PROSPECT OF STEM CELL THERAPY TO AVOID CYTOKINE STORM IN SEVERE COVID-19

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ABSTRACT
Severe COVID-19 cases are mostly due to severe inflammatory reaction and cytokine storm, which may lead to multiple organ failure and death. Until recently, there is no proven effective treatment for severe COVID-19. Mesenchymal stem cells (MSCs) have anti-inflammatory and regenerative properties. Therefore, they are supposed to work on COVID-19, which has failed to recover using other treatments. Therefore, studies are needed to determine the best tissue source of MSCs, the dose, repeat, and route of administration. For this review, we searched various databases, i.e. Pubmed, Science Direct, Springer, and WHO website using keywords: “mesenchymal stem cells” and “COVID-19” at 7 May 2020, without time limits. Various clinical trials on the use of MSCs for COVID-19 were registered, and initial results were reported. Initial results were promising but should be interpreted cautiously, as one was a case report, another one was a case series, and one was a preliminary study of seven treated patients compared to three controls, so that the baseline conditions were unequal. Therefore, well design randomized clinical trials are needed to get more robust prove.

Keywords: SARS-CoV-2, COVID-19, Mesenchymal stem cells, Immune-modulation, Anti-inflammation, Cytokine storm

INTRODUCTION
The first pneumonia case, which was presumably due to a novel Coronavirus, was identified in Wuhan, China on 11 November [1], but cases were communicated to WHO on 31 December 2019 as pneumonia of unknown cause [2]. On 27 December, three patients, who were ill for four to seven days, were admitted to a hospital in Wuhan, and on 30 December their broncho-alveolar-lavage samples were collected. RNA extraction, direct PCR, whole-genome sequencing, and virus isolation from the lavage samples showed the presence of a new betacoronavirus with more than 85% similarity to a bat SARS-like CoV (bat-SL-CoVZC45, MG772933.1) [3]. The new virus, which was previously named 2019 novel coronavirus (2019-nCoV), is named SARS-CoV-2 and the disease it causes is named coronavirus disease (COVID-19) [4]. The new virus infects cells through angiotensin-converting enzyme 2 (ACE2) that is present in various types of cells including type 2 alveolar cells of lungs, stratified epithelial cells of the tongue, oral mucosa, and esophagus; columnar epithelial cells of ileum and colon, and myocardial cells. Further, to enter a cell, viral S (spike) protein should be primed by host cell serine protease TMPRSS2 [5, 6]. COVID-19 spreads very fast crossing the borders to other countries, and on 11 March, the WHO has declared COVID-19 as a pandemic [7].

Till to date, there is no proven effective treatment for COVID-19, though dozens of existing compounds were suggested to be tested. A mega-trial on thousands of COVID-19 confirmed cases, which is called Solidarity, is recently underway to test four most promising compounds or combinations of compounds [8].

Around 15% of COVID-19 patients will fall into a severe state that makes hospitals become overwhelmed [8], so that many patients are neglected and cannot get appropriate treatment. Severe cases are mostly due to cytokine storms, which may lead to multiple organ failure and death [9], and might be managed by anti-inflammatory agents. One of the anti-inflammatory agents is a certain kind of stem cells, namely mesenchymal stem cells.

The main aim of this review is to present a brief outline of the properties of stem cells, general properties of mesenchymal stem cells, requirement of mesenchymal stem cell use in patients, the theoretical justification of mesenchymal stem cell use in COVID-19, and various published results and on-going clinical trials on mesenchymal stem cell use in COVID-19 to prevent or modulate severe COVID-19.

For this review, we searched various databases, i.e. Pubmed, Science Direct, Springer, and WHO website using keywords: “mesenchymal stem cells” and “COVID-19” at 7 May 2020, without time limits. Only English literatures were used. In addition, mesenchymal stem cell and COVID-19 related articles that were found during the writing of this article were included.

The properties of stem cells
Stem cells are the origin of all other cells in the body, and have two main capacities i.e. self-renewal and differentiation. According to the source, there are two main types of natural stem cells, i.e. embryonic and adult stem cells. Adult stem cells are more preferred, as their use is not restricted by ethical problems [10], and usually does not cause teratoma as the use of embryonic stem cells.

