38].

10. ANTIPARASITIC TREATMENT

Ivermectin is still being studied as a therapy for COVID -19; however, it has shown activity in vitro against the SARS-CoV-2 virus [39].

Table 1. List of ongoing clinical trials for exploring the use of mesenchymal cells (MSCs) or their derivatives in the treatment of COVID-19.#

S.No	Trial ID	Title	Site	Tissue source	No. of patients
1	**ChiCTR2000029569**	Safety and efficacy of umbilical cord blood mononuclear cells conditioned medium in the treatment of severe and critically novel coronavirus pneumonia (COVID-19): a randomized controlled trial	China, Hubei	Conditioned Media from Umbilical Cord MSCs	15 Control; 15 Exp
2	**ChiCTR2000030173**	Key techniques of umbilical cord mesenchymal stem cells for the treatment of novel coronavirus pneumonia (COVID-19) and clinical application demonstration	China, Hunan	Umbilical Cord	30 Control; 30 Exp
3	**ChiCTR2000030116**	Safety and effectiveness of human umbilical cord mesenchymal stem cells in the treatment of acute respiratory distress syndrome of severe novel coronavirus pneumonia (COVID-19)	China, Jiangxi	Umbilical Cord	16 Exp
4	**NCT04269525**	Umbilical Cord(UC)-Derived Mesenchymal Stem Cells(MSCs) Treatment for the 2019-novel Coronavirus(nCOV) Pneumonia	China, Hubei	Umbilical Cord	10 Exp
5	**ChiCTR2000030138**	Clinical Trial for Human Mesenchymal Stem Cells in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	China, Beijing	Umbilical Cord	30 Control; 30 Exp
6	**ChiCTR2000029990**	Clinical trials of mesenchymal stem cells for the treatment of pneumonitis caused by novel coronavirus (COVID-19)	China, Beijing	Not Specified	60 Control; 60 Exp
7	**ChiCTR2000030088**	Umbilical cord Wharton's Jelly derived mesenchymal stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19)	China, Beijing	Umbilical Cord	20 Control; 20 Exp
8	**ChiCTR2000030020**	The clinical application and basic research related to mesenchymal stem cells to treat novel coronavirus pneumonia (COVID-19)	China, Hu'nan	Not Specified	20 Exp
9	**ChiCTR2000030261**	A study for the key technology of mesenchymal stem cells exosomes atomization in the treatment of novel coronavirus pneumonia (COVID-19)	China, Jiangsu	MSC Exosomes (origin not specified)	13 Control; 13 Exp
10	**NCT04276987**	A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia	China, Hubei	Adipose Tissue—MSC Exosomes	30 Exp
11	**ChiCTR2000030484**	HUMSCs and Exosomes Treating Patients with Lung Injury following Novel Coronavirus Pneumonia (COVID-19)	China, Hubei	Umbilical Cord + Exosomes	30 Control; 30 Exp 1; 30 Exp 2
12	**ChiCTR2000029580**	Severe novel coronavirus pneumonia (COVID-19) patients treated with ruxolitinib in combination with mesenchymal stem cells: a prospective, single blind, randomized controlled clinical trial	China, Hubei	MSCs (origin not specified) + Ruxolitinib	35 Control; 35 Exp
13	**ChiCTR2000030866**	Open-label, observational study of human umbilical cord derived mesenchymal stem cells in the treatment of severe and critical patients with novel coronavirus pneumonia (COVID-19)	China, Hu'nan	Umbilical Cord	30 Exp
14	**ChiCTR2000030835**	Clinical study for the efficacy of Mesenchymal stem cells (MSC) in the treatment of severe novel coronavirus pneumonia (COVID-19)	China, He'nan	Umbilical Cord	10 Exp 1; 10 Exp 2
15	**NCT04302519**	Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells	China, Hubei	Dental Pulp	24 Exp
16	**NCT04313322**	Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells	Jordan	Umbilical Cord	5 Exp
17	**ChiCTR2000031319**	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe Pneumonia of COVID-19	China, Hubei	Dental Pulp	10 Control; 10 Exp
18	**ChiCTR2000031494**	Clinical study for stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19)	China, Hubei	Umbilical Cord	18 Control; 18 Exp
19	**ChiCTR2000031430**	Clinical study of human umbilical cord mesenchymal stem cells in the treatment of novel coronavirus pneumonia (COVID-19) induced pulmonary fibrosis	China, Beijing	Umbilical Cord	100 Control; 100 Exp

