Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Promising impacts of mesenchymal stem cell therapy in treatment of SARS-CoV-2 (COVID-19)

Masoud Khorshidi, Ph.D.[a,b], Meysam Zarezadeh, Ph.D.[c,d,**], Mohammadreza Emami, M.Sc.[e], Beheshteh Olang, MD, Ph.D[b], Omid Moradi Moghaddam, MD, FCCM[f,*]

[a] Student Research Committee, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran
[b] Pediatric Gastroenterology, Hepatology and Nutrition Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Clinical Nutrition, Nutrition Research Center, School of Nutrition and Food Science, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[e] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[f] Trauma and Injury Research Center, Critical Care Medicine Department, Iran University of Medical Sciences, Tehran, Iran

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To the Editor

A novel coronavirus named COVID-19 has begun to spread in Wuhan, China from December 2019 and become a global health concern.[1] Individuals with underlying diseases are at greater risk and more prone to be critically ill in case of infection so that mortality rate is 49% in subjects entering intensive care units.[2] It has been reported that critically ill COVID-19 patients remarkably have elevated levels of pro-inflammatory cytokines including IL-6, G-CSF, IP10, MCP1, MIP1A, and TNFα, contributing to outbreak of cytokine storm.[3] These turn of events lead to acute respiratory distress syndrome and ultimately maybe death[2] and glucocorticoids were not efficient in reducing rate of mortality.[4]

It has been suggested that mesenchymal stem cell (MSC) transplantation could be considered as a beneficial approach in treatment many disease. MSC exerts its positive impacts through immunomodulation and differentiation stimulation.[5] It has proposed that pathogen molecules such as double-stranded RNA in virus is able to increase induction of toll-like receptors (TLRs) on MSC resulting in manifestation of immunomodulatory effects of MSC.[6] Darwish et al. demonstrated that MSC is potentially able to treat H5N1 infection which has a cytokine profile similar to COVID-19.[7] The mechanisms of action of MSC on COVID-19 treatment schematically are shown on Fig. 1.

Therefore, MSC therapy potentially could be considered as an efficacious and safe treatment approach in COVID-19-induced pneumonia. In this regard, Leng et al. recently demonstrated that with perfusion of 1×10^6 cells per kilogram of weight, almost all the clinical symptoms such as fever, breath shortness, and low oxygen saturation disappeared and the inflammation levels were relieved 2-4 days after MSC transplantation.[8] Moreover, in a critically ill 65 years old woman, MSC transplantation with 5×10^7 cells three times resulted in significant decrease in CRP and increase in CD3+, CD4+ and CD8+ T cells to the normal ranges. Also, CT images implied to remarkable relieve in pneumonia.[9] Furthermore, there are 30 registered studies investigating MSC therapy on COVID-19 to explore whether MSC transplantation could be able to shed the light in COVID-19 treatment. A summary of characteristics of registered studies are presented in Table 1.

Author contribution

Masoud Khorshidi: Conceptualiation, Investigation, Methodology, Software, Visualization; Meysam Zarezadeh: Data curation, Investigation, Validation, Visualization, Writing - original draft, Writing - review and editing; Mohammadreza Emami: Data curation, Visualization; Beheshteh Olang: Data curation, Visualization, Validation; Omid Moradi Moghaddam: Conceptualization, Project administration, Supervision, Visualization.

* Corresponding author at: Trauma and Injury Research Center, Critical Care Medicine Department, Iran University of Medical Sciences, Shahid Hemmat Highway, Tehran, Iran.
** Corresponding author at: Ph.D. of Nutritional Sciences, School of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Attar-Neishaburi St., Golgasht Alley, Azadi Blvd., Tabriz, Iran.
E-mail addresses: zarezadehm@tbzmed.ac.ir (M. Zarezadeh), moradimoghadam@yahoo.com (O.M. Moghaddam).

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Table 1
Characteristics of registered studies investigating the effect of stem cell therapy on COVID-19 outcomes.

