The world has witnessed unimaginable damage from the coronavirus disease-19 (COVID-19) pandemic. Because the pandemic is growing rapidly, it is important to consider diverse treatment options to effectively treat people worldwide. Since the immune system is at the hub of the infection, it is essential to regulate the dynamic balance in order to prevent the overexaggerated immune responses that subsequently result in multiorgan damage. The use of stem cells as treatment options has gained tremendous momentum in the past decade. The revolutionary measures in science have brought to the world mesenchymal stem cells (MSCs) and MSC-derived exosomes (MSC-Exo) as therapeutic opportunities for various diseases. The MSCs and MSC-Exos have immunomodulatory functions; they can be used as therapy to strike a balance in the immune cells of patients with COVID-19. In this review, we discuss the basics of the cytokine storm in COVID-19, MSCs, and MSC-derived exosomes and the potential and stem-cell-based ongoing clinical trials for COVID-19. [BMB Reports 2020; 53(8): 400-412]

INTRODUCTION

The world has been facing a dreadful situation due to the spread of the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) (1). However, neither confirmed effective antiviral medications nor vaccines are available to deal with this emergency (2). Many reports have suggested that it is the cytokine storm in COVID-19 that leads to acute respiratory distress syndrome (ARDS) (3). The cytokine storm in COVID-19 refers to the fact that a variety of cytokines are rapidly produced after viral infections (4). In addition, such a cytokine storm induces hypoxia, and direct viral infection can cause cellular damage. Multiorgan damage and injury have been concomitant with COVID-19, and can be observed more in patients with a more severe form of the disease (5).

Stem cells are specialized cells that can renew themselves by means of cell division and can differentiate into multilineage cells. Mesenchymal stem cell (MSCs) have immunomodulatory features and secrete cytokines and immune receptors that regulate the microenvironment in the host tissue (6). In addition, it has been observed that the crucial role of MSCs in therapy has been mediated by exosomes released by the MSCs. These exosomes have exhibited immunomodulatory, antiviral, anti-fibrotic, and tissue-repair-related functions in vivo; similar effects have been observed in vitro (6).

COVID-19 AND THE IMMUNE SYSTEM

The dynamic equilibrium maintained by innate and adaptive immunity is essential for impeding the progression of COVID-19 (7). In patients infected with SARS-CoV-2, the plasma levels of IL-1β, IL-1RA, IL-7, IL-8, IL-10, IFN-γ, monocyte chemotactic peptide (MCP)-1, macrophage inflammatory protein (MIP)-1A, MIP-1B, G-CSF, and TNF-α are significantly higher than in controls. The levels of these factors are also increased in patients who were admitted to ICUs (8). Similarly, reductions in the levels of T cells and NK cells have been observed in COVID-19 patients (9). The loss of such cells can impair the immune system (10). The levels of the helper T cells, cytotoxic suppressive T cells, and regulatory T cells are much lower in...
patients with COVID-19 than in their healthy and less severe counterparts. The decrease in the regulatory T cells may hamper their ability to inhibit the chronic inflammation (11). Interestingly, a remarkable increase is observed in the naïve T cells, where as the memory T cells are reduced in infected patients (10). The reduced expression of memory cells may be a plausible explanation for the increased rates of reinfection by SARS-CoV-2.

