**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 64794

**Manuscript Type:** MINIREVIEWS

**Stem cell therapy: A promising treatment for COVID-19**

Zheng ZX. Stem cell therapy for COVID-19

Zhi-Xue Zheng

**Zhi-Xue Zheng,** Department of General Surgery, Beijing Jishuitan Hospital, Beijing 100035, China

**Author contributions:** Zheng ZX contributed to writing the manuscript, drafting conception and design.

**Corresponding author: Zhi-Xue Zheng, MD, Doctor, Surgeon, Surgical Oncologist,** Department of General Surgery, Beijing Jishuitan Hospital, No. 31 Xinjiekou East Street, Beijing 100035, China. pollitzheng@sina.com

**Received:** March 26, 2021

**Revised:** May 12, 2021

**Accepted:** August 23, 2021

**Published online:**

**Abstract**

Novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global pandemic. SARS-CoV-2 is an RNA virus and has a glycosylated spike (S) protein used for genome encoding. COVID-19 can lead to a cytokine storm and patients usually have early respiratory signs and further secondary infections, which can be fatal. COVID-19 has entered an emergency phase, but there are still no specific effective drugs for this disease. Mesenchymal stem cells (MSCs) are multipotent stromal cells, which cause antiapoptosis and can repair damaged epithelial cells. Many clinical trials have proved that MSC therapy could be a potential feasible therapy for COVID-19 patients, especially those with acute respiratory distress syndrome, without serious adverse events or toxicities. However, more studies are needed in the future, in order to confirm the effect of this therapy.

**Key Words:** COVID-19; SARS-CoV-2; Mesenchymal stem cells; Pandemic; Stem cell therapy

Zheng ZX. Stem cell therapy: A promising treatment for COVID-19. *World J Clin Cases* 2021; In press

**Core tip:** Coronavirus disease 2019 (COVID-19) has become a global pandemic and entered an emergency phase. However, there are still no specific effective drugs for the COVID-19. Many previous studies have shown that mesenchymal stem cell transplantation is a promising choice for COVID-19-infected patients, and further studies need to be done in the future.

**INTRODUCTION**

Novel coronavirus disease 2019 (COVID-19) is a severe respiratory disease that was first identified in December 2019 in Wuhan, China. COVID-19 is caused by severe acute respiratory syndrome coronavirus (SARS-CoV)-2 and has become a global pandemic. To date, > 100 million SARS-CoV-2 infections and > 2 million deaths have been reported by the World Health Organization (WHO)[1,2]. It has been established that SARS-CoV-2 has sequence homology with SARS-CoV-1, one of the coronaviruses found in bats[3-7].

SARS-CoV-2 is one of the Coronaviridae family of viruses, which includes four types, α, β, γ and δ. SARS-CoV-2, SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV),belong to the β group[4,8]. SARS-CoV-2 is an RNA virus and has a glycosylated spike (S) protein used for genome encoding. The angiotensin-converting enzyme (ACE)2, a membrane receptor, binds the S protein. ACE2 is highly expressed on lung alveolar type II cells, and is commonly found in heart, liver, kidney and digestive system cells, but not in bone marrow, spleen, lymph nodes and macrophages[9,10]. The transmembrane protease, serine 2 is also commonly expressed on type II lung cells, which can initiate S protein and help the virus to invade host cells[6,10].

Furthermore, this viral infection leads to cytokine release syndrome, also called cytokine storm, and increases the level of inflammatory cytokines [interleukin (IL)-2, IL-6, IL-8, IL-17, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor (CSF), granulocyte–macrophage CSF], and chemokines (monocyte chemoattractant protein-1, macrophage inflammatory protein 1α, interferon-induced protein 10)[11-13]. As a result, patients show early signs of fever, cough, headache, followed by high fever, pulmonary edema, difficult breathing, acute respiratory distress syndrome (ARDS) and further secondary infections, which can result in potentially fatal consequences[14-17]. COVID-19 usually affects the upper and lower respiratory tract with an incubation period of 2 wk. The diagnosis of SARS-CoV-2 infection is based on an RT-PCR test and specific IgM and IgG in patients[18-20]. However, there are still no specific drugs for treating this infection at present.