	Applicant and registry number	Study design	Country	Disease	Sample size	Age (year)	Duration	Intervention	Outcomes
1	Cao Yang ChiC TR2000029580	RCT	China	COVID-19 with severe pneumonia	70	18-75	NR	G1: Ruxolitinib + MSC G2: SCT	Safety, efficacy, improvement rates at 7-days and 1-month, pulmonary function, long-term disability rates and quality of life
2	Huang Guoxin ChiC TR2000029569	RCT	China	Severe and critical type of COVID-19	30	≥18	NR	G1: SCT G2: MSC + SCT	PSI, arterial blood gas analysis, mortality, hospitalization day
3	Charlie Xiang ChiC TR2000029606	RCT	China	COVID-19 pneumonia	63	1-99	NR (IV infusion)	G1: MSC + SCT G2: SCT G3: SCT + Artificial liver therapy G4: SCT + MSC + Artificial liver therapy G5: SCT	Mortality, improvement rate, incidence of shock and multiple organ failure, days in hospital and ICU, ventilation modes and parameters
4	Fu-Sheng Wang *NCT04252118*	Non-RCT	China	COVID-19 pneumonia	40	18-70	180 days (IV infusion at Day 0, Day 3, Day 6)	G1: MSC + SCT G2: SCT	Size of chest lesion by CT, side effects, 28 day mortality rate, CD4+ and CD8+ T cell, CRP, ALT, Creatine kinase
5	Ouyang Qi ChiC TR2000030866	Non-RCT	China	COVID-19 (without severe type)	30	≥18	28 days (IV infusion at Day 0, Day 3, Day 6)	G1: MSC + SCT	Oxygenation index, mortality, total T cells, CD4 + T cells, CD8 + T cells, B cells, NK cells, IL-1β, IL-2, IL-6, IL-10, TNF-α, APACHE II score, D-dimer, CRP, procalcitonin
6	ZhiYong Peng *NCT04269525*	Non-RCT	China	COVID-19 pneumonia	10	18-75	28 days (IV infusion at Day 1, Day 3, Day 5, Day 7)	G1: Umbilical Cord-Derived MSC	Oxygenation index, 28 day mortality, hospital stay, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, γ-IFN
7	Yongxiang Yi ChiC TR2000030300	Non-RCT	China	COVID-19 pneumonia	9	18-75	NR	G1: MSC	Time and rate of coronavirus become negative
8	Tianhe Stem Cell Biotech, Inc. *NCT04299152*	RCT	USA	COVID-19 pneumonia	20	18-60	4 weeks	G1: MSC G2: SCT	Feasibility, activated T cells, Th17, chest CT scan
9	Fu-Sheng Wang *NCT04288102*	RCT	China	COVID-19 pneumonia	60	18-70	28 days (IV infusion at Day 0, Day 3, Day 6)	G1: SCT + MSC G2: SCT + placebo	Improvement in CTI, side effects of the MSC, all-cause mortality, duration of oxygen therapy and hospitalization
10	Ruijin Hospital *NCT04276987*	A Pilot Clinical Trial	China	COVID-19 with severe pneumonia	30	18-75	28 days (aerosol inhalation at Day 1, Day 2, Day 3, Day 4, Day 5)	G1: aerosol inhalation of MSCs-derived exosomes	Adverse reaction, TTIC, duration of mechanical ventilation and ICU monitoring, rate of mortality, CRP, pro-BNP, IL-1β, IL-6, IL-8, IL-2R
11	Robert Chunhua Zhao ChiC TR2000029990	RCT	China	COVID-19 with Pneumonia(moderate to severe)	120	18-95	NR	G1: MSC G2: placebo (saline)	blood oxygen saturation, recovery time
12	CAR-T Biotechnology Co., Ltd. *NCT04302519*	A Pilot Clinical Trial	China	COVID-19 pneumonia	24	18-75	14 days (IV infusion at Day 1, Day 3, Day 7)	G1: MSC	Disappear time of ground-glass shadow in the lungs, changes of blood oxygen
13	Yang Jin *NCT04273646*	RCT	China	COVID-19 with severe pneumonia	48	18-65	12 weeks (IV infusion at Day 1, Day 3, Day 5, Day 7)	G1: SCT + MSC G2: SCT + placebo	Pneumonia severity index, oxygenation index, side effects, 28 day mortality rate, CRP, procalcitonin, CD3+, CD4+ and CD8+ T cell, lymphocyte count
14	Jianjun Li ChiC TR2000030484	RCT	China	COVID-19 pneumonia	90	18-70	NR (IV infusion at Day 1, Day 7)	G1: MSC G2: MSC + exosomes G3: placebo	PaO2 / FiO2 or respiratory rate, number of chest lesion by CT, time for cough and dyspnea to become mild or absent, CRP, PCT, SAA
15	Li Weilin ChiC TR2000030173	RCT	China	COVID-19 pneumonia	60	18-60	NR	G1: MSC G2: SCT	pulmonary function, pulmonary CT, chest radiography, nucleic acid test
16	Jian Bo ChiCT R2000030138	RCT	China	COVID-19 pneumonia	60	16-75	NR (IV infusion)	G1: MSC G2: SCT + placebo	Clinical index
17	Liu Yu ChiC TR2000030116	RCT	China	COVID-19 with severe pneumonia	16	18-75	28 days	G1: MSC G2: MSC in different dose	28 day mortality rate, incidence of long-term complications, serum inflammatory cytokines
18	Ningkun Zhang ChiC TR2000030088	RCT	China	COVID-19 with severe pneumonia	40	18-80	NR (IV infusion)	G1: MSC G2: normal saline	nucleic acid of COVID-19, CT scan of ground glass shadow disappeared
19	Liu Sha ChiC TR2000030020	Non- RCT	China	COVID-19 pneumonia	20	18-70	NR (4 times IV infusion)	G1: MSC	FEV1, lymphocyte subpopulation changes, symptoms improved, inflammation
20	Stem Cells Arabia NCT04313322	Non- RCT	Jordan	COVID-19 pneumonia	5	≥18	8 weeks (IV infusion)	G1: MSC	Improvement of clinical symptoms, Side effects, Real-Time Polymerase Chain Reaction
21	Ye Qingsong *NCT04336254*	RCT	China	COVID-19 with severe pneumonia	20	18-65	28 days (IV infusion at Day 1, Day 4, Day 7)	G1: SCT + MSC G2: SCT + normal saline	TTCI, Lung lesion, IL-1β, IL- 2, TNF-a, ITN-γ, IL- 4, IL- 6, IL- 10, Immunoglobulins, Lymphocyte counts, CRP
22	Azidus Brasil *NCT04315987*	Non- RCT	Brazil	COVID-19 with severe pneumonia	66	≥18	28 days (IV infusion at Day 1, Day 3, Day 7)	G1: SCT + MSC	Disappearance of ground-glass shadow in lung, 28 day mortality rate, CD4+ and CD8+, blood oxygen

