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Review Article

Mesenchymal stem cell therapy for COVID-19

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Abstract: The coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) started in December 2019 and affected the whole world in a short time. The course of the disease depends on the person's immune system, physical properties, health status, etc. as it varies according to its characteristics while it is asymptomatic in some people, it causes fatal processes that start with flu-like symptoms such as cough, fever, respiratory distress in some people and progress to acute respiratory distress syndrome (ARDS), severe pneumonia and multi-organ dysfunction, and the basic mechanism underlying these effects known as a cytokine storm. There is no specific effective antiviral drug or vaccine in treatment yet. Supportive/alternative treatment methods are needed as both the desired effect cannot be achieved and undesirable side effects are seen with the current treatments used in the clinic. Mesenchymal stem cells (MSCs) are frequently preferred recently from basic studies to clinical studies and are effective and safe in immune-mediated inflammatory diseases such as Systemic Lupus Erythematosus, Graft-versus-Host disease. MSCs can secrete many types of cytokines through paracrine secretion or directly interact with immune cells leading to immunomodulation. According to the results of the completed studies; it has been stated that the cytokine storm caused by the overstimulation of the immune system decreases and even damage of the cytokine storm on organs decreases, respiratory distress is relieved and contributes to the healing process by repairing damaged tissues. In this review, clinical trials completed/ongoing on MSCs recommended for treating COVID-19, a global problem, are reviewed and the review is prepared to specify the existence of such a route to clinicians.

Keywords: COVID-19, coronavirus, mesenchymal stem cells, SARS-CoV-2, cytokine storm, clinical trials

Introduction

Due to the SARS-CoV-2 infection, which affects all countries globally, the number of cases and deaths is increasing day by day. According to WHO's (World Health Organization) April 20, 2021 status report data, the cumulative number of cases seen since December 2019 was announced as 140,332,386, while the cumulative number of deaths was 3,004,088. (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/).

COVID-19, which is an important public health problem, can be transmitted from person to person by asymptomatic individuals or because of close contact and droplets released by an infected person through coughing or sneezing [1]. Through the spike protein found on the SARS-CoV-2 surface, it is primarily the lungs, heart, kidney, liver. It binds to Angiotensin-converting enzyme-2 (ACE-2) on the cell surface of tissues and organs and penetrates the cell. ACE-2, which is expressed by almost all organs, causes it to spread rapidly after the virus is taken into the body [2]. This disease, which has an incubation period of 2-14 days, causes different symptoms according to individual characteristics. Although it affects all age groups, it poses a risk in terms of mortality by having a more severe course in people with weak immune systems, the elderly, and those with chronic diseases [3]. Starting with flu-like symptoms such as coughing, fever, muscle pain, respiratory distress, the most dangerous process for COVID-19 is the appearance of ARDS, severe pneumonia, and multiple organ dysfunction caused by cytokine storms. The cytokine storm, which affects the pathophysiology of the disease, worsens the course of the COVID-19 and increases deaths due to the disease. In the cytokine storm caused by excessive stimulation