THE CYTOKINE STORM

SARS-CoV-2 binds to the Angiotensin-converting enzyme 2 (ACE2) receptor and enters the host cell (1). During infection, the innate and adaptive immune systems work together to inactivate the virus. Since leukocytes and neutrophils are present in higher concentrations in COVID-19 individuals, these immune cells may result in the cytokine storm (10). After viral entry, the virus induces pyroptosis and cell death. The dead cells recruit macrophages to the site of injury that phagocytose them. The phagocytes then express damage-associated molecular patterns (DAMPs), which bind to the toll-like receptors (TLR) and induce nuclear factor kappa B (NF-κB) signalling by means of the MyD88 pathway. NF-κB enters the nucleus and catalyzes the transcription of pro-IL-1β and procaspase-1. When additional signals are detected, the pro-IL-1β and procaspase 1 are cleaved into IL-1β and caspase 1 (12). The activated NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) recruits the apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and procaspase-1 to form the NLRP3 inflammasome (13). In addition, the phagocytosis releases ATP, which binds to the P2X purinoreceptor 7 (P2RX7) and activates the inflammasome (14). The increased calcium levels caused by the viral proteins results in lysosomal damage, thereby releasing cathepsins that activate the inflammasome (15). Further, the binding of SARS-CoV-2 to the ACE2 reduces the available ACE2 receptors on the cell surface. This increases the levels of Angiotensin II (AngII) in the extracellular space, because ACE2 converts AngI and AngII into Ang 1-9 and Ang1-7, respectively. AngII increases the levels of TNF-α and IL-6 in the cell that upregulates NF-κB, activating the inflammasome (12). The continuous activation of the inflammasome results in a cytokine storm, which recruits more immune cells, necrosis, and cell death. This inflammasome pathway further causes tissue injury in various organs (Fig. 1).

MSCs AND IMMUNOMODULATION

MSCs are predominantly isolated from the bone marrow, adipose tissue, dental pulp, umbilical cord, Wharton’s jelly, placenta, synovial fluid, endometrium, and peripheral blood. These cells exhibit different cell-surface markers and can be used for a variety of treatment options (Table 1). MSCs can undergo in vitro amplification and self-renewal, and have low immunogenicity and immune-modulatory functions; the latter have attracted attention in clinical trials (16). MSCs have been widely used in various cellular therapies, such as pre-clinical studies, as well as in some clinical trials, because of their high safety and efficacy (17, 18). MSCs can exert immune-modulatory effects in the host cells of both the innate and the
Table 1. Commonly used sources of MSCs

| S. No | Source                  | Extraction route                        | Purity level | Proliferation rate | Doubling time | MSCs Marker         |
|-------|-------------------------|-----------------------------------------|--------------|--------------------|---------------|---------------------|
| 1.    | Bone Marrow             | Bone Marrow Aspiration                  | High         | Lowest             | 40 Hrs        | Stro-1, CD271, SSEA-4, CD146 |
| 2.    | Adipose Tissue          | Liposuction, lipectomy                   | Medium       | Higher             | 5 days        | CD271, CD146        |
| 3.    | Dental pulp             | Tooth extraction or root canal          | Low          | High               | 30-40 Hrs     | Stro-1, SSEA-4, CD146 |
| 4.    | Umbilical Cord          | After birth from umbilical cord         | High         | Medium             | 30 Hrs        | CD146               |
| 5.    | Wharton’s jelly         | After birth from umbilical cord         | High         | High               | 30 Hrs        | CD73, CD90, CD105   |
| 6.    | Placenta                | Obtained after delivery                 | High         | High               | 36 Hrs        | SSEA-4, CD146       |
| 7.    | Synovial Fluid          | Synovium or synovial fluid              | High         | High               | 10 days       | Stro-1, SSEA-4, CD146 |
| 8.    | Endometrium             | Endometrium biopsies or menstrual blood | High         | High               | 18-36 Hrs     | Stro-1, CD146       |
| 9.    | Peripheral Blood        | Density Gradient Centrifugation         | Low          | Low                | 95 Hrs        | CD133               |