(*continued*)

Table 1 (*Continued*)

	Applicant and registry number	Study design	Country	Disease	Sample size	Age (year)	Duration	Intervention	Outcomes
23	Qi Zhou *NCT04331613*	Non- RCT	China	COVID-19 with severe pneumonia	9	≥18	28 days (IV infusion)	G1: 3 G2: 5 G3: 10 million cell/kg	Adverse reactions, Time to SARS-CoV-2, Improvement of clinical symptoms, Lymphocyte count, CRP, ALT, IL-1beta, IL-2, IL-6, IL-8
24	Assistance Publique *NCT04333368*	RCT	France	COVID-19 with severe pneumonia	60	≥18	28 days (IV infusion at Day 1, Day 3, Day 5)	G1: MSC G2: placebo	PaO2/FiO2 ratio, oxygenation index, mortality, IL1, IL6, IL8, TNF-alpha, IL10, TGF-beta, sRAGE, Ang2
25	Qingsong Ye ChiC TR2000031319	RCT	China	COVID-19 pneumonia	20	18-65	NR (IV infusion)	G1: SCT + MSC G2: SCT + placebo	TTCI, Immune biomarkers, Improvement of clinical symptoms,
26	Lei Shi ChiC TR2000031430	Non- RCT	China	COVID-19 pneumonia	200	18-80	NR (IV infusion at Day 0, Day 3, Day 6)	G1: SCT + MSC G2: SCT	Electrocardiogram, chest CT, Blood gas analysis, blood routine, Liver and kidney function, cytokine analysis, immunoglobulins, CRP, D-Dimer
27	Leng Nannan ChiCT R2000031494	Non- RCT	China	COVID-19 with severe pneumonia	36	18-90	NR (IV infusion)	G1: SCT + MSC G2: SCT	Chest imaging, lung function
28	Nader Tavakoli IRCT 20140528017891N8	RCT	Iran	COVID-19 pneumonia	10	18-95	28 days (IV infusion at Day 1, Day 3, Day 6)	G1: SCT + MSC G2: SCT + placebo	Death, pneumonia severity index, oxygen index, CRP, procalcitonin, lymphocyte count, CD3 +, CD4 + and CD8 +, chest CT
29	Hassan Abolghasemi IRCT 20200325046860N2	Non- RCT	Iran	COVID-19 pneumonia	10	18-70	28 days (IV infusion at Day 1, Day 3, Day 6)	G1: SCT + MSC	mortality rate; duration of hospital stay, chest CT
30	Abbas Pardakhty IRCT 20140911019125N6	Non- RCT	Iran	COVID-19 pneumonia	10	18-95	28 days (IV infusion at Day 1)	G1: SCT + MSC	Pulmonary condition, Lymphocytes count, clinical signs

Source: http://www.chictr.org.cn, https://clinicaltrials.gov, https://www.irct.ir.
All the registered studies are conducted on both genders
MSC: mesenchymal stem cells; SCT: supportive and conventional treatment; NR: not reported; RCT: randomized controlled trial; IV: intravenous; CT: computed tomography; G: group; CTI: critical treatment index; TTCI: time to clinical improvement; pro-BNP: pro-type B natriuretic peptide; ALT: alanine aminotransferase.

