Should mesenchymal stem cell therapy be used in the treatment of COVID-19?

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KEY FINDINGS

There is some short-term benefit from the use of mesenchymal stem cell therapy for severe COVID-19 in a low-quality small randomized controlled trial. This needs further study to confirm benefit and safety.

- In COVID-19, severe disease is attributed to uncontrolled viral replication and cellular destruction, hyperactivity of the inflammatory response (cytokine storm), and hypercoagulability. Mesenchymal stem cell therapy (MSCs) is a relatively novel treatment with broad pharmacological effects, including anti-inflammatory, immunomodulatory, regenerative, pro-angiogenic and anti-fibrotic properties. (1) A recent review showed improved disease-associated parameters in experimental acute respiratory distress syndrome (ARDS). (2)
- We found three studies (one case report and two small clinical trials) reporting the effects of MSC on COVID-19.
- There are 52 registered and ongoing clinical trials to investigate the efficacy and safety of mesenchymal stem cells as treatment for COVID-19.
- Mesenchymal stem cell therapy is not included in any of the existing guidelines for the treatment of COVID-19.

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RESULTS

Liang et al 2020 reported his experience in treating a 65-year old woman with critical COVID-19. Within two days after completing three infusions of human UC-derived MSC, the patient was stable enough to be transferred out of the ICU. Throat swab was negative for the virus after the last infusion.

Leng et al 2020 found that after intravenous injection of MSCs, there was a significant decrease in serum pro-inflammatory cytokine TNF-α and a significant increase in anti-inflammatory cytokine IL-10 ($p<0.05$). The serum levels of chemokines like IP-10 and growth factor VEGF were both increased, though not significantly. All 7 patients in the intervention group recovered or were discharged from the hospital in 1-3 days after MSC infusion, while in the control group, one died, one had ARDS, and one had stable severe disease.

Shu et al described that none of 12 patients given hUC-MSC had clinical deterioration, while 4 of the 29 in the control group deteriorated and three of them died. There was a significantly shorter length of hospital stay (around 50% reduction in hospital days, $p<0.006$) in the hUC-MSC group, in both <65 years and ≥65 years old groups. On Day 7 post-infusion, 58% of the hUC-MSC group had symptom relief and 66% were off oxygen supplementation compared to 3.5% and 10.34%, respectively, in the control group ($p=0.02$ and $p=0.002$, respectively). In hUC-MSC treatment group, clinical symptoms of weakness and fatigue, shortness of breath, and low oxygen saturation improved beginning on the third day of stem cells infusion, and reached a significant difference on day 7 ($p=0.02$). Reduction in CRP and IL-6 and increase in lymphocyte count were significant beginning at Day 3 post-infusion and improvement in oxygen saturation significant from Day 7 post-infusion ($p<0.001$). Resolution of lung inflammation seen on CT imaging was also faster. However, over-all clinical improvement and mortality were not significantly different between the MSC and the control groups on Day 28.

Leng et al did not observe any infusion reactions or hypersensitivity during the course of hospitalization. Liang and Shu did not report the presence or absence of any adverse reactions during the short observation period of two weeks.

CONCLUSION

Based on low-quality evidence, it appears that human umbilical cord blood-derived MSC, given to severe and critical COVID-19 patients after failure to improve with standard treatment, has beneficial effects in terms of earlier onset of clinical improvement. However, 28-day clinical improvement and mortality are not significantly different compared to standard treatment. There is no reported adverse reaction.

The efficacy and safety of MSC for COVID-19 need to be confirmed through randomized controlled trials; several of which are ongoing.

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Table 1. Characteristics of included studies