20	**ChiCTR2000029606**	Clinical Study for Human Menstrual Blood-Derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19)	China, Zhejiang	Menstrual Blood—MSCs ± artificial liver therapy	25 Control; 18 Exp 1; 10 Exp 2; 10 Exp 3
21	**NCT04252118**	Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19	China, Zhejiang	Umbilical Cord	10 Control; 10 Exp
22	**NCT04273646**	Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19	China, Hubei	Umbilical Cord	24 Control; 24 Exp
23	**NCT04288102**	Treatment With Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19)	China, Hubei	Not Specified	45 Control; 45 Exp
24	**NCT04315987**	NestCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE)	Brazil, Sao Paulo	Not Specified	66 Exp
25	**NCT04336254**	Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients	China, Hubei	Dental Pulp	10 Control; 10 Exp
26	**NCT04339660**	Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia	China, Hubei	Umbilical Cord	15 Control; 15 Exp
27	**NCT04341610**	ASC Therapy for Patients With Severe Respiratory COVID-19 (ASC COVID-19)	Denmark, Copenhagen	Adipose Tissue	20 Control; 20 Exp
28	**NCT04345601**	Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease)	USA, Texas	Bone Marrow	30 Exp
29	**NCT04346368**	Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19)	China, Guangdong	Bone Marrow	10 Control; 10 Exp
30	**NCT04348461**	BAttLe Against COVID-19 Using MesenchYmal Stromal Cells	Spain, Madrid	Adipose Tissue	50 Control; 50 Exp
31	**NCT04349631**	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	USA, Texas	Adipose Tissue	56 Exp
32	**EUCTR2019-002688-89-ES**	Clinical Study to Assess the Safety and Preliminary Efficacy of HCR040 in Acute Respiratory Distress Syndrome	Spain, Bizkaia	Not Specified	14 Control; 14 Exp
33	**EUCTR2020-001682-36-ES**	Treatment of COVID-19 with allogeneic mesenchymal cells (MSVÂ®)	Spain, Madrid	Not Specified	12 Control; 12 Exp
34	**EUCTR2020-001266-11-ES**	Clinical trial of administration of MSC to patients with respiratory distress type COVID-19	Spain, Madrid	Adipose Tissue	50 Control; 50 Exp
35	**IRCT20140911019125N6**	The effect of dental pulp mesenchymal stem cells in treatment of corona disease	Iran	Dental Pulp	10 Exp
36	**IRCT20140528017891N8**	The effect of stem cell transplantation in the treatment of COVID-19	Iran	Umbilical Cord	10 Exp
37	**IRCT20200325046860N2**	Mesenchymal Stem Cell therapy in COVID19	Iran	Not Specified	5 Exp
38	**IRCT20200217046526N1**	Mesenchymal Stem Cell Therapy for Acute Respiratory Distress Syndrome in Coronavirus Infection	Iran	Not Specified	6 Exp
39	**NCT03042143**	Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) (REALIST), Phase I/II	UK, Belfast	Umbilical Cord	9 Phase I; 33 Control; 33 Exp
40	**NCT04293692**	Therapy for Pneumonia Patients Infected by 2019 Novel Coronavirus	China, Hubei	Umbilical Cord	12 Control; 12 Exp
41	**NCT04352803**	Adipose Mesenchymal Cells for Abatement of SARS-CoV-2 Respiratory Compromise in COVID-19 Disease	USA + Spain	Adipose Tissue	10 Control; 10 Exp
42	**NCT04366830**	Intermediate-size Expanded Access Program (EAP), Mesenchymal Stromal Cells (MSC) for Acute Respiratory Distress Syndrome (ARDS) Due to COVID-19 Infection	USA, New York	Not Specified	50 Exp
43	**EUCTR2020-001364-29-ES**	Study with stem cells from allogenic adipose tissue, in patients with coronavirus severe pneumonia	Spain, Seville	Adipose Tissue	13 Control; 13 Exp