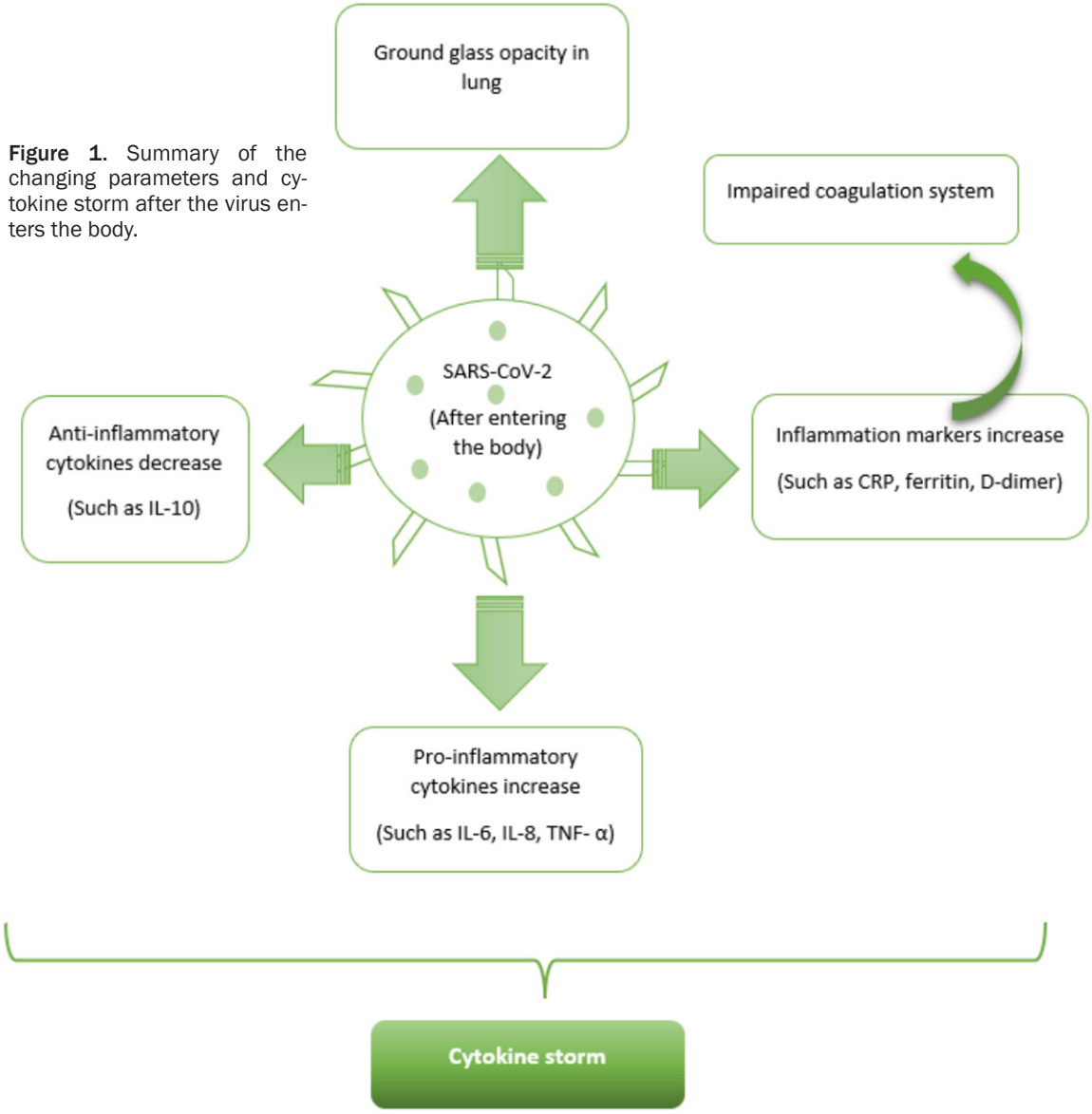

Figure 1. Summary of the changing parameters and cytokine storm after the virus enters the body.

of the immune system, pro-inflammatory cytokines are released from the immune system cells that are over-stimulated and are released into the circulation, and these cytokines are found in high concentrations in the circulation, causing damage to tissues and organs such as the lung, heart, kidney, spleen and lymph nodes [4]. In cases admitted to the hospital with suspected COVID-19, the appearance of ground glass in the lungs draws attention. In serum, pro-inflammatory cytokines/chemokines (such as interleukin-6 (IL-6), IL-8, tumor necrosis factor-alpha (TNF-α), CC-chemokine ligand 2 (CCL2)) and inflammation markers (such as C-reactive protein (CRP), ferritin, D-dimer) increased and anti-inflammatory cytokines such as IL-10 decreased (as summarized in **Figure 1**) [5-7]. High D-dimer levels are associated with increased coagulopathy, and another complication in the prognosis of COVID-19. Abnormalities in the coagulation system cause organ damage, mortality, and thrombus in vital organs such as the heart, brain, and kidney [8]. Although there is no specific treatment method, antiviral drug, or vaccine with proven reliability for treating COVID-19, the drugs recommended by the World Health Organization are used. The effectiveness and efficiency of these drugs are controversial. In addition to these drugs, alternative treatment approaches are needed.