No.	Title/Author	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes	Key findings
1	Shu et al 2020 Treatment of Severe COVID-19 with human Umbilical Cord Mesenchymal Stem Cells	RCT, open-label	China	Confirmed COVID-19 with severe disease* whose symptoms were not alleviated after 7-10 days of standard therapy Exclusion: any kind of cancer, severe liver disease, known allergy or hypersensitivity to hUC-MSCs, and other conditions that the clinician deems inappropriate to participate.	Human umbilical cord mesenchymal stem cells infusion group, 2 x 10^6 cells/kg weight over an hour (hUC-MSCs group) and standard therapy, n=12	Standard therapy, n=29	Death, 28-day Worsened to critical Median time to clinical improvement, days Days to clinical improvement Age <65 years Age >65 years Day 7 Symptom relief Without Oxygen supplement D28 clinical improvement	0/12 (hUC) vs 3/29 (10.34%) 0/12 (hUC) vs 4/29 (13.79%) 9 (hUC) vs 14 days P=0.006 6 (3,7) vs 12 (7.25, 15.5) days 13 (11.75,14) vs 23 (18.5, 29) days 58.33% vs 3.45%, p=0.02 66.67% vs 10.34% p=0.002 100% vs 86.21%, p=0.32
2	Liang B 2020 Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells	Case report	China	Critical COVID-19 with multi-organ failure	Standard treatment pre-hUCMSC** Plus allogenic hUCMSCs produced under GMP condition administrated intravenously for three times (5×107cells each time) on D12, 15, 18 illness	none	ICU confinement Virus detection	Transferred out of ICU and negative virus on swab on D20 of illness
3	Leng Z 2020 Transplantation of ACE2-Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-	Non-randomized trial	China	10 patients with confirmed COVID-19 with no response to standard therapy Excluded- cancer, critical COVID, participation in clinical trial within 3 months	Standard therapy plus MSc 1 × 106 cells/ kilogram of weight infused in 40 min, n=7 patients 1-Critically severe 4-severe 2- common	Standard therapy, placebo infusion n=3 severe COVID	primary safety data (infusional and allergic reactions, secondary infection and life-threatening adverse events) and the primary efficacy data (the level of the cytokines variation, the level of C-reactive protein in plasma and the oxygen	No infusion reactions in all. After intravenous injection of MSCs, the decrease ratio of serum pro-inflammatory cytokine TNF-α before and after MSC treatment was significant ($p<0.05$). Meanwhile, the increase ratio of anti-inflammatory IL-10 ($p<0.05$) also showed remarkably in the MSC treatment group. The serum

	19 Pneumonia						saturation). The secondary efficacy outcomes mainly included the total lymphocyte count and subpopulations, the chest CT, the respiratory rate, and the patient symptoms	levels of chemokines like IP-10 and growth factor VEGF were both increased, though not significantly. All 7 patients recovered/discharged in 1-3 days after MSc infusion while in control group, 1 died, 1 had ARDS, 1 stable severe.

*Severe COVID-19: any of the following-(a) respiratory distress, respiration rate (RR) ≥ 30 times / min; (b) the oxygen saturation ≤ 93% in the resting state; (c) PaO2 / FiO2 ≤ 300 mmHg (1mmHg = 0.133 kPa).
** lopinavir/ritonavir, IFN- α inhalation and oseltamivir (oseltamivir given only once), and IV moxifloxacin, Xuebijing, methylprednisolone, and immunog

Table 2. Characteristics of clinical trials

No.	Clinical Trial ID / Title	Status	Start and estimated primary completion date	Study design	Country	Population	Intervention Group(s)	Comparison Group(s)	Outcomes
1	ChiCTR2000030173	Not Recruiting	2/17/2020 - 4/17/2020	Interventional study (Parallel)	China	Patients with signs and symptoms and confirmed COVID-19; informed consent	Umbilical cord mesenchymal cells (Nt=30)	Conventional treatment (Nc=30)	pulmonary function;Novel coronavirus pneumonic nucleic acid test
2	ChiCTR2000030116	Recruiting	2/01/2020 - 8/31/2020	Interventional study (Dose comparison)	China	Patients 5-7 days in the ICU, with ARDS needing intubation, primary disease caused by NCoV infection; imaging shows bilateral lung lesions, informed consent	Different stem cell doses	Different stem cell doses	Time to leave ventilator on day 28 after receiving MSCs infusion
3	ChiCTR2000030138	Not Recruiting	2/24/2020 - 5/31/2020	Interventional study (Parallel)	China	Patients with confirmed COVID-19 (RT-PCR and imaging of pneumonia); informed consent	Intravenous hUCMSC	Routine treatment + placebo	Clinical index
4	ChiCTR2000030088	Not Recruiting	3/01/2020 - 12/31/2020	Interventional study (Parallel)	China	Confirmed critical cases of NCoV pneumonia	Wharton's Jelly mesenchymal stem cells ($1x10^6$/kg)	Saline	nucleic acid of the novel coronavirus is negative;CT scan of ground glass shadow disappeared
5	ChiCTR2000030020	Recruiting	February 6, 2020 to February 5, 2022	Case Series	China	Confirmed critical cases of NCoV pneumonia or COVID suspect based on panel	Mesenchymal stem cell therapy	--	Coronavirus nucleic acid markers negative rate (primary); trough and peak of FEV1 (secondary)
6	ChiCTR2000029990	Recruiting	January 1, 2020 to March 31, 2020	Interventional study (Parallel)	China	Patients with confirmed COVID-19 (RT-PCR and imaging of pneumonia); moderate to severe cases of NCoV pneumonia ; informed consent	Mesenchymal stem cell	Saline	Improved respiratory system function (blood oxygen saturation) recovery time (primary)