MESENCHYMAL STEM CELLS (MSCs) AND MSC SECRETOME

It has currently become apparent that MSCs induce therapeutic characteristics by a paracrine pathway by releasing bioactive substances known as secretomes (25). MSC-secretomes are made of soluble proteins, including cytokines, chemokines, growth factors, and extracellular vesicles (EVs), which include microvesicles and exosomes (26). Stem cells release these secretomes by common secretory mechanisms. When the culture medium or secretome are injected into the patients, the neighboring cells assimilate the molecules by paracrine signalling (27). The exosomes themselves contain numerous bioactive molecules, which include microRNAs (miRNA), transfer RNAs (tRNA), long noncoding RNAs (lncRNA), growth factors, proteins, and lipids. The lipid content of the exosomes provide an added advantage by aiding in the infusion of the exosomes with the plasma membrane of the neighboring cells (28). The molecules involved in regulation of cell growth, proliferation, survival, and immune responses are released by exosomes, are elaborately illustrated in Fig. 2. Upon internalization of the molecules in the secretome, the neighboring cells modulate various downstream pathways, including immunomodulation, suppression of apoptosis, prevention of fibrosis, and remodelling of the injured tissues (25).
IMMUNOMODULATORY POTENTIAL OF MSC-EXOS

Exosomes are nanoparticles with a diameter of 40–150 nm. To generate and isolate the exosomes, MSCs can be conditioned to increase the release of exosomes by treatment with cytokines or by serum starvation or hypoxia (29). The exosomes are then purified and can be subsequently introduced into the body. MSC-Exos can inhibit CD4+ and CD8+ T cells and NK cells (30). They inhibited T cells expressing IL-17 and induced IL-10-expressing regulatory cells that are involved with suppression of inflammation. MSC-Exos also aid in suppressing the differentiation of CD4+ and CD8+ T cells by releasing molecules like TGFβ and prevent inflammation in vivo (31). Similarly, treatment with MSC-Exos reduced the proliferation and activation of NK cells (32). MSC-Exos could shift macrophages from the M1 to the M2 phenotype, further suppressing pro-inflammatory states (33). Moreover, sepsis is an important lethal factor in COVID-19 patients, and treatments with MSC-Exos have increased the rate of survival in mice with sepsis (34). Concomitantly, MSC-Exos also suppressed release of the pro-inflammatory factors TNF-α, IFN-γ, IL-6, IL-17, and IL-1β (35) and promoted release of anti-inflammatory factors, such as IL-4, IL-10 and TGF-β (36). Additionally, MSC-Exos also reduced the number of chemokines in the serum when injected (37). These immunomodulatory effects of MSC-Exos have also been attributed to their anti-inflammatory cargo, such as IDO, HLA-G, PD-L1 and galectin-1 (38, 39). These mechanisms are illustrated in Fig. 3.

MSC-EXOS THERAPY FOR COVID-19

In COVID-19, multiorgan damage has been seen in many-infected individuals. MSC-Exos is known to alleviate lung injury in asthmatic models and ARDS (40, 41). MSC-Exos may also be useful in the treatment of cardiovascular (42) and renal problems (43). Hence, they can be used to treat organ damage associated with COVID-19. Similarly, MSC-EVs have also exhibited inhibitory activity on the hemagglutination of avian, swine, and human influenza viruses (44). Likewise, MSC-Exos lowered the death rate in H7N9 patients without any toxic effects during follow-up examinations (45). In addition, these exosomes consist of adhesion molecules that accurately guide them to the injured site. The usage of the exosomes may be preferred to the MSCs, since they can easily cross the blood-brain barrier, are inexpensive, and cannot undergo independent self-renewal, hence preventing adverse consequences, such as tumor formation. In this pandemic situation, MSC-Exos may be considered as a good treatment option to alleviate the effect of SARS-CoV-2 infection.