Current treatments include antiviral drugs (remdesivir, favipiravir, lopinavir/ritonavir umifenovir, etc.), monoclonal antibodies, corticosteroids, plasma therapy, and vaccines. The efficacy of these treatments has not been clinically proven and studies are ongoing [9]. It has been reported that there was no statistically significant difference in clinical improvement in studies with remdesivir, and patients with symptom duration of less than 10 days showed rapid clinical improvement compared to placebo [10]. Randomized controlled studies with lopinavir/ritonavir found no significant effect on clinical improvement [11]. Although promising results have been obtained in treatment with monoclonal antibodies, it is disadvantageous due to cost and difficulties in the production process [12]. Chloroquine/hydroxychloroquine, which was used at the beginning of the pandemic, was removed from the treatment guide due to side effects and failure to achieve the desired effects (https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19) hydroxychloroquine). The combination of antiviral drugs, high-dose steroids, and some agents used in the treatment cannot provide the desired effect and serious side effects seen during treatment also limit the use of these agents [13]. Additionally, plasma therapy is an option used in the clinic, but there are not enough data (optimal dose, administration time, possible side effects, etc.) to support this application [14, 15]. For tocilizumab (Actemra®), which is an IL-6 inhibitor, clinical trials have been conducted on critically ill patients, considering that it will be effective by reducing cytokine storm, but it has been observed that it does not improve survival or even increases mortality [16-18]. There is a need for alternative/supportive methods such as MSC treatments in addition to existing treatments for reasons such as correcting this bad picture, reducing mortality, contributing to the recovery of individuals by supporting the immune system, and shortening the duration of hospital stay.

In this study, clinical studies in which mesenchymal stem cells were used for treating COVID-19 between December 2019 and April 2021 were evaluated. In line with the data obtained using the databases of international studies, the ongoing and completed studies are presented comprehensively with detailed information such as the study name, the country where the study was conducted, the number of participants, the phase, the source and dose of MSCs used, and the route of administration of MSC. Unlike previous studies, recent clinical trials were also included, examined in detail, and completed studies were evaluated with their results.

Methods

In this review, databases such as PubMed, Science Direct, Google Scholar and clinicaltrials.gov database (a database supported by WHO, for clinical studies) that contain international research, published articles, and latest developments in the field of health and medical sciences were used. Clinical studies and articles between December 2019 and April 2021 were reviewed. Literature search was performed on databases using the keywords: Mesenchymal stem cells, mesenchymal stromal cells, SARS-CoV-2, coronavirus, stem cell therapy. While 70 studies were registered in total, 30 studies were not included because they were not active yet, and only ongoing/completed studies were selected.

Patients over the age of 18 with a positive diagnosis of COVID-19 according to clinical and laboratory test results, patients who provided informed consent, and patients with pneumonia due to COVID-19 confirmed by chest radiography and computed tomography were included in the studies. Pregnant, lactating mothers, patients with known infection other than coronavirus infection, those with organ failure problems such as liver or kidney failure, those with a known history of allergy to MSC components, those with serious systemic disorders, a history of malignant disease, or those receiving treatment for malignancy, independent of COVID 19 Patients with coagulation problems, who are declared unfit for resuscitation due to underlying comorbidities or current critical conditions, patients with a survival expectancy of fewer than 24 hours in the opinion of the treating service, patients who have used immunosuppressive agents or who have had an organ transplant within the last 6 months, cardiac problems patients were excluded from the studies.