7	ChiCTR2000030261	Not Recruiting	February 28, 2020 to May 31, 2020 to	Interventional study (Parallel)	China	Patients with confirmed COVID-19 (symptoms, RT-PCR, exposure within 14 days from symptoms onset)	Inhaled mesenchymal stem cell exosomes	--	Lung CT (primary), nucleic acid, Leukocytes and lymphocytes in blood routine (secondary)
8	ChiCTR2000029580	Recruiting	January 1, 2020 to December 31, 2020	Interventional study (Parallel)	China	Confirmed critical cases of NCoV pneumonia or COVID suspect; informed consent	Ruxolitinib combined with mesenchymal stem cell	Routine treatment	safety
9	ChiCTR2000030866	Recruiting	February 1, 2020 to December 31, 2020	Open-label, observational study	China	Confirmed critical cases of NCoV pneumonia or COVID suspect; informed consent	Intravenous infusion of MSC based on conventional treatments	--	Mortality in serious and critical patients (primary)
10	ChiCTR2000030835	Recruiting	February 14, 2020 to February 14, 2021	Single arm interventional study	China	Confirmed critical cases of NCoV pneumonia. Severe pneumonia. Informed consent	Routine Treatment plus High dose MSC ($2x10^6$/kg per infusion)	Routine Treatment + Low dose MSC ($1x10^6$/kg per infusion)	Serious Adverse Events (primary) DRP (secondary)
11	ChiCTR2000030224	Not Recruiting	February 14, 2020 to May 31, 2020	Interventional study (Parallel)	China	Critical and severe patients	mesenchymal stem cells	Nomral saline	SP02;lesions of lung CT;temperature;Blood routine;Inflammatory biomarkers;
12	ChiCTR2000031319	Not Recruiting	April 1, 2020 to July 31, 2020	Randomized Clinical Trial	China	Patients with confirmed COVID-19 (symptoms, RT-PCR and imaging of pneumonia); severe cases of NCoV pneumonia ; informed consent	Routine treatment plus IV human dental pulp stem cells	Routine treatment plus placebo	TTCI
13	ChiCTR2000031430	Recruiting	March 14, 2020 to December 31, 2021	Non-randomized case control study	China	Patients with confirmed COVID-19. High-resolution CT indicates interstitial injures in the lungs (honeycomb shadows or grid shadows). Informed consent	Conventional treatment regimen plus MSC treatment	Conventional treatment regimen	Electrocardiogram;St George's Respiratory Questionnaire Score;High resolution CT for chest;Blood gas analysis;Percutaneous blood oxygen saturation;6 min walking distance;Pulmonary function VCmax;Blood routine;Liver and kidney function;Cytokine analysis;Immunoglobulin;Lymph ocyte subsets;Coagulation;Myocardial enzymes;Serum ferritin;Procalcitonin;IL-6;Lactic acid;D-Dimer;CRP;
14	EUCTR2019-002688-89-ES	Ongoing	July 26, 2019-July 26, 2020	Phase I/II randomized control	Spain	Patients with moderate to severe ARDS. With invasive mechanical ventilation (included COVID-19 patients)	HCR040, a drug whose active substance is HC016	placebo	Adverse events, average stay in ICU (primary)