CURRENT CLINICAL TRIALS OF STEM CELL-BASED THERAPY IN COVID-19

Of late, stem-cell-based studies in the treatment of COVID-19 have been gaining momentum. The efficiency and safety of usage of exosomes that had been obtained from BM-MSCs was recently tested on 24 SARS-CoV-2 patients (46). These patients exhibited moderate to severe ARDS. When the exosomes were introduced into the patients, there were no side effects, and patients improved in clinical status and oxygenation (46). In a similar study, patients treated with MSCs showed a remarkable improvement in pulmonary function, higher levels of peripheral lymphocytes, and a reduction in the cells that trigger the cytokine storm. Interestingly, the MSCs did not exhibit ACE2 or TMPRSS2 expression, showing that they may not be infected with COVID-19 (47). Several clinical trials are in the pipeline for usage of stem cells for the treatment of COVID-19 (Table 2). Wharton’s jelly-derived MSCs (WJ-MSCs), which have been used in various studies based on stem-cell therapy and trials, are in progress for their usage for COVID-19 treatment (48). Moreover, adipose tissue-derived AD-MSCs have been used in a few studies in various doses and protocols for COVID-19 therapy (49). Likewise, a novel trial includes inhalation of MSC-Exos for alleviation of symptoms (50). In addition, MSCs from dental pulp (51) and olfactory mucosa