Mesenchymal stem cells

MSCs are multipotent stromal cells that can differentiate into various cell types, including

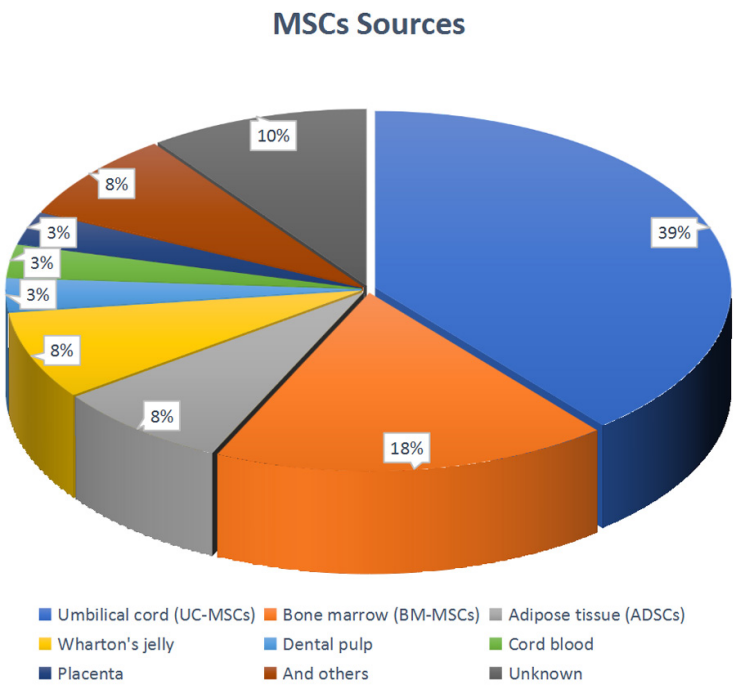

Figure 2. MSC resources used for treating COVID-19.

osteoblasts, adipocytes, and chondrocytes. They are found in many tissues of the organism, such as bone marrow, adipose tissue, nerve tissue, dental tissues, umbilical cord, muscle tissue, liver, and skin. Although MSCs may exhibit different properties depending on the source tissue, they must meet three minimum criteria defined by the International Society for Cellular Therapy (ISCT): First, MSCs must be able to adhere to plastic when grown in vitro. Second, MSCs must have characteristic cell surface marker profiles. (Must express CD73, CD90, and CD105 while lacking expression of CD45, CD34, CD14, CD11b, CD79a, CD19, and HLA-DR). Third, MSCs must differentiate into mesodermal cell types (adipocytes, chondrocytes, and osteoblasts) when cultured under certain conditions [19]. MSCs are effective in both innate and adaptive immune cells with their immunomodulatory properties [20]. MSCs can regulate the proliferation and activation of all immune system cells that play an active role in the pathogenesis of diseases such as dendritic cells, B lymphocytes, regulators, and effector T cells. It is one of the recently preferred treatment options in regenerative medicine with its differentiation potential, strong immunoregulation, and endogenous repair mechanisms [21, 22]. It attracts attention as an effective potential agent for lung damage, especially by the regeneration of damaged lung tissue and controlling inflammatory processes [23]. Although the mechanism of action is not fully understood, it has been reported that its therapeutic effects are mediated by direct cell contact [24] or paracrine secretions [25]. Paracrine secretions contain cytokines, chemokines, and exosomes to act on damaged tissue and provide tissue regeneration [26].

The use of MSCs for treating Systemic Lupus Erythematosus, Graft-versus-Host disease autoimmune diseases has been found to be effective and reliable [27-29]. Based on the promising results obtained from these studies, trials have been made using MSCs of different origins on infectious diseases and their effectiveness has been proven [30]. In a randomized, placebo-controlled study involving 12 adult patients, intravenous administration of allogeneic adipose-induced MSCs on ARDS was examined. According to the results, while there were no serious side effects related to the treatment, it was concluded that the treatment was safe and applicable [31].