							(allogeneic adipose-derived adult mesenchymal stem cells)		
15	EUCTR2020-001682-36-ES	Ongoing	April 14, 2020-April 14, 2021	Double-blind, placebo-controlled phase I/II	Spain	Patients with SARS-CoV-2 infection confirmed by molecular testing. Admitted to ICU for severe pneumonia..	allogeneic mesenchymal stem cells (MSV®-allo)	placebo	Proportion of patients in whom removal of invasive mechanical ventilation has been achieved in less than 7 days after IMP administration. Survival rate at Day 28. (primary) 1. Time to recovery after MSV-allo administration 2. Time to normal imaging 3. Modification in the inflammatory response (labs) 4. Modification in leukocytes and lymphocyte populations. 5. Safety, tolerability and immunogenicity profiles
16	EUCTR2020-001266-11-ES	Ongoing	April 16, 2020-April 16, 2021	Two-center, randomized, control	Spain	Patients with COVID-19 (by RT-PCR) in respiratory failure requiring intubation and mechanical ventilation	Allogeneic mesenchymal stromal cells isolated from adipose tissue	Placebo	Survival rate at Day 28. Days to normalization of body temp. Days until patient was extubated. and laboratory (primary). Days of ICU/hospitatlization/oxygen therapy. Improvement of other clinical and analytical parameters.
17	IRCT20140911019125N6	Recruiting	April 4, 2020-July 10, 2020	Phase II clinical trial without control group, community based, not blinded, Non-randomized control	Iran	Patients with COVID-19 pneumonia	Conventional medications plus dental pulp mesenchymal stem cells	--	Pulmonary condition, RNA expression of COVID19 virus, Lymphocytes count, Study of clinical signs on Days 14 and 28.
18	IRCT20140528017891N8	Not Recruiting	March 24, 2020-April 13, 2020	Phase III, parallel randomized controlled, double blind	Iran	Patients with acute form of COVID-19 infection who are confirmed by RT-PCR and HRCT	Routine medication plus initial dose of 0.5–1 million / kg of mesenchymal stem cells on Days 1, 3 and 6 (3 doses)	Routine medication plus placebo	Death, Pneumonia severity index, Oxygen index, C reactive protein, Procalcitonin, Lymphocyte count, CD3 +, CD4 + and CD8 + T cells count, Improved pneumonia using CT scan up to Day 28
19	IRCT20200325046860N2	Trial ended	March 28, 2020-April 29, 2020	Phase I	Iran	Patients with confirmed COVID-19 and pneumonia (symptoms, chest CT) . No improvement in next 48 hours.	Conventional medications plus mesenchymal stem cells on	Conventional medications plus placebo	Respiratory function of patients (every 24 hours after MSC infusion)

							Days 1, 3 and 6 (3 doses)		
20	IRCT20200217046526N1	Trial ended	March 15, 2020- April 25, 2020	Phase I and II, non-controlled non-randomized	Iran	Confirmation of 2019-nCoV infection by RT-PCR Diagnosis of ARDS. Pneumonia via symptoms and imaging. Mild to Moderate 2019-nCoV pneumonia/ stay in the ICU <48 hours SOFA score between 2-3 point	Conventional medications plus mesenchymal stem cells on Days 1, 3 and 6 (3 doses)	--	Adverse events assessed 24 hours after each intervention, on days 6, 7, 14 and 28 after the first intervention.
21	EUCTR2020-001364-29	Ongoing	4/20/2020	Phase I/II	Spain	Severe COVID-19 pneumonia	Allogenic adipose tissue-derived mesenchymal stem cells (2 doses)	Hydroxychloroquine + Azithromycin or Lopinavir / ritonavir + Interferon β-1b + Hydroxychloroquine))	Adverse Events and Serious Adverse Events. Reduction of the SARS-CoV-2 viral load by PCR on days 6 and 15.Mortality at day 15, 28. Proportion of patients in categories 5, 6 or 7 of the ordinal scale of 7 points on days 15 and 28 days. Proportion of patients needing rescue therapy (Tocilizumab, corticosteroids, or therapies under investigation in clinical trials). Time to get an improvement in a category since admission to the ordinal scale.
22	NCT04315987 HOPE	Not yet recruiting	Apr-20 Jun-20	Single Group Assignment, Open Label	Sao Paulo, Brazil	COVID-19 Pneumonia	NestCellÂ®	none	Change in Clinical Condition Rate of mortality within 10-days Change of Clinical symptoms - respiratory rate Hypoxia, PaO2 / FiO2 ratio CD4+ and CD8+ T cell count Changes of blood oxygen Side effects in the treatment group Complete blood count, cardiac, hepatic and renal profiles
23	NCT04252118 2020003D	Recruiting	January 27, 2020 Dec- 21	Non-Randomized Open Label	Beijing, China	COVID-19	MSCs	none	Size of lesion area by chest radiograph or CT Side effects in the MSCs treatment group Improvement of Clinical symptoms including duration of fever and respiratory Time of nucleic acid turning negative Rate of mortality within 28-days