44	**EUCTR2020-001505-22-ES**	Efficacy and safety evaluation of umbilical cord mesenchymal stem cells for the treatment of patients with respiratory failure due to coronavirus (COVID-19)	Spain, Barcelona	Umbilical Cord	15 Control; 15 Exp
45	**NCT04348435**	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	USA, Texas	Adipose Tissue	50 Control; 50 Exp
46	**NCT04355728**	Use of UC-MSCs for COVID-19 Patients	USA, Florida	Umbilical Cord	12 Control; 12 Exp
47	**NCT04361942**	Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV) COVID_MSV	Spain, Valladolid	Not Specified	12 Control; 12 Exp
48	**NCT04366063**	Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome	Iran	Not Specified	20 Control; 20 Exp 1; 20 Exp 2
49	**NCT04371601**	Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019	China, Fujian	Umbilical Cord	30 Control; 30 Exp
50	**NCT04377334**	Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS)	Germany	Bone Marrow	20 Control; 20 Exp
51	**NCT04366271**	Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19 MESCEL-COVID19	Spain, Madrid	Umbilical Cord	53 Control; 53 Exp
52	**NCT04390139**	Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 COVIDMES	Spain, Barcelona	Umbilical Cord	15 Control; 15 Exp
53	**NCT04390152**	Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19	Colombia	Umbilical Cord	20 Control; 20 Exp
54	**NCT04392778**	Clinical Use of Stem Cells for the Treatment of Covid-19	Turkey	Not Specified	15 Control; 15 Exp
55	**NCT04400032**	Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome—Vanguard CIRCA-19	Canada	Bone Marrow	3 Exp 1; 3 Exp 2; 3 Exp 3
56	**ACTRN12620000612910**	The MEND (MEseNchymal coviD-19) Trial: a pilot study to investigate early efficacy of mesenchymal stem cells in adults with COVID-19	Australia	Mesenchymo-Angioblast	12 Control; 12 Exp
57	**NCT04382547**	Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells	Belarus	Olfactory-Mucosa	20 Control; 20 Exp
58	**NCT04397796**	Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation	USA, California	Bone Marrow	23 Control; 23 Exp
59	**NCT04416139**	Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 COVID-19	Mexico	Umbilical Cord	5 Control; 5 Exp
60	**IRCT20200421047150N1**	Stem cell treatment for COVID-19	Iran	Umbilical Cord	45 Control; 45 Exp
61	**IRCT20160809029275N1**	stem cell therapy in Covid-19	Iran	Umbilical Cord	10 Control; 10 Exp
62	**NCT04366323**	Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogeneic Adult Mesenchymal Stem Cells of Expanded Adipose Tissue in Patients With Severe Pneumonia Due to COVID-19	Spain, Andalucia	Adipose Tissue	13 Control; 13 Exp
63	**NCT04399889**	hCT-MSCs for COVID19 ARDS	USA, North Carolina	Umbilical Cord	15 Control; 15 Exp
64	**NCT04428801**	Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19	USA, Texas	Adipose Tissue	100 Control; 100 Exp
65	**NCT04429763**	Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia CELMA	Colombia	Umbilical Cord	15 Control; 15 Exp

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Table 2: List of completed clinical trials for the use of MSC in the treatment of ARDS.

S.No	Trial ID	Title	Ref*	Site	MSC source	No.of Pts	Route	Outcomes for MSC group
1	**NCT01902082**	Adipose-derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome	47	China, Zhejiang	AT	6 Control; 6 Exp	IV	No adverse reactions. Modest clinical improvements
2	**NCT02097641**	Human Mesenchymal Stromal Cells For Acute Respiratory Distress Syndrome (START)	48	USA, multi-centre	BM	20 Control; 40 Exp	IV	No adverse reactions. Modest clinical improvements
3	**ChiCTR-OCC-15006355**	Clinical Study of Mesenchymal Stem Cell Treatment for Acute Respiratory Distress Syndrome Induced by Epidemic Influenza A (H7N9) Infection: A Hint for COVID-19 Treatment	49	China, Zhejiang	MB	44 Control; 17 Exp	IV	No adverse reactions. Reduction of Fatality rate
4	**NCT02611609**	A phase 1/2 study to assess MultiStem therapy in ARDS (MUST-ARDS)	50	USA, UK	BM-MAPC	9 Control; 9 Exp 1; 9 Exp 2; 9 Exp 3	IV	Preliminary: No adverse reactions. Reduction of Fatality rate. Reduction of ventilator assistance time

AT: adipose tissue; BM: bone marrow; MAPC: multi-adult progenitor cell; MB: menstrual blood; IV: intravenous; Exp: experimental.

11. CONVALESCENT PLASMA

Passive immunization with plasma (antibodies-carrying plasma) donated from a recovered patient to a patient who has not recovered was also explored as a treatment option. Convalescent plasma is becoming more widely available with more patients recovering from the condition, and it prevents any posttreatment immune suppression side effects associated with monoclonal antibodies and is cost-effective compared to alternative therapy regimens. The risk of transfusion responses and varied levels of antibodies per donor are among the issues associated with this treatment [40].

12. ANTICOAGULANTS

These agents prevent microthrombi formation, one of the disease's various underlying pathophysiology mechanisms. Also, low-molecular-weight heparin is the most frequently prescribed medication for this disease [41].