MSC sources used in clinical and preclinical studies are preferred according to the advantages and disadvantages of each origin. For example, umbilical cord MSCs are frequently preferred in studies with their easy obtaining, easy reproduction in vitro, high immunomodulation, and tissue repair capabilities [32, 33]. The MSC sources used in the clinical studies used in this review are shown in **Figure 2**.

Clinical studies

MSCs have started to be used in clinical studies, although the number of completed studies is small, most studies continue. The studies given in **Table 1** in this article were obtained from the *clinicaltrials.gov* database supported by WHO and containing international studies. Country of study, the number of participants, phase stages, MSC sources, administration

Table 1. Clinical studies of the use of MSC for treating COVID-19 (clinicaltrials.gov)

Article name (ID)	Country	Estimated Enrolment	Phase	MSC source	MSC dose/product	Method	Status
Mesenchymal Stem Cell Infusion for COVID-19 Infection (NCT04444271)	Pakistan	20	2	Bone marrow	2×10^6 cells/kg	IV	Recruiting
Mesenchymal Stem Cells Therapy in Patients With COVID-19 Pneumonia (NCT04713878)	Turkey	21	-	Unknown	1 million cells/kg	IV	Completed
Clinical Use of Stem Cells for the Treatment of Covid-19 (NCT04392778)	Turkey	30	1/2	Umbilical cord	3 million cells/kg	IV	Recruiting
Cord Blood-Derived Mesenchymal Stem Cells for the Treatment of COVID-19 Related Acute Respiratory Distress Syndrome (NCT04565665)	USA	70	1	Cord blood	Unknown	IV	Recruiting
Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (COVID-19) (NCT04416139)	Mexico	10	2	Umbilical cord	$1\times10^6\times$Kg of weight	IV	Recruiting
Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19 (NCT04252118)	China	20	1	Umbilical cord	3.0×10e7	IV	Recruiting
Treatment of COVID-19 Patients Using Wharton's Jelly-Mesenchymal Stem Cells (NCT04313322)	Jordan	5	1	Wharton's Jelly	1×10e6/kg	IV	Recruiting
Safety and Efficacy Study of Allogeneic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients (NCT04336254)	China	20	1/2	Dental pulp	3.0×10e7	IV	Recruiting
Mesenchymal Stem Cells in Patients Diagnosed With COVID-19 (NCT04611256)	Mexico	20	1	Adipose tissue	1×10^6/kg	IV	Recruiting
Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Severe Corona Virus Disease 2019 (COVID-19) (NCT04288102)	China	100	2	Umbilical cord	4.0×10e7	IV	Completed
Clinical Trial of Allogeneic Mesenchymal Cells From Umbilical Cord Tissue in Patients With COVID-19 (MESCEL-COVID19) (NCT04366271)	Spain	106	2	Umbilical cord	Unknown	IV	Recruiting
Treatment of Severe COVID-19 Patients Using Secretome of Hypoxia-Mesenchymal Stem Cells in Indonesia (NCT04753476)	Indonesia	48	2	Unknown	1 cc	IM	Recruiting
Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia (NCT04339660)	China	30	1/2	Umbilical cord	1×10e6/kg	IV	Recruiting
Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome (NCT04366063)	Iran	60	2/3	Bone marrow and umbilical cord	100×10e6	IV	Recruiting
Administration of Allogenic UC-MSCs as Adjuvant Therapy for Critically-Ill COVID-19 Patients (NCT04457609)	Indonesia	40	1	Umbilical cord	1×10^6/kg	IV	Recruiting
Mesenchymal Stem Cells for the Treatment of COVID-19 (NCT04573270)	USA	40	1	Umbilical cord	Product: Primepro	IV	Completed
Treatment of Coronavirus COVID-19 Pneumonia (Pathogen SARS-CoV-2) With Cryopreserved Allogeneic P_MMSCs and UC-MMSCs (NCT04461925)	Ukraine	30	1/2	Placenta and umbilical cord	1 million cells/kg	IV	Recruiting
Use of UC-MSCs for COVID-19 Patients (NCT04355728)	USA	24	1/2	Umbilical cord	100×10^6 cells	IV	Completed
An Exploratory Study of ADR-001 in Patients With Severe Pneumonia Caused by SARS-CoV-2 Infection (COVID-19) (NCT04522986)	Japan	6	1	Adipose tissue	1×10^8 cells	IV	Completed
Therapeutic Study to Evaluate the Safety and Efficacy of DW-MSC in COVID-19 Patients (DW-MSC) (NCT04535856)	Indonesia	9	1	DW-MSC	5×10^7cells (low-dose group) 1×10^8 cells (high-dose group)	IV	Completed
Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal Stem Cells in Acute Respiratory Distress Syndrome Due to COVID 19 (NCT04390152)	Colombia	40	1/2	Wharton's Jelly	50×10e6	IV	Recruiting
A Phase II Study in Patients With Moderate to Severe ARDS Due to COVID-19 (NCT04780685)	USA	40	2	Bone marrow	Unknown	IV	Recruiting
Umbilical Cord Lining Stem Cells (ULSC) in Patients With COVID-19 ARDS (NCT04494386)	USA	60	1/2	Umbilical cord	100 million cells	IV	Recruiting

Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome-Vanguard (CIRCA-19) (NCT04400032)	Canada	9	1	Bone marrow	25, 50 and 90 million cells/unit dose	IV	Recruiting
Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the Treatment of Patients With Respiratory Distress Due to COVID-19 (COVIDMES) (NCT04390139)	Spain	30	1/2	Wharton's Jelly	1e6 cells/kg	IV	Recruiting
Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) (NCT03042143)	United Kingdom	75	1/2	Umbilical cord	400×10^6 cells	IV	Recruiting
Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease) (NCT04345601)	USA	30	1/2	Bone marrow	2×10^6 cells/kg	IV	Recruiting
Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults With COVID-19 Infection Requiring Mechanical Ventilation (NCT04397796)	USA	45	1	Bone marrow	Product: BM-Allo.MSC	IV	Recruiting
Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan (NCT04492501)	Pakistan	600	-	Bone marrow	2×10^6 cells/kg	IV	Completed
The MEseNchymal coviD-19 Trial: a Pilot Study to Investigate Early Efficacy of MSCs in Adults With COVID-19 (MEND) (NCT04537351)	Australia	24	1/2	Product: CYP-001 (Cymerus MSCs)	2 million Cymerus MSCs/kg	IV	Recruiting
A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury Who Are Receiving Renal Replacement Therapy (NCT04445220)	USA	22	1/2	Product: SBI-101	250 million MSCs (low-dose group) 750 million MSCs (high-dose group)	IV	Recruiting
A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia (NCT04276987)	China	24	1	Adipose tissue	2.0×10e8 nano vesicles/3 m	Aerosol inhalation	Completed
Multiple Dosing of Mesenchymal Stromal Cells in Patients With ARDS (COVID-19) (NCT04466098)	USA	30	2	Unknown	300×10^6	IV	Recruiting
Study of Descartes-30 in Acute Respiratory Distress Syndrome (NCT04524962)	USA	30	1/2	Product: Descartes 30	Product: Descartes 30	Unknown	Recruiting
Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS-CoV-2 Associated Pneumonia (COVID-19EXO) (NCT04491240)	Russian Federation	30	1/2	Unknown	Unknown	inhalation	Completed
Efficacy of Intravenous Infusions of Stem Cells in the Treatment of COVID-19 Patients (NCT04437823)	Pakistan	20	2	Umbilical cord	5×10^5 UCMSCs/kg	IV	Recruiting
Umbilical Cord (UC)-Derived Mesenchymal Stem Cells (MSCs) Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia (NCT04269525)	China	16	2	Umbilical cord	3.3×10^7 cells/50ml	IV	Recruiting
Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID_MSV) (NCT04361942)	Spain	24	2	Bone marrow	1 million cells/kg	IV	Recruiting
Treatment of Covid-19 Associated Pneumonia With Allogenic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells (NCT04382547)	Belarus	40	1/2	Olfactory mucosa	Unknown	IV	Enrolling by invitation
Regenerative Medicine for COVID-19 and Flu-Elicited ARDS Using Longeveron Mesenchymal Stem Cells (LMSCs) (NCT04629105)	USA	70	1	Product: Longeveron	100 million	IV	Recruiting