http://bmbreports.org
| Study title                                                                 | Intervention                | Study size | Description                                                                 | Status  | Country | Reference |
|---------------------------------------------------------------------------|----------------------------|------------|------------------------------------------------------------------------------|---------|---------|-----------|
| Treatment of COVID-19 patients using Wharton’s Jelly-Mesenchymal Stem Cells | WJ-MSCs                    | 5          | Dose: 3 IV doses of $1 \times 10^6$kg / Time: 3 days apart                    | Phase 1 | Jordan  | 55        |
| Safety and Efficacy study of Allogenic Human Dental Pulp Mesenchymal Stem Cells to Treat Severe COVID-19 Patients | Allogenic Human Dental Pulp MSCs Placebo: Intravenous Saline | 20         | Dose: IV of $3.0 \times 10^7$ human dental pulp stem cell solution (30 ml) on day 1, day 4 and day 7 IV of 3 ml of 0.9% saline at the same interval | Phase 2 | China   | 56        |
| NestCell Mesenchymal Stem Cells to Treat Patients with Severe COVID-19 Pneumonia | NestCell                   | 66         | Dose: 2 $\times 10^7$ cells (20 million cells) / Time: days 1, 3 and 5 in addition to standard care, On day 7, cells will only be administered if necessary | Phase 1 | Brazil  | 57        |
| A Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Determine the Safety and Efficacy of Hope Biosciences Allogenic Mesenchymal Stem Cell Therapy (HB-adMSCs) to Provide Protection Against COVID-19 | HB-adMSCs                  | 100        | 3 groups of patients, will receive five IVs at 200, 100 and 50 million cells/dose Infusions will occur at week 0, 2, 6, 10 and 14. Placebo is saline | Phase 2 | USA     | 58        |
| Clinical Trial to Assess the Safety and Efficacy of Intravenous Administration of Allogenic Adult Mesenchymal Stem Cells of Expanded Adipose Tissue in Patients With Severe Pneumonia Due to COVID-19 | Allogenic expanded adMSCs  | 26         | Two doses of 80 million adipose-tissue derived mesenchymal stem cells        | Phase 2 | Spain   | 59        |
| 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 | HB-adMSCs                  | 56         | Dose: five IV infusions Time: follow-up inflammatory data will be obtained at 6, 14, 26 weeks; and PHQ-9 Questionnaires at weeks 2, 6, 10, 14, 18, 22, 26 | Phase 2 | USA     | 60        |
| Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem cells | Dental pulp MSCs           | 24         | Dose: $1.0 \times 10^7$ cells/kg / The injection of dental mesenchymal stem cells will be increased on day 1, 3 and 7 | Early   | China   | 51        |
| Mesenchymal Stem Cell Treatment for Pneumonia Patients Infected With COVID-19 | MSCs                       | 20         | 3 times of MSCs (3.0 $\times 10^7$ MSCs intravenously at Day 0, Day 3, Day 6)    | Phase 1 | China   | 62        |
| Treatment With Mesenchymal Stem Cells for Severe Coronavirus Disease 2019 (COVID-19) | MSCs Saline containing 1% Human serum albumin (solution of MSC) | 90         | 3 times of MSCs (3.0 $\times 10^7$ MSCs intravenously at Day 0, Day 3, Day 6)    | Phase 1 | China   | 62        |
| Bone Marrow-Derived Mesenchymal Stem Cell Treatment for Severe Patients With Coronavirus Disease 2019 (COVID-19) | BM-MSCs                    | 20         | Participants will receive conventional treatment plus BM-MSCs (1 $\times 10^6$/kg body weight intravenously at Day 1) | Phase 2 | China   | 63        |
| Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Severe COVID-19 | UC-MSCs                    | 48         | 4 times of UC-MSCs (0.5 $\times 10^6$ UC-MSC/kg body weight intravenously at Day 1, Day 3, Day 5, Day 7) Not yet recruiting | Not yet recruiting | China | 64        |
| Study title                                                                 | Intervention                          | Study size | Duration/Protocol                                                                 | Status   | Country | Reference |
|---------------------------------------------------------------------------|---------------------------------------|------------|-----------------------------------------------------------------------------------|----------|---------|-----------|
| Safety and Effectiveness of Mesenchymal Stem Cells in the Treatment of Pneumonia of Coronavirus Disease 2019 | Drug: Oseltamivir and hormones MSCs   | 60         | Umbilical cord mesenchymal stem cells were given at 106/kg body weight/time, once every 4 days for a total of 4 times Peripheral intravenous infusion was given within 3 days of first admission | Early    | China   | 53        |
| Clinical Research of Human Mesenchymal Stem Cells in the Treatment of COVID-19 Pneumonia | UC-MSCs                               | 30         | Protocol 1 (n=20); Two doses of MSCs 100×10^6 (± 10%) at Day 0 and Day 2 plus Conventional treatment Protocol 2: Two doses of MSCs 100×10^6 (± 10%) at Day 0 and Day 2, intravenously plus two doses of EVs at Day 4 and Day 6 plus conventional treatment | Phase 2  | China   | 65        |
| Mesenchymal Stem Cell Therapy for SARS-CoV-2-related Acute Respiratory Distress Syndrome | Cell therapy                         | 60         | UC-MSC will be administered at 100×10^6 cells/administration intravenously in addition to the standard of care treatment | Phase 3  | Iran    | 66        |
| Role of Immune and Inflammatory Response in Recipients of Allogeneic Haematopoietic Stem Cell Transplantation (SCT) Affected by Severe COVID19 | No intervention                       | 40         | Comparison of biomarkers                                                          | Active, not recruiting | United Kingdom | 67        |