One type of adult stem cells that are widely used is the mesenchymal stem cell. Mesenchymal stem cells (MSCs) can be isolated easily from various tissues, including bone marrow [11], adipose tissue [12], umbilical cord [13], dental pulp [14], etc. Bone marrow MSCs were the first studied, followed by adipose tissue, umbilical cord, and various other tissues. MSCs from various sources show similar properties but may have subtle differences that can be seen in different DNA methylation pattern [15].

General properties of mesenchymal stem cells
Mesenchymal stem cells should fulfill minimal requirements that were set by International Society for Cell Therapy (ISCT), i.e. their shape should be fibroblastic, they should adhere to plastic vessel where they get attached and not detach, and they should be positive for CD73, CD90, CD105, CD29, CD44, CD106, CD166, CD146, and HLA-DR. The new MSCs should be able to differentiate into three lineages, i.e. into chondrocyte, osteocyte, and adipocyte lineages [16].

The acronym MSCs recently may stand for mesenchymal stem cells, mesenchymal stromal cells, multipotent stem cells, or medicinal signalling cells. The BCT, which is now broadened to the International Society for Cell and Gene Therapy, has formed an MSC committee that supports the use of the acronym MSCs as mesenchymal stem cells with certain requirements. The requirements include: the naming should be followed by an explanation of the tissue source, stemness should be proven in vitro and in vivo, and functional assays are needed to demonstrate MSC properties that are related to the intended therapeutic use of the MSCs [17].
MSC properties that are related to therapeutic use are secretion of trophic factors that may help in regeneration of injured tissue/organ, immunomodulation and promotion of angiogenesis. The assay to prove those properties, which are recommended by the BTC's MSC committee, include quantitative RNA analysis of a certain gene, flow cytometry to prove the presence of surface markers, MSC secretome protein analysis, and characterization of MSC exosomes and their contents including microRNAs (miRNAs) [17].

**Requirement of mesenchymal stem cell use in patients**

To be used in patients, US Food and Drug Administration (FDA) has set a regulation that MSC production should be done in a current Good Manufacturing Practice (cGMP) facility to ensure that the product is safe and sterile, and following current Good Tissue Practice (cGTP) to prevent transmission of diseases from donors. In addition, various additional testing, including sterility, mycoplasma and endotoxin test should be conducted [18], and when post-thawed MSCs are used, viability should be ≥70% (FDA) or ≥80% (European Medicines Agency [EMA]) [19, 20]. To prevent zoonotic infectious agents and immune reaction due to xeno-material use, animal free material usage is encouraged, and to ensure efficacy, early passage use (passage-3 to passage-7) is recommended [20].

**Theoretical justification of stem cell use in COVID-19**

In severe COVID-19, patients may develop a severe inflammatory reaction and cytokine storm that causes acute respiratory distress syndrome (ARDS) and/or multiple organ failure, which finally leads to death [9]. Various studies showed the safety and efficacy of mesenchymal stem cells either against various inflammatory conditions, such as diseases with underlying inflammatory reactions, or conditions that needs immunomodulation [21]. Mesenchymal stem cells are immune-privileged as they have very few MHC class II human leucocyte antigen (HLA-II/HLA-DR) major histocompatibility complex (MHC) class II, and co-stimulatory CD80 and CD86 molecules that are required for T-lymphocyte activation, so that allogeneic MSCs might not be rejected. They also have immunosuppressant and anti-inflammatory properties. MSCs are attracted to site of inflammation, where they interact with immune cells and cause a shift in cytokine profile from inflammatory to anti-inflammatory profile [22]. Moreover, MSCs communicate with cells in injured tissues and secrete trophic factors that are needed for tissue repair [23]. Therefore, it is supposed that MSCs may prevent or modulate severe inflammatory reactions, and may promote repair in the injured lung due to COVID-19. However, there are some matters that need to be solved, such as the dose and route of administration and tissue source of the MSCs.