doses, administration routes (intravenous-IV-etc.), and status of the studies are summarized. Information was provided about the studies conducted/ongoing in clinical trials between December 2019-April 2021. There are 40 studies from many countries such as China, Pakistan, Turkey, Spain, and the USA. While 9 of these studies have completed their clinical trials, other studies are ongoing. The main objectives of these studies are to provide immunomodulation with MSC treatment, to reduce the damage caused by the cytokine storm to tissues and organs, to correct immunosuppression by regulating B and T cells, to combat COVID-19, and to accelerate recovery in organ damage by increasing growth factors. According to the targeted primary results, improvement in clinical symptoms in patients and a decrease in a cytokine storm. With a decrease in a cytokine storm, serious mortality causes such as ARDS complications will be eliminated. Potential effects of MSCs appear promising for treating ARDS complications [34, 35]. According to the secondary results, it is healed the lung damage and to discharge the patients after recovery.

According to the results of the completed studies, A placebo-controlled randomized study was conducted in China; 41 patients were randomly divided into 2 groups. The first group (treatment group) was 12 people and while UC-MSCs were being treated, the second group (control group) was 29 people and the current treatment procedure (antiviral drugs, systemic glucocorticoids, etc.) were applied. According to the primary results, all patients treated with UC-MSCs recovered on an average of 13 days and were discharged, while the patients in the control group recovered on an average of 23 days, and 4 patients died with worsening. A significant reduction in clinical symptoms and levels of inflammatory markers such as CRP and IL-6 was observed in the treatment group compared to the control group, while no side effects related to the treatment were observed [36].

In the study conducted with the participation of 13 patients in Spain, ADSCs were applied to patients who had previously received standard COVID-19 treatment and received mechanical ventilation support due to severe SARS-CoV-2 infection. 10 patients received 2 doses and 3 patients received 3 doses. Two of the critically ill patients died (one patient's death was associated with major gastrointestinal bleeding independent of MSC treatment). Patients showed reductions in CRP, IL-6, D-dimer levels and improvements in clinical symptoms after treatment, while no adverse effects were reported [37].

In China, a 65-year-old critically ill patient with ground-glass opacity and other symptoms in his lungs was applied standard treatments first, but after the patient's clinical symptoms worsened and serious side effects were observed due to the treatment, UC-MSCs were applied to the patient after 12 days of standard treatment (3 times per day, 5×10^7 cells). Because of the treatment, the patient whose clinical symptoms improved, the ground glass opacity in the lungs disappeared and the laboratory values reached normal levels, the patient was discharged on the 30th day of hospitalization [38].

In the study conducted with 10 participants in China, there were 7 patients with pneumonia and a placebo group of 3 people. Of the patient group, one is critical, 4 is severe and 2 is mild. After MSC application (1×10^6 stem cells/kg), all participants, including the critically ill person, were followed for 14 days and it was observed that lung images and laboratory findings reached normal values. In the placebo group, 1 patient died, 1 patient had ARDS, and 1 patient became serious [2].