| Use of UC-MSCs for COVID-19 Patients                                      | UC-MSCs                               | 24         | SCE therapy circulates a patient's blood through a blood cell separator, briefly cocultures the patient's immune cells with adherent CB-SC in vitro, and returns the autologous immune cells to the patient's circulation | Phase 2  | USA     | 68        |
| Stem Cell Educator Therapy Treat the Viral Inflammation in COVID-19       | Stem Cell Educator-Treated Mononuclear Cells Apheresis | 20         | No intervention                                                                   | Phase 2  | USA     | 69        |
| Efficacy and Safety Study of Allogeneic HB-adMSCs for the Treatment of COVID-19 | Drug: HB and MSC                      | 110        | Dose: 4 IV of HB-adMSCs at 100 million cells/dose + hydroxychloroquine and azithromycin HB-adMSC infusions will occur at day 0, 3, 7, and 10 Placebo: similar intervals without the HB-adMSCs | Phase 2  | USA     | 54        |
| Therapy for Pneumonia Patients Infected by 2019 Novel Coronavirus         | Biological: UC-MSCs                   | N.A        | 0.5×10^6 UC-MSC/kg body weight suspended in 100 ml saline containing 1% human albumin intravenously at Day 1, Day 3, Day 5, Day 7 | Withdrawn | China   | 70        |
| Battle Against COVID-19 Using Mesenchymal Stromal Cells                  | Allogeneic and expanded adipose-tissue-derived MSCs | 100        | Two serial doses of 1.5 million adipose-tissue derived mesenchymal stem cells/kg | Phase 2  | Madrid  | 71        |
| Safety and Efficacy of CASstem for Severe COVID-19 Associated With/Without ARDS | CASstem                               | 9          | A dose-escalation with 3 cohorts with 3 patients/cohort who receive doses of 3, 5 or 10 million cells/kg | Phase 2  | China   | 72        |
| Study title                                                                 | Intervention                                      | Study size | Description                                                                                     | Status  | Country | Reference |
|---------------------------------------------------------------------------|--------------------------------------------------|------------|-------------------------------------------------------------------------------------------------|---------|---------|-----------|
| ASC Therapy for Patients With Severe Respiratory COVID-19                  | Stem Cell Product                                | 40         | 100 million allogeneic adipose-derived mesenchymal stromal cells diluted in 100 ml saline       | Phase 2 | Denmark | 73        |
| Mesenchymal Stem Cells (MSCs) in Inflammation-Resolution Programs of Coronavirus Disease 2019 (COVID-19) Induced Acute Respiratory Distress Syndrome (ARDS) | MSC                                              | 40         | Infusion of allogeneic bone marrow-derived human mesenchymal stem (stromal) cells               | Phase 2 | Germany | 74        |
| Umbilical Cord (UC)-Derived Mesenchymal Stem Cells/MSCs Treatment for the 2019-novel Coronavirus (nCOV) Pneumonia | UC-MSCs                                          | 10         | UC-MSCs infusion intravenously on day 1, day 3, day 5, and day 7                              | Phase 2 | China   | 75        |
| A Pilot Clinical Study on Inhalation of Mesenchymal Stem Cells Exosomes Treating Severe Novel Coronavirus Pneumonia | MSC-derived exosomes                             | 30         | 5 times aerosol inhalation of MSCs-derived exosomes (2.0*10^8 nano vesicles/3 ml at Day 1, Day 2, Day 3, Day 4, Day 5) | Phase 1 | China   | 50        |
| MultiStem Administration for COVID-19 Induced ARDS (MACoVIA)              | MultiStem                                        | 400        | IV infusion of MultiStem                                                                          | Phase 3 | USA     | 76        |
| Cell Therapy Using Umbilical Cord-Derived Mesenchymal Stromal Cells in SARS-CoV-2-Related ARDS | UC Wharton's jelly-derived human Placebo: NaCl 0.9% | 60         | Dose: 1 million/kg through an intravenous route                                                  | Phase 2 | France  | 48        |
| Treatment of Severe COVID-19 Pneumonia With Allogeneic Mesenchymal Stromal Cells (COVID-MSV) | Mesenchymal Stromal Cells                         | 24         | IV injection of 1 million MSV cells/Kg diluted in 100 ml saline                                  | Phase 2 | Spain   | 77        |
| Mesenchymal Stromal Cells for the Treatment of SARS-CoV-2 Induced Acute Respiratory Failure (COVID-19 Disease) | Mesenchymal Stromal Cells                         | 30         | Dose: 1 × 10^8 MSCs through IV                                                                  | Early Phase 1 | USA | 78        |
| Repair of Acute Respiratory Distress Syndrome by Stromal Cell Administration (REALIST) (COVID-19) | Remestemcel-L                                    | 300        | Administered twice during the first week, with the second infusion at 4 days following the first injection (± 1 day) | Phase 3 | USA     | 79        |
| Treatment of Covid-19 Associated Pneumonia With Allogeneic Pooled Olfactory Mucosa-derived Mesenchymal Stem Cells | Allogeneic pooled olfactory mucosa-derived MSCs | 40         | IV injection                                                                                     | Phase 2 | Minsk   | 52        |
| Autologous Adipose-derived Stem Cells (AdMSCs) for COVID-19               | Autologous adMSCs                                | 200        | 3 doses of 200 million cells through IV every 3 days                                            | Phase 2 | USA     | 49        |