									CD4+ and CD8+ T celll count, Alanine aminotransferase C-reactive protein|Creatine kinase
24	NCT04366323 AdiQure/COVID-19	Not yet recruiting	Apr-20 Oct -21	Randomized Parallel Assignment Open Label		Sars-CoV2	allogeneic and expanded adipose tissue-derived mesenchymal stem cells		Safety of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Adverse Event Rate Efficacy of the administration of allogeneic mesenchymal stem cells derived from adipose tissue assessed by Survival Rate
25	NCT04313322 COVID-19	Recruiting	March 16, 2020 Sep 30 2020	Single Group Assignment Open Label	Amman, Jordan	Use of Stem Cells for COVID-19 Treatment	WJ-MSCs	none	Clinical outcome CT Scan RT-PCR results
26	NCT04336254 2020K-G005|hDPSC-CoVID-2019-02-2020	Recruiting	April 6, 2020 March 31, 2021	Randomized Parallel Assignment Masking: Triple blind	Wuhan, Hubei, China	COVID-19	allogeneic human dental pulp stem cells (BSH BTC & Utooth BTC)|	Intravenous saline injection (Placebo)	TTCI Lung lesion Immune function Time of SARS-CoV-2 clearance Blood test, SPO2, C-reactive protein (mg/L) RR, Body temperature Side effects in the treatment group
27	NCT04288102 2020-013-D	Recruiting	March 5, 2020 July 31, 2020	Randomized Parallel Assignment Masking: Quadruple blind	Wuhan, Hubei, China	Corona Virus Disease 2019(COVID-19)	MSCs	Saline containing 1% Human serum albumin	Size of lesion area and severity of pulmonary fibrosis by chest CT mMRC (Modified Medical Research Council) dyspnea scale Oxygenation index(PaO2/FiO2) Duration of oxygen therapy(days) Duration of hospitalization(days) Blood oxygen saturation CD4+ T cell count and cytokine level Side effects in the MSCs treatment group

									6-minute walk test, Maximum vital capacity (VCmax), Diffusing Capacity (DLCO)
28	NCT04346368 SC-2020-01	Not yet recruiting	Apr-20 Dec-20	Randomized Parallel Assignment Masking: Single (Participant)	Guangzhou, Guangdong, China	Coronavirus Disease 2019 (COVID-19)	BM-MSCs	Placebo	Changes of oxygenation index (PaO2/FiO2) Side effects in the BM-MSCs treatment group Clinical outcome, Hospital stay CT Scan Changes in viral load Changes of CD4+, CD8+ cells count and concentration of cytokines, Changes of C-reactive protein Rate of mortality within 28-days
29	NCT04273646 202001	Not yet recruiting	April 20, 2020 Feb 15, 2022	Randomized Parallel Assignment Open Label	Wuhan, Hubei, China	2019 Novel Coronavirus Pneumonia|COVID-19	UC-MSC	Placebo	Pneumonia severity index Oxygenation index (PaO2/FiO2) Side effects in the UC-MSCs treatment group 28-days survival Sequential organ failure assessment C-reactive protein, Procalcitonin, Lymphocyte count,CD3+, CD4+ and CD8+ T celll count, CD4+/CD8+ratio
30	NCT04348435 Allogeneic COVID-19 Protection	Enrolling by invitation	April 23, 2020 April 30, 2021	Randomized Parallel Assignment Masking: Quadruple blind	Texas, United States	COVID-19	HB-adMSCs	Placebos	Incidence of hospitalization for COVID-19 Incidence of symptoms associated with COVID-19 Absence of upper/lower respiratory infection Laboratory tests, inflammatory markers Cytokine levels- TNF alpha, IL-6, IL-10 SF-36, PHQ-9
31	NCT04366063 991919|IRCT20200217046526N2	Recruiting	April 5, 2020 December 10, 2020	Randomized Parallel Assignment Open Label	Tehran, Iran	Covid-19	Cell therapy		Adverse events assessment Blood oxygen saturation Intensive care unit-free days Clinical symptoms Respiratory efficacy