**MSCs against various inflammatory or autoimmune diseases**

Various diseases have underlying inflammatory or autoimmune reaction, such as inflammatory bowel disease in the form of perianal fistula in Crohn's disease and ulcerative colitis; multiple sclerosis, systemic lupus erythematosus, graft versus host disease, inflammatory lung disease, type-1 and type-2 diabetes mellitus, etc. MSC immunomodulation properties have been used to treat those diseases, using various MSC sources, various doses, and various route of administration with variable degrees of success, but showed no lasting effect, as improvement is usually temporary and last between six months to one year. This temporary effect might be due to the characteristics of treated diseases that were mostly chronic in nature [24-26]. COVID-19 is not a chronic disease, thus the use of MSCs that is intended to alleviate the cytokine storm and inflammatory reaction at the moment is justified, as after the inflammation and cytokine storm subsided MSCs are not needed any more.

Most MSC therapy, which used hospital-based-laboratory grown MSCs, for graft versus host disease, showed good results, but a large phase III study, which used commercial industrial product 2x10⁶ cells/kg body weight, twice a week for four weeks, failed to reach its primary clinical endpoint. This failure was supposed to be due to over-expansion of MSCs that were directly used after thawing [27]. Therefore, for COVID-19, the MSCs should meet the requirements that were set by US-FDA or EMA [18-20]. In addition, when cryopreserved MSCs were used, re-culture to regain their immunomodulatory property is recommended.

**Dose and route of administration**

Previous studies on MSC use in diseases with underlying inflammatory or autoimmune reactions showed that those studies used various MSC sources, doses and routes of administration [24-26]. Therefore, MSC use in COVID-19 might take advantage from the knowledge of optimal and safe doses of MSC from a certain source. As such, MSCs are intended to alleviate ARDS due to cytokine storm, the optimal route is supposed to be intravenous. A tracing study in mice, which used in vivo imaging system, revealed that 24 h after injection, most of the MSCs will be trapped in the lungs (30-60%), and liver (5-15%) [28]. A study on the clinical trial, Gov from 2008 through 2018, which consisted of 914 MSC trials, showed that 43 % used the intravenous (IV) route. From the 914 trials, 16 had published their results. Most of the 16 published results showed that improved outcomes were attained using minimal effective dose (MED) between 70—190 million MSCs/patient/dose for IV route. However, four trials, which reported a dose response data, showed a narrower MED of 100-150 million MSCs/patient, while higher or lower IV doses were less effective [29].

A more direct route, such as on site transplantation into the bronchial tree and alveoli, theoretically may place the MSCs in the real battle field, but the fact that in ARDS there is accumulation of proteinaceous and fibrin exudate inside alveoli, and abundant macrophages infiltrating air spaces [30], this approach may be counterproductive as the MSCs may stay in the lumen of bronchial tree and cannot reach the battle field. Moreover, vehicle solution to suspend the MSCs may prevent oxygenation in alveoli, and aggravate the condition.

**Tissue source of MSCs**

Immune modulation property of MSCs might cope with severe inflammatory reaction in the lungs or other affected organs, and may mitigate the cytokine storm. In addition, MSC capacity to secrete trophic factors may aid in regeneration of injured tissues/organ. MSCs can be taken from various tissues, but for immune-modulatory purposes, MSCs from bone marrow (BM-MSCs), adipose tissue (AT-MSCs) and birth-related tissue, namely umbilical cord MSCs (UC-MSCs), umbilical cord blood MSCs (HUC-MSCs) are usually used in clinical trials [31]. Therefore, the most appropriate source need to be determined. Autologous MSCs need to be isolated and cultured to attain a certain number that is needed, thus need time around three to four weeks to be ready. As COVID-19 patients with ARDS needs fast management, ready to use allogeneic MSCs are more appropriate.