| Mesenchymal Stem Cell Infusion for COVID-19 Infection                    | MSC                                              | 20         | Dose: 2 × 10^6 cells/kg, administered on day 1, 7 in addition to supportive care                | Phase 2 | Pakistan | 80        |
| Safety and Efficacy of Mesenchymal Stem Cells in the Management of Severe COVID-19 Pneumonia (CELMA) | UC-MSCs                                          | 30         | Dose: 1 × 10^9 cells/kg                                                                          | Phase 2 | USA     | 81        |
| Mesenchymal Stem Cell for Acute Respiratory Distress Syndrome Due for COVID-19 (COVID-19) | MSC                                              | 10         | Dose: 1 million/Kg                                                                               | Phase 2 | Mexico  | 82        |
| NestaCell® Mesenchymal Stem Cell to Treat Patients With Severe COVID-19 Pneumonia (HOPE) | NestaCell®                                       | 90         | Dose: 2 × 10^7 cells on days 1, 3, 5 and 7                                                        | Phase 2 | Brazil  | 83        |
| Study title                                                                 | Intervention                  | Study size | Description                                                                 | Status | Country | Reference |
|---------------------------------------------------------------------------|-------------------------------|------------|-----------------------------------------------------------------------------|--------|---------|-----------|
| Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for   | UC-MSCs                       | 100        | Dose: 3 of 4.0*10E7 cells at Day 0, Day 3, Day 6                           | Phase 2| China   | 84        |
| Severe Corona Virus Disease 2019 (COVID-19)                              |                               |            |                                                                             |        |         |           |
| Efficacy of Intravenous Infusions of Stem Cells in the Treatment of      | MSCs                          | 20         | IV injection of Cultured stem cells at days 1, 3 and 5                     | Phase 2| Turkey  | 85        |
| COVID-19 Patients                                                        |                               |            |                                                                             |        |         |           |
| Clinical Use of Stem Cells for the Treatment of Covid-19                 | MSCs                          | 30         | Dose: 3 million cells/kg on days 0, 3 and 6                               | Phase 2| Turkey  | 86        |
| Safety and Efficacy of Intravenous Wharton's Jelly Derived Mesenchymal   | WJ-MSCs                       | 40         | 2 doses                                                                     | Phase 2| Colombia| 87        |
| Stem Cells in Acute Respiratory Distress Syndrome Due to COVID-19         |                               |            |                                                                             |        |         |           |
| MSCs in COVID-19 ARDS                                                    | RemestenseL                   | 300        | Twice in the first week with a gap of 4 days between the injections        | Phase 3| USA     | 88        |
| Efficacy and Safety Evaluation of Mesenchymal Stem Cells for the         | WJ-MSCs                       | 30         | Administration along with standard care                                    | Phase 2| Spain   | 89        |
| Treatment of Patients With Respiratory Distress Due to COVID-19 (Covid-19) |                               |            |                                                                             |        |         |           |
| Cellular Immuno-Therapy for COVID-19 Acute Respiratory Distress Syndrome | MSCs                          | 9          | IV administration                                                           | Phase 1| Canada  | 90        |
| - Vangard (CIRCA-19)                                                     |                               |            |                                                                             |        |         |           |
| ACT-20 in Patients With Severe COVID-19 Pneumonia                        | Allogenic UC-MSCs             | 70         | 1 million cells/kg body weight in 100 ml in conditioned media             | Phase 2| USA     | 91        |
| Study of the Safety of Therapeutic Tx With Immunomodulatory MSC in Adults | Allogenic BM-MSC              | 45         | IV administration                                                           | Phase 1| USA     | 92        |
| With COVID-19 Infection Requiring Mechanical Ventilation                |                               |            |                                                                             |        |         |           |
| Double-Blind, Multicenter, Study to Evaluate the Efficacy of PLX PAD for | MSCs                          | 140        | 15 IM injections (1 ml each). Twice with an interval of 1 week             | Phase 2| USA     | 93        |
| the Treatment of COVID-19                                                |                               |            |                                                                             |        |         |           |
| A Study of Cell Therapy in COVID-19 Subjects With Acute Kidney Injury    | MSCs and a                    | 24         | Administered through integration into a Continuous Renal Replacement        | Phase 2| USA     | 94        |
| Who Are Receiving Renal Replacement Therapy                               | plasmapheresis device         |            | Therapy circuit                                                            |        |         |           |