									Biomarkers concentrations in plasma
32	NCT04382547 IBCE_MSC2(Covid)	Not yet recruiting	May 11, 2020 June 30, 2021	Non-Randomized Parallel Assignment Open Label	Minsk, Belarus	COVID|Covid-19|Coronavirus|Pneumonia|Pneumonia Viral|Pneumonia, Interstitial|Sars-CoV2	Allogenic pooled olfactory mucosa-derived mesenchymal stem cells	Standard treatment according to the Clinical protocols	Number of cured patients Number of patients with treatment-related adverse events
33	NCT04339660 Pr20200402	Recruiting	February 1, 2020 June 30, 2020	Randomized Parallel Assignment Masking: Triple blind	Wuhan, Hubei, China	COVID-19	UC-MSCs	Placebo	Cytokine levels- TNF, IL-1, IL-6, TGF, IL-8, TGF-beta CRP, Peripheral blood count Blood oxygen saturation Rate of mortality within 28-days Size of lesion area by chest imaging CD4+ and CD8+ T cells count Recovery time Duration of respiratory symptoms (fever, dry cough, difficulty breathing, etc.) COVID-19 nucleic acid negative time
34	NCT04349631 Protection Against COVID-19	Enrolling by invitation	May 7, 2020 Dec 31, 2020	Single Group Assignment Open Label	Texas, United States	COVID-19	HB-adMSCs	none	Incidence of hospitalization for COVID-19 Incidence of symptoms for COVID-19 absence of upper/lower respiratory infection Laboratory tests Cytokine levels- TNFalpha, IL-6, IL-10 C-reactive protein SF-36, PHQ-9
35	NCT04352803 COVID-MSCIV	Not yet recruiting	Apr-20 Apr-26	Non-Randomized Sequential Assignment Open Label		Covid-19 Pneumonia|Cyotokine Storm	Autologous Adipose MSC's	none	Safety - Incidence of unexpected adverse events Efficacy - Frequency of progression to mechanical ventilation, Changes in length of mechanical ventilation, Changes in length of weaning of mechanical ventilation, Changes in length of hospital stay, Changes in mortality rate

36	NCT04302519 KT005HB001	Not yet recruiting	March 5, 2020 July 30, 2021	Non-randomized Single Group Assignment Open Label		COVID-19	Dental pulp mesenchymal stem cells	none	Disappearance time of ground-glass shadow in the lungs Absorption of Lung shadow absorption by CT Scan-Chest Changes of blood oxygen
37	NCT04355728 20200370	Recruiting	April 25, 2020 May 1, 2021	Randomized Parallel Assignment Masking: Single (Outcomes Assessor)	Miami, Florida, United States	Corona Virus Infection|ARDS|ARDS, Human|Acute Respiratory Distress Syndrome|COVID-19	Umbilical Cord Mesenchymal Stem Cells	Standard of Care	Incidence of pre-specified infusion associated adverse events Incidence of Severe Adverse Events Survival rate after 90 days post first infusion Ventilator-Free Days|Change in Oxygenation Index (OI) Plat-PEEP Sequential Organ Failure Assessment (SOFA) Scores Small Identification Test (SIT) scores Troponin I levels|C-Reactive Protein levels|Arachidonic Acid (AA). Eicosapentaenoic Acid (EPA) Ratio, D-dimer levels, 25-Hydroxy Vitamin D levels, Alloantibodies levels, Blood white cell count, Platelets count
38	NCT04371601 MSC-CoViD-2020	Active, not recruiting	March 1, 2020 Dec 31, 2022	Randomized Parallel Assignment Open Label	Fujian, China	COVID-19 Pneumonia	Oseltamivir Hormones Oxygen therapy mesenchymal stem cells		Changes of oxygenation index (PaO2/FiO2) ,blood gas Detection of TNF-Î± levels, IL-10 levels Detection of immune cells that secret cytokines, including CXCR3+, CD4+, CD8+, NK+ cells, and regulatory T cells (CD4 + CD25 + FOXP3 + Treg cells). Changes of c-reactive protein and calcitonin
39	NCT04366271 MESCEL-COVID19|2020-001450-22	Recruiting	May 7, 2020 May 31, 2021	Randomized Parallel Assignment Open Label	Madrid, Spain	COVID	Mesenchymal cells	Standard of care	Mortality due to lung involvement due to SARS-CoV-2 virus infection at 28 days of treatment 440Mortality due to lung involvement due to SARS-