Bone marrow MSCs are the first studied and used in many clinical trials, but bone marrow aspiration is painful and may pose risks to the donor. Moreover, a study reviewed the immune-modulatory properties of MSCs from various tissues and showed that AT-MSCs had stronger immune-modulatory property compared to BM-MSCs, while UC-MSCs were similar to BM-MSCs, in term of inhibiting CD4+/CD8+lymphocyte activation. In term of dendritic cell differentiation inhibition, AT-MSCs showed more profound effect compared to BM-MSCs, and in term of dendritic cell maturation inhibition, UC-MSCs were equal to BM-MSCs, but UC-MSCs showed stronger effect in reducing dendritic cell endocytotic ability compared to BM-MSCs. In term of cytokine release inhibition, UCB-MSCs were the most potent [31]. However, the isolation of UCB-MSC compared to BM-MSCs is easy and safe. Therefore, studies are needed to determine the best tissue source of MSCs, the dose, repeat, and route of administration.

**Various on-going clinical trials on stem cell use in COVID-19 and a published result**

A search in WHO International Clinical Trials Registry Platform (ICTRP) [32] on 26th March 2020 for COVID-19 yielded 648 clinical trials, twenty-eight of which are using MSCs, MSC's product (exosome and conditioned medium) or MSCs combined with other type of therapy. The clinical trials were registered in ClinicalTrial. Gov [nine trials [clinical trial identifier: NCT]], and Chinese Clinical Trial Registry (nine teen Trials [clinical trial identifier: ChiCTR]); mostly were from China (twenty-six), one from Jordan and one from Brazil. Four out of the registered clinical trials in Chinese Clinical Trial Registry were cancelled by the investigator and one that was registered in clinical trial. Gov was withdrawn. Most of the clinical trials used UC-MSCs, and were mostly given by intravenous route. The dose was variable, and given once to five times. However, the age range was very broad (table I). These broad age ranges and simple randomization may result in unequal baseline age characteristics, so that the control and treatment group will not be comparable.
Table 1: MSC clinical trials registered in WHO international clinical trials registry platform (ICTRP)