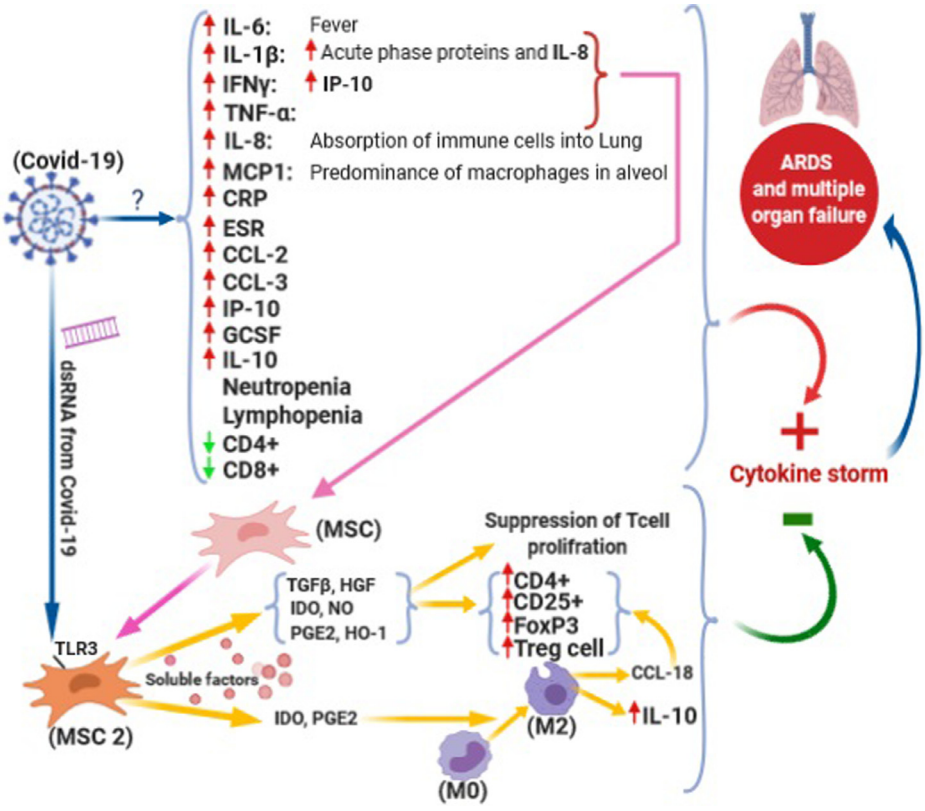

Fig. 1. Mechanims of action MSC therapy on inflammatory process. COVID-19 cause a remarkable increase in pro-inflammatory and inflammatory biomarkers through unknown mechanisms which lead to a critical situation named "cytokine storm" and known as main cause of acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF). Mesenchymal stem cells (MSCs), as a new approach in COVID-19 treatment, convert to anti-inflammatory MSC (MSC2) due to the increase in levels of inflammatory factors such as interferon γ (IFN γ), TNF-α and Interleukin-1β (IL-1β). MSC2 suppress proliferation of T cells and give assistance to developing Treg cells by increase in secretion of soluble factors such as transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF), Indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), prostaglandin E_2 (PGE_2), and hemoxygenase (HO). The secreted IDO and PGE_2 from MSC2 result in conversion of monocytes into macrophages M2 cells which produce anti-inflammatory cytokines such as Interleukin-10 (IL-10) and CC chemokine ligand 18 (CCL18). In addition to indirect impact of COVID-19 in production of MSC2 through inflammatory pathway, it also induces production of soluble factors from MSC2 through direct stimulation of toll-like receptor 3 (TLR3) in MSC2 membrane by its double stranded RNA (dsRNA). All of these processes lead to alleviation in the intensity of cytokine storm and therefore interruption in progress of ARDS and MOF. (Question mark (?): unknown mechanism; Upside arrow: Increase; Down side arrow: Decrease) (Figure is created at biorender.com)

Declaration of Competing Interest

Authors declare that there is no conflict of interest.

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