									CoV-2 virus infection at 14 days of treatment Mortality from any cause at 28 days Days without mechanical respirator and without vasopressor treatment for 28 days Patients alive without mechanical ventilation and without vasopressors on day 28 Patients alive and without mechanical ventilation on day 14, day 28 Patients alive and without vasopressors on day 28 Days without vasopressors for 28 days Patients cured at 15 days Incidence of Treatment-Emergent Adverse Events
40	NCT04293692 Pr20200225	Withdrawn	February 24, 2020 February 25, 2020	Randomized Parallel Assignment Masking: Triple blind	Wuhan, Hubei, China	COVID-19	UC-MSCs	Placebo	Size of lesion area by chest imaging Blood oxygen saturation Rate of mortality within 28-days Sequential organ failure assessment Side effects in the UC-MSCs treatment group Electrocardiogram, the changes of ST-T interval mostly Concentration of C-reactive prote Immunoglobulin, CD4+ and CD8+ T cells count Concentration of the blood cytokine (IL-1Î², IL-6, IL-8,IL-10,TNF-Î±), Concentration of the myocardial enzymes
41	NCT04362189 Allogeneic Treatment COVID-19	Not yet recruiting	May 15, 2020 October 31, 2020	Randomized Parallel Assignment	Houston, Texas, United States	COVID-19	HB-adMSC	Placebo	28-day mortality Invasive mechanical ventilation Leukocyte differential, C Reactive protein

				Masking: Quadruple blind					TNF alpha, IL-6 Blood chemistry NK cell surface antigen (CD3-CD54+) CD4+/CD8+ ratio IL-10, VEGF, D-dimer, Myoglobin, Troponin, Creatinine kinase, Serum ferritin
42	NCT04377334 RESCOVID	Not yet recruiting	May-20 Feb-21	Randomized Parallel Assignment Open Label	Tuebingen, Germany	ARDS|COVID-19	MSC		lung injury score D-dimers, phenotype, pro-resolving lipid mediators cytokines|chemokines Survival, extubation, lymphocyte subpopulations SARS-CoV-2-specific antibody titers Complement molecules (C5-C9)
43	NCT04348461 BALMYS-19	Not yet recruiting	April 6, 2020 September 30, 2020	Randomized Parallel Assignment Masking: Quadruple blind		COVID|Respiratory Distress Syndrome	Allogeneic and expanded adipose tissue-derived mesenchymal stromal cells		Efficacy- Survival Rate Safety- Adverse Event Rate
44	NCT04371393 GCO 08-1078-0014	Recruiting	April 30, 2020 Apr-22	Randomized| Parallel Assignment Masking: Triple blind	United States	Mesenchymal Stromal Cells Remestemcel-L	Remestemcel-L	Placebo	Number of all-cause mortality Number of days alive off mechanical ventilatory support Number of adverse events Number of participants alive at day 7, 14, 60, 90 Number of participants with resolution and/or improvement of ARDS Change from baseline of the severity of ARDS Length of stay Clinical Improvement Scale Change in serum hs-CRP, IL-6, IL-8, TNF-alpha