| Reference | Clinical trial identifier/regi- | Institution/Primary sponsor | Title                                                                 | MSC source, dose/vol, route | Study type/design/retrosp | Groups/Tar get size/age range | Status          |
|-----------|--------------------------------|-----------------------------|----------------------------------------------------------------------|-----------------------------|-----------------------------|-------------------------------|-----------------|
| 32        | ChiCTR2000030                   | The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China | 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) | UC-MSC, NR/NR, IV          | Intervention, dose comparison | 2 groups: 16-18 y            | Recruiting     |
| 32        | NCT04269525/7 Feb 2020          | Zhong Nan Hospital, Wuhan University, Wuhan, Hebei, China | Clinical Research Regarding the availability and safety of UC-MSCs treatment for Serious Pneumonia and Critical Pneumonia Caused by the 2019-nCoV Infection | UC-MSC, 10x 10^7/150 ml IV d-1-3-5-7 | Intervention, Phase 2, open label | 1 group: 10-18 y            | Recruiting     |
| 32        | ChiCTR2000030/138/24 Feb 2020   | Chinese PLA General Hospital, Hainan Medical University, Haikou, Hainan, China | Clinical Trial for Human Mesenchymal Stem Cells in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19) | UC-MSC, NR/NR, IV          | Intervention, phase 2, parallel, randomized, double-blind | 2 groups: Tr: 30 C: 30-16 y | Recruiting     |
| 32        | NCT04273646/14 Feb 2020         | Wuhan Union Hospital, China | Clinical Study of Human Umbilical Cord Mesenchymal Stem Cells in the Treatment of Novel Coronavirus Severe Pneumonia | UC-MSC, 5x 10^9/kg BW/NR, 4x | Intervention, randomized, parallel | 2 groups: Tr: 24, C: 24-16 y | Recruiting     |
| 32        | ChiCTR2000030/30/28 Feb 2020    | Nanjing Second Hospital, Nanjing, Jiangsu, China | Umbilical cord mesenchymal stem cells for the treatment of patients at high risk of novel coronavirus pneumonia (COVID-19): a single-center, prospective, open clinical study | UC-MSC, NR/NR, NR          | Intervention, Phase 1, case series | 1 group: 9-18 y            | Recruiting     |
| 32        | NCT04252118/27 Jan 2020         | Beijing 302 Hospital, China (multi center) | Safety and Efficiency of Mesenchymal Stem Cell in Treating Pneumonia Patients Infected With 2019 Novel Coronavirus | MSC, 3x 10^7/NC, IV d-0-3-6 | Intervention, phase 1, parallel, non-randomized | 2 groups: Tr: 10, C: 10 18-70 y | Recruiting     |
| 32        | NCT04276987/16 Feb 2020         | Ruijin Hospital, China | A Pilot Clinical Study on Aerosol Inhalation of the Exosomes Derived From Allogenic Adipose Mesenchymal Stem Cells in the Treatment of Patients With Novel Coronavirus Pneumonia | Allo-AT-MSC, exosome, 2x 10^9/3 ml aerosol inhalation d1-2-3-4-5 | Intervention, phase 1 | 1 group: 30-18 y | Recruiting     |
| 32        | ChiCTR2000030/44/3 March 2020   | HuBei Shiyian Taihe hospital, Shiyian, HuBei, China | HUMSCs and Exosomes Treating Patients with Lung Injury following Novel Coronavirus Pneumonia (COVID-19) | UG-MSC, 5x 10^9/NCIV-, IV d-1-2-3-4-5 | Intervention, parallel | Not recruiting | Recruiting     |
| 32        | ChiCTR2000030/86/16 March 2020  | The First Hospital of Changsha, Changsa, Hu'nan, China | Open-label observational study of human umbilical cord derived mesenchymal stem cells in the treatment of severe and critical COVID-1 | UC-MSC IV d-0-3-6. Low dose: 10^7/kg BW/2.5 ml, high dose: 2x10^7/kg BW/1.25 ml | Intervention | 2 groups: Low dose: 10 High dose: 10-18 y | Recruiting     |
| 32        | NCT04288102/24 Feb 2020         | Beijing 302 Hospital, China | Clinical study on the efficacy of Mesenchymal stem cells (MSC) in the treatment of severe novel coronavirus pneumonia (COVID-19) | UC-MSC IV d-0-3-6. Low dose: 10^7/kg BW/2.5 ml, high dose: 2x10^7/kg BW/1.25 ml | Intervention, phase 1-2 | 2 groups: Tr: 60 | Recruiting     |
| Trial_ID | Title                                                                 | Withdrawal | Description                                                                 | Inclusion Criteria                                                                 |
|---------|-----------------------------------------------------------------------|------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| NCT043 13322/15 March 2020 | Stem Cells Arabia, Jordan: Treatment of COVID-19 Patients Using Wharton’s Jelly-Mesenchymal Stem Cells | 1 group: 5 18-28 years, 1 group: 5 ≥50 years, 2 group: ≥50 years | Intervention, phase 1, randomized, double blind, parallel | Placebo C: 30 18-70 y |
| ChiCTR2000030 944/18 March 2020 | The 2nd Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China: An open, multi-center, control, exploratory clinical study of human NK cells and UC-MSC transplantation for severe novel coronavirus pneumonia | 2 group: Tr: 10 C: 10, 4-80 y | Intervention, phase 1, randomized, parallel | Not Recruiting |