13. VACCINES

Vaccines provide the patient with acquired protection against infectious illnesses. The world's first registered vaccination against SARS-CoV-2 was a recombinant adenovirus-based vaccine. Vaccines based on mRNA and inactivated viruses are now also accessible. The global immunization campaign has already begun and has accomplished its first milestones. Despite the best attempts to find a vaccine in the shortest time feasible, there is still a chance of reinfection following vaccination. Moreover, new changes in the SARS-CoV-2 virus pose a more significant threat to vaccination efficacy [42]. To control this pandemic, vaccines as effective preventative measures and the development of new medicines for better clinical management of severe SARS-CoV-2 are necessary.

14. WHY MESENCHYMAL STEM CELLS?

Because of their multipotent nature, MSCs can regenerate the lung tissue by differentiation capacity. They are readily available from various human sources, have a low invasive nature, and have a low risk of cross-immune reaction to infect an individual. Also, MSCs have a high proliferative rate and immune-modulatory and anti-inflammatory properties on the surface, which helps to counter cytokine storms. MSCs help reduce the levels of C-reactive proteins and TNF-alpha. In addition, they help increase the level of IL-10 [43].

Inflammation is a major hurdle to the regeneration process, but MSCs have been shown to curb the inflammation, thereby initiating regeneration [44].

The proposed dose required to fight against the disease is approx. 1 million cells per kilogram of body weight in the individual who has been infected by the virus.

15. MODE OF ACTION OF MSCS

Cytokine storm is a dreadful complication of COVID-19 infection characterized by an increased level of multiple inflammatory cytokines, culminating in multiple organ failure and death in some instances. A cytokine storm can be associated with multiple etiologies, infections, autoimmune conditions, immune therapies, or other diseases. After injecting MSCs intravenously into the human body, these cells localize in the lung tissue, which is the primary site of attachment of COVID-19 on account of its affection towards ACE receptors. Then they secrete various soluble factors like antimicrobial peptides, inflammatory or anti-inflammatory cytokines, extracellular vesicles, and angiogenic growth factors. The function and secretion of all soluble factors are regulated by the differential activation of pathogen-associated molecular pathogen receptors (PAMPRs), which are abundantly present on the MSC surface. Once the MSCs are deposited in the lung tissue, they start secreting the keratinocyte growth factor and angiopoietin-1, which mainly help restore disrupted alveolar-capillary barriers, which were crossed by the virus. The secreted extracellular vesicles contain a specific miRNA that helps regulate the protective effects of MSCs for a very long time. Once MSCs are injected, the levels of CRP decrease in the infected body, thereby lowering the cytokine storm within approximately 6 days. It is speculated that treatment by MSCs increases dendritic stem cells while decreasing the levels of TNF-alpha with significant elevation in the level of IL-10. These factors help overcome the cytokine storm induced by the SARS-CoV–2 viruses. Once the MSCs are fully differentiated in the lung tissue, they replace the old tissue, thereby recovering the pulmonary damage and restoring the pulmonary microenvironment, thus preventing sequelae, namely, pulmonary fibrosis and acute respiratory distress syndrome (ARDS) [45]. Table 3 presents the delivery method and a number of cell doses for MSCs in ongoing human trials for COVID-19 in detail.

Table 3. Delivery method and number of cell doses for MSC therapy for COVID-19-related conditions *(Clinicaltrials.gov)*.**

Delivery methods	Total number %	Number of doses to be administered					
		1	2	3	4	5	Unknown
Intramuscular injection	1 (2.6)	1*	0	0	0	0	0
Intravenous	36 (92.3)	5	6	10	5	2	8
Unknown	2 (5.1)	1	1	0	0	0	0
Total # of doses (%)		7 (17.9)	7 (17.9)	10 (25.6)	5 (12.8)	2 (5.1)	8 (20.5)

Durand, N., Mallea, J. & Zubair, A.C. Insights into the use of mesenchymal stem cells in COVID-19 mediated acute respiratory failure. *npj Regen Med* **5, 17 (2020). https://doi.org/10.1038/s41536-020-00105-z

16. CONCLUSION

According to the results of a phase I trial, the use of MSCs has shown to be a potential treatment in critically ill patients with SARS-CoV-2. All of the studies reviewed highlighted the importance of considering MSC-based therapy for patients with ARDS COVID-19 who are severely or critically unwell. Because the trials are still in their early stages, the safety profile of MSC treatment in COVID-19 individuals has yet to be determined. Due to the pandemic situation, there is currently no approved MSC therapy in COVID-19 treatment, and it is given to patients with COVID-19 on a compassionate basis. To further confirm the therapeutic efficacy of MSCs in the treatment of COVID-19, long-term trials with a large number of patients and extensive investigation of clinical results and side effects are warranted.

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