45	NCT04345601 H-47561 MSC for COVID-19	Not yet recruiting	May-20 Feb-22	Single Group Assignment Open Label	Houston, Texas, United States	Sars-CoV2 Acute Respiratory Distress Syndrome COVID-19	Mesenchymal Stromal Cells	none	Incidence of unexpected adverse events Improved oxygen saturations Decrease in oxygen supplementation by non-invasive or invasive interventions Frequency of progression to mechanical ventilation or ECMO Duration of mechanical ventilation, ICU stay, hospital stay All-cause mortality at day 28
46	NCT04361942 TerCel_007|2020-001682-36	Recruiting	Apr-20 December 31, 2020	Randomized Parallel Assignment Masking: Triple blind	Valladolid, Spain	COVID-19 Pneumonia	Mesenchymal Stromal Cells	Placebo	Proportion of patients who have achieved withdrawal of invasive mechanical ventilation Rate of mortality Proportion of patients who have achieved clinical response Proportion of patients who have achieved radiological responses
47	NCT03042143 16154DMcA-AS	Recruiting	January 7, 2019 Oct-22	Randomized Parallel Assignment Masking: Quadruple blind	Belfast, Northern Ireland, United Kingdom	Acute Respiratory Distress Syndrome	Human umbilical cord derived CD362 enriched MSCs:	Placebo (Plasma-Lyte 148)	Oxygenation index (OI) Incidence of Serious Adverse Events (SAEs) Oxygenation index|Sequential Organ Failure Assessment (SOFA) score Respiratory compliance (Crs) Partial pressure of arterial oxygen to the fraction of inspired oxygen ratio (P/F ratio) Driving Pressure|Extubation and reintubation Ventilation free days at day 28 Length of ICU and hospital stay 28-day and 90-day mortality
48	NCT04269525 2020002	Recruiting	February 6, 2020	Single Group Assignment Open Label	Wuhan, Hubei, China	Pneumonia, Viral|Pneumonia, Ventilator-Associated	UC-MSCs	none	Oxygenation index 28 day mortality|Hospital stay

			September 30, 2020						2019-nCoV nucleic acid test Improvement of lung imaging examinations White blood cell count,Lymphocyte count, Lymphocyte percentage Procalcitonin interleukin(IL)-2,IL-4IL-6IL-8, IL-10 Tumor necrosis factor(TNF), interferon(IFN)
49	NCT04333368 APHP200395|2020-001287-28	Recruiting	April 6, 2020 July 31, 2021	Randomized Parallel Assignment Masking: Triple blind	Paris, France	Severe Acute Respiratory Syndrome Coronavirus 2 Severe Acute Respiratory Distress Syndrome	Umbilical cord Wharton's jelly-derived human	NaCl 0.9%	Respiratory efficacy evaluated by the increase in PaO2/FiO2 ratio from baseline to day 7 in the experimental group compared with the placebo group Lung injury score, Oxygenation index In-hospital mortality, Total mortality Ventilator-free days Number of days between randomization and the first day the patient meets weaning criteria o Number of days between randomization and the first day the patient meets PaO2/FiO2 > 200 (out of a prone positioning session) Cumulative use and duration of sedatives Cumulative use & duration of neuromuscular blockers ICU-acquired weakness and delirium Treatment-induced toxicity & adverse events up to day 28 Quality of life at one year (EQ5D-3L) Measurements of plasmatic cytokines (IL1, IL6, IL8, TNF-alpha, IL10, TGF-beta, sRAGE, Ang2) level

									Anti-HLA antibodies plasmatic dosage
50	NCT04299152 2020-TH-001	Not yet recruiting	May 10, 2020 November 10, 2020	Randomized Parallel Assignment Masking: Single (Care Provider)		Severe Acute Respiratory Syndrome (SARS) Pneumonia	Stem Cell Educator-Treated Mononuclear Cells Apheresis		Determine the number of Covid-19 patients who were unable to complete SCE Therapy Examine the percentage of activated T cells after SCE therapy by flow cytometry Assess the percentage of Th17 cells by flow cytometry Chest imaging changes by computed tomography (CT) scan of the chest Quantification of SARS-CoV-2 viral load (real time RT-PCR)
51	NCT04341610 EudraCT number: 2020-001330-36	Not yet recruiting	April 20, 2020 April 30, 2021	Randomized Parallel Assignment Masking: Quadruple blind	Copenhagen, Denmark	Respiratory Tract Diseases	Stem Cell Product		Changes in clinical critical treatment index Days of respirator treatment|Improvement of clinical symptoms including duration of fever and respiratory need Mortality CD4+ and CD8+ T cell count, Cytokine profile C-reactive protein , leucocyte Glomerular Filtration Rate, Duration of hospitalization
52	NCT04276987 MEXCOVID	Not yet recruiting	February 15, 2020 July 31, 2020	Single Group Assignment Open Label		Coronavirus	MSCs-derived exosomes	none	Adverse reaction (AE) and severe adverse reaction (SAE) Time to clinical improvement (TTIC) Number of patients weaning from mechanical ventilation Duration (days) of ICU monitoring Duration (days) of vasoactive agents usage Duration (days) of mechanical ventilation supply Number of patients with improved organ failure Rate of mortality

Last Updated: 13/May/2020