| ChiCTR2000030 224/26 Feb 2020 | Tongi Hospital, Tongji Medical College, Huzhong University of Science and Technology, Wuhan, Hubei, China: Clinical study of mesenchymal stem cells in treating severe novel coronavirus pneumonia (COVID-19) | C: 8, Cr C: 8, Se: 8, Se C: 18-100 y | Intervention, parallel | Not Recruiting |
| ChiCTR2000039 569/4 Feb 2020 | Xiangyang 1st People’s Hospital, Xiangyang, Hubei, China: Safety and efficacy of umbilical cord blood mononuclear cells conditioned medium in the treatment of severe and critically novel coronavirus pneumonia (COVID-19) and clinical application demonstration | 2 group: Tr= 15 C= 15, 18-80 years | Intervention, parallel, randomized, open label | Not Recruiting |
| ChiCTR2000030 173/24 Feb 2020 | Hu’nan Yuapan Cell Biotechnology Co., Ltd., Changsha, Hunan, China: Key techniques of umbilical cord mesenchymal stem cells for the treatment of novel coronavirus pneumonia (COVID-19) and clinical application demonstration | 2 group: Tr= 30 C= 30, 18-70years | Intervention, parallel, randomized | Not Recruiting |
| ChiCTR2000039 660/7 Feb 2020 | The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang, China: Clinical Study for Human Menstrual Blood-derived Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) | 5 groups: TrA= 18, TrB= 10, TrB2= 10, C= 15, C= 10, 1-99 y | Intervention, parallel, randomized, open label | Recruiting |
| ChiCTR2000030 088/22 Feb 2020 | The Sixth Medical Center of PLA General Hospital, Beijing, China: Umbilical cord Wharton’s Jelly-derived mesenchymal stem cells in the treatment of severe novel coronavirus pneumonia (COVID-19) | 2 group: Tr= 20 C= 20 18-80 y | Intervention, parallel, randomized | Not Recruiting |
| ChiCTR2000030 990/18 Feb 2020 | Institute of basic medicine, Chinese Academy of medical sciences, Beijing, China: Clinical trials of mesenchymal stem cells for the treatment of pneumonitis caused by novel coronavirus (COVID-19) | 2 group: Tr= 60 C= 60 Age range NR | Intervention, parallel, randomized | Recruiting |
| ChiCTR2000030 020/20 Feb 2020 | Second Hospital of University of South China, Hengyang, Hunan, China: The clinical application and basic research related to mesenchymal stem cells to treat novel coronavirus pneumonia (COVID-19) | 1 group: 20 (case series), 18-70 y | Intervention, sequential, non-randomized | Recruiting |
| ChiCTR2000030 261/26 Feb 2020 | Wuji Fifth People’s Hospital, Jiangsu, China: A study for the key technology of mesenchymal stem cells exosomes atomization in the treatment of novel coronavirus pneumonia (COVID-19) | 2 group: Tr= 13 C= 13 Age range NR | Intervention, parallel, randomized | Not Recruiting |
| ChiCTR2000030 580/5 Feb 2020 | Department of Hematology, Tongji Hospital: Severe novel coronavirus pneumonia (COVID-19) patients treated with MSC×ruxolitinib, NR, NR | 2 group: Tr= 35 C= 35 | Intervention, parallel, randomized | Recruiting |
| Study ID   | Date of Registration | Institution (City/Province) | Study Details                                                                 | Intervention                              | Groups | Withdrawal Reason |
|-----------|----------------------|------------------------------|--------------------------------------------------------------------------------|-------------------------------------------|--------|-------------------|
| ChICTR2000029 | 817/14 Feb 2020     | Guangzhou, China             | Clinical Study of Cord Blood Mesenchymal Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) | UCB-NK+UCB-MSC, 5x10^5+5x10^6 –5x E2d 3x10^4+3x10^5 –3x E2d 3x 10^6+3x10^6-1x/wk /NR IV | 3 groups: HD= 20, conventional doses= 20, preventive doses= 20, 18-NR years | Canc by the invest |
| ChICTR2000029 | 816/14 Feb 2020     | Guangzhou, China             | Clinical Study of Cord Blood Mesenchymal Stem Cells in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19) | UCB-MSC, NR/NR IV | 2 groups: Tr= 30, C= 30 18-NR years | Canc by the invest |
| NCT04293692 | 24 Feb 2020 - 3 March 2020 | Guangzhou, China             | Human Umbilical Cord Mesenchymal Stem Cells Treatment for Pneumonia Patients Infected by 2019 Novel Coronavirus | UC-MSC, 0.5x10^6/kg BW/100 ml IV, d-1-3-5-7 | 2 groups: Tr= 0 C= 0 18-75 y | Withdrawn |
| NCT04302519 | 27 Feb-10 March 2020 | Shanghai, China              | Clinical Study of Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells | Dental pulp MSC, 10^6/kg BW/50 ml saline-cell, 50 ml saline, IV, d1-3-7 | 1 group: 24 18-75 y | Not recruiting |
| NCT04315697 | 18-20 March 2020    | Azidus Brasil/ Hospital Vora Cruz São Paulo, Brasil | Exploratory Clinical Study to Assess the Efficacy of Mesenchymal Stem Cell NestCell® to Treat Patients With Severe COVID-19 Pneumonia Safety and Effectiveness of Human embryonic stem cell-derived M cells (GASTem) for Pulmonary Fibrosis Correlated with novel coronavirus pneumonia (COVID-19) | MSC (NestCell®-Celavita), 2x10^7/NR, IV, d=1-3-5-7(7) | 1 group: 66 18-NR years | Not recruiting |
| ChICTR2000031 | 139/22 Maret 2020   | Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital), Wuhan, Hubei, China | Clinical Study of Novel Coronavirus Induced Severe Pneumonia Treated by Dental Pulp Mesenchymal Stem Cells | ESC derived M cells (GASTem), 3x10^6/kg BW/NR, IV, 3x-2x (1wk apart) | 1 group: 20 (case series) 18-80 y | Recruiting |