MSCs were applied to 11 critically ill patients with comorbid diseases and receiving treatment in the intensive care unit in Iran. When UC-MSCs (600×10^6 cells) were administered to 6 patients 3 times a day and PL-MSCs (200×10^6 cells) were administered to 5 patients 3 times a day, CRP, TNF-α, IL-6 levels decreased in 7 patients, while clinical symptoms improved. Four patients with symptoms of multiple organ failure and sepsis died on average 10 days after MSC infusion [39].

In a randomized study conducted with 100 patients in China, the patients were divided into two groups as treatment (65 people) and placebo (35 people). Patients in the treatment group received 3 doses of UC-MSCs. When lung lesions were evaluated at the beginning, 10th, and 28th days of the patients, it was observed that lung damage decreased and ground glass appearance returned to normal in

the treatment group compared to the placebo group [40].

A product containing exosomes derived from bone marrow stem cells (ExoFlo™) was administered to 24 patients. According to the treatment results, 17 patients improved, 3 patients critically continued, while 4 patients died due to non-treatment reasons. While the general clinical condition of the patients improved, their oxygenation, laboratory values (decrease in CRP, D-dimer, and ferritin levels) returned to normal levels, no side effects related to the treatment was observed [41].

Discussion

The advantages of MSCs such as being easily accessible, being multipotent cells, not showing side effects in treatment, and getting successful results in clinical trials may cause them to be used as potential agents for treating COVID-19 [42]. In line with the data obtained from clinical studies, the umbilical cord is the most preferred source of MSCs, followed by the bone marrow, adipose tissue, and other sources. An optimal treatment procedure will be formed when the MSC sources and dose used in the treatment are different in each study, and there are no standards.

According to the main goals of ongoing studies and trial reports, MSCs are seen as a promising treatment option to alleviate the effects of COVID-19. With the completion of the studies, more contributions will be made to the literature and with these new treatments, a lower mortality rate will occur. In addition to the completed studies, it is necessary to contribute to the literature by making more and more comprehensive studies in this field.

MSC therapy plays an active role in clinical recovery by reducing the cytokine storm that occurs in COVID-19 patients and causes serious complications and with immunomodulation functions. It has been shown that MSCs contribute to the improvement of damage for treating lung diseases such as ARDS, pneumonia, asthma, and to normalize impaired lung function as an effective and reliable treatment [23]. For coagulopathy, another complication that causes mortality of patients, it has been reported that the levels of parameters such as D-dimer decrease after MSC application [37].

According to the study, 5 patients with severe COVID-19 were treated with Wharton jelly mesenchymal stem cells. After the treatment, IL-10 and Stromal derived factor-1 levels of the patients increased, whereas Vascular Endothelial Growth Factor, Transforming Growth Factor-β, Interferon-γ, IL-6, and TNF-α levels decreased. Additionally, it was observed that the zonal involvement score in both lungs of the patients improved [43].

Twenty four patients with COVID-19 and ARDS were divided into 2 groups as control and treatment groups. Allogeneic mesenchymal stem cells (100 ± 20×106 UC-MSCs) were administered to patients in the treatment group and improved patient survival compared to the control group. The recovery period of the patients in the treatment group was also shorter, while the IFN-γ, IL-5, IL-6, IL-7, TNF-α, TNF-β values were found to be lower than the control group [44].

Results from completed clinical trials also show that mesenchymal stem cells are promising for treating COVID-19. While reducing the progression of the disease by reducing the cytokine storm, it also heals the damage in the body with its immunomodulatory properties [45].

Conclusion

As a result, COVID-19 has been damaging the whole world from the moment it emerged, and this damage is increasing day by day. Treatment options are unclear and alternative/supportive treatments are needed to reduce mortality rates. In this sense, mesenchymal stem cell therapies seem promising as an effective therapeutic agent for treating COVID-19 in line with the results obtained.

Disclosure of conflict of interest

None.

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