WJ: Wharton's Jelly; MSC: Mesenchymal stem cells; adMSCs: adipose derived MSCs; UC: Umbilical cord; IV: Intravenous; BM: Bone marrow; HC: hydroxychloroquine; AZ: azithromycin.
(52) were administered in various doses. MSCs in the clinical trials are predominantly administered intravenously; i.v. injection and, in some studies, MSCs have been given as adjuvant therapy in addition to drugs like oseltamivir, hormones, hydroxychloroquine, and azithromycin (53, 54). These trials reveal promising new routes for the battle against COVID-19 (55-94).

**FUTURE DIRECTIONS**

Stem cells have been studied extensively for their ability to regenerate and for the treatment of various diseases. Recently, we devised an improved protocol for the isolation of urine-derived stem cells and their further differentiation into immune cells (95). Moreover, our research group promoted the hematopoietic differentiation of hiPSCs using a novel small molecule (96). At the advent of COVID-19, it has become mandatory to discover therapeutic strategies that are easily reproducible and cost effective. Drugs currently available for the treatment of COVID-19 include ones that target viral replication. These drugs include camo-stat mesylate, which is involved in the inhibition of viral fusion to the cell membrane, and favipiravir and remdesivir, which are anti-viral drugs. However, because the cytokine storm is found predominantly in COVID-19 patients, it is essential to consider drugs that inhibit viral replication while treating the cytokine storm. Hence, MSC-Exos may be appropriate therapeutic agents for COVID-19 (97). MSCs can be more advantageous than other anti-inflammatory agents, because they can provide immunomodulatory effects based on the host cells. In addition to these effects, MSCs can prevent fibrosis of tissues, enable reversal of lung dysfunction, and aid in the regeneration of damaged tissue, which can be significantly beneficial for COVID-19-associated organ damage (98, 99). Because the healing properties of the MSCs can be primarily attributed to the secretomes or exosomes, using them may be more effective than using MSCs themselves. Exosomes can be mass-produced, administered systematically with minimal toxicity, and be able to reach the cell targets more efficiently. In addition to their inherent immunomodulatory potential, the MSC-Exos can also be used as a drug-delivery system (100). MSC-Exos can be modified in vivo to release exosomes that have a higher immunomodulatory potential (101) and can be cultured using various cytokines to exhibit an anti-inflammatory state (102). Although MSC-Exos appear to be promising therapeutic agents for COVID-19, more experimental research is necessary for them to be used clinically. Moreover, it is essential to optimize the protocols for storage and isolation of MSC-Exos for the treatment of COVID-19. It is also imperative to do experiments to understand the underlying mechanisms of COVID-19 in order to optimize MSC-Exo therapy for treatment (97). Further, it is also essential to find the optimum dosage, route of administration, and treatment schedule for MSC-Exos. Hence, since MSCs are more widely studied in these aspects than are MSC-Exos, they are predominantly preferred in clinical trials for COVID-19 (103).

**CONCLUDING REMARKS**

COVID-19 has invoked frenzy in individuals worldwide. The unceasing increase of infection and death has halted the lives of the citizens of countries everywhere. Hence, it is important to discover novel therapeutic platforms and productive measures without further delay (104). The therapies produced must be easily reproducible and available in large quantities so that enough bioactive molecules will be available for all individuals who have succumbed to COVID-19. MSCs and MSC-Exos can be used for their immunomodulatory effects in individuals with COVID-19.

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**CONFLICTS OF INTEREST**

The authors have no conflicting interest.

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