ChiCTR= Chinese Clinical Trial Registry, UCB-MSC= umbilical cord MSC, NR= not reported, IV= intravenous, NCT= ClinicalTrials.gov, d= day, Tr= treatment, C= control, MSC= mesenchymal stem cell, Allo= allogeneic, AT=MSC= adipose tissue MSC, Co= course, BW= body weight, Canc= cancelled, invest= investigator, NK cell= natural killer cell, Cr= critically severe, Se= severe, UCB= umbilical cord blood, MNC= mononuclear cell, CM= conditioned medium, hu= human, SC= stem cell, E2d= every 2 d, wk= week, ESC= Embryonic stem cell

One of the clinical trials that used MSCs for COVID-19 pneumonia (ChICTR20000299900), which intended to enroll 60 MSC treated subjects and 60 controls [table 1], has published part of the study. This report by Leng et al. [33] enrolled seven MSC treated subjects and three controls and showed promising results in term of clinical recovery and serum cytokine profile. The MSCs were given only once intravenously, 10^6 cells/kg body weight; all of the critically severe, severe, and common type of COVID-19 in the treatment group recovered, while none of the control group, which were all of the severe type, recovered. In the control group, one died, one developed ARDS, and one remains stable. However, the treatment and control groups were unequal in term of their age and severity of the disease. The treatment group consisted of one critically severe, four severe and two common, while the control group consisted of three severe types of COVID-19, which means that the treatment group was more variable compared to the control group. Moreover, the ages of patients were not equal; the control group, who died and the one that developed ARDS, were much older than in the treatment group. The oldest patient in the treatment group, who had a critically severe type, was 65 y old, while the patients in the control group, who died and developed ARDS, were 75 and 74 y old, respectively [33]. A study on 1099 confirmed COVID-19 patients showed that subjects of ≥ 65 y old were more prone to end in ICU, needed mechanical ventilation or death compared to those of at younger ages, which were 49.2%, 32.3, 18.5, and 0% for patients aged ≥ 65, 50-64, 15-49, and 0-14 y old, respectively [34].
cases was 20.6% [33]. AEZ low/negative expression is a property that is supposedly shared by most stem cells, which are undifferentiated cells, as AEZ expression depends on cell differentiation state [36]. The information concerning tissue source, method of isolation and culture, passage or cumulative population doubling are necessary, as they may interfere with MSC quality and properties [15]. The MSCs in Leng et al. study were apparently derived from the umbilical cord, as stated by Zhao that MSCs with Chinese FDA authorization number 2004L04792, 2006L01037, CXSBB1900004 were derived from umbilical cords that were free who were conducted case series, and claimed that 75% of the twelve patients, who were refractory to other experimental therapies, showed recovery of 168 deaths due to confirmed COVID-19, but the results should be interpreted cautiously, and well design randomized clinical trials are needed to get more robust prove.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

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CONCLUSION

Several studies showed that MSCs seemed promising to alleviate inflammation and cytokine storm in severe COVID-19, but the results should be interpreted cautiously, and well design randomized clinical trials are needed to get more robust prove.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.
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