**MESENCHYMAL STEM CELLS**

Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into many different types of cells including chondrocytes, osteoblasts and adipocytes, which has been confirmed in a variety of cells. MSCs are usually found in bone marrow, umbilical cord, placenta, adipose fat pads and dental pulp[21,22]. MSCs, which secrete numerous cytokines and chemokines, cause antiapoptosis, and can repair damaged epithelial cells[23,24]. MSCs secrete cytokines and modulate the immune response by regulating cell function and downregulating inflammatory cytokines in graft versus host disease and systemic lupus erythematous [25,26]. Therefore, MSCs may be a potential treatment for COVID-19, as they could move towards injured lung cells and repair them.

MSCs have proved effective in both experimental research and clinical studies, including many immune-mediated inflammatory diseases, with good safety and low risk[23,24]. Previous studies have shown that MSCs could reduce H5N1 influenza virus in older patients with acute lung injury, and improve the survival rate of H7N9-infected patients with ARDS without serious complications[27,28]. MSCs can also intervene in the activation of inflammatory cytokine secretion in dendritic cells (DCs)[29,30]. Ling *et al*[31] found that stage-specific embryonic antigen-1, stem cell antigen-1, cytokeratin-7 and ACE2 were expressed in lung epithelial cells and ACE2 was expressed in lung stem cells. Furthermore, SARS-CoV-infected lung cells that lacked differentiated stem cells failed to repair. For this reason, MSC transplantation may be a feasible therapy for COVID-19.

**MSC THERAPY FOR COVID-19**

The COVID-19 pandemic has entered an emergency phase, but there are still no specific effective drugs for this infection[32]. Due to the lack of effective therapy for COVID-19, current treatment is based on individual symptoms and supportive treatment. Most patients receive oxygen therapy and extracorporeal membrane oxygenation is recommended for refractory hypoxemia[33].

At present, drugs for COVID-19 include antiviral drugs, antimalarial drugs, anti-human immunodeficiency virus drugs, anti-inflammatory drugs, and monoclonal antibodies, such as remdesivir, chloroquine, lopinavir/ritonavir, nitazoxanide, and traditional Chinese medicine, which have been used in China and western countries[34-41]. Many studies on IL-1, IL-2, IL-6 and TNF-α drugs have demonstrated that they can suppress the inflammatory response in COVID-19 patients, and have provided some clues on anti-inflammatory therapy to treat SARS-CoV-2 infection with better outcomes[42]. Etoposide-based therapy has been proposed as a new treatment for COVID-19, which requires further clinical trials[43]. There are currently several ongoing clinical trials of drugs and vaccines for the treatment of COVID-19.

Zheng *et al*[44]showed that MSC therapy for ARDS resulted in no infusion toxicity or serious adverse events. Another study involving patients with ARDS who were treated with an infusion of allogenic bone-marrow-derived human MSCs demonstrated good safety and no treatment-related adverse events. Furthermore, this treatment reduced lung injury in a sheep model[23,45]. Therefore, MSC-based therapy demonstrated promising results for ARDS without any prespecified adverse events, and was both tolerable and safe. However, there are no long-term data on MSC-therapy-associated adverse events[46,47].

CD147 is a marker of undifferentiated embryonic stem cells, and is the second entry receptor for SARS-CoV-2. Its protein is expressed in tissue-specific stem cells of human bone marrow origin. Inhibition of CD147 can prevent inflammatory processes in diabetic complications[48,49]. SARS-CoV-2 infection can trigger pulmonary fibrosis in normal tissue, and probably originates from resident stem cells, which are also called MSC-like cells. In the early stage of COVID-19 pneumonia, type II pneumocytes are involved in the initial step of pulmonary fibrosis. Anti-CD147 antibodies that can suppress the normal lung cell differentiation of fibroblasts *in vitro* have been investigated, and MSC transplantation may lead to immunosuppression and tissue regeneration[50,51].

In the first study of MSCs, Leng *et al*[14] treated seven patients with COVID-19 pneumonia with an injection of MSCs, and showed a significant reduction in clinical symptoms and a decrease in serum proinflammatory cytokines without adverse effects. Most of the patients were negative on the SARS-CoV-2 nucleic acid test within 2 wk after MSCs transplantation. Chen *et al*[52] observed that all patients showed clinical improvement, including 64% of patients with chest CT improvement, but little improvement in immunomodulation and cardiotoxicity during MSC therapy.

Human umbilical cord-derived MSC (UC-MSC) transplantation has been carried out in COVID-19 patients. A female patient with severe COVID-19 was treated with an human UC-MSC injection, which resulted in good efficacy without side effects[53]. Twelve patients with severe COVID-19 treated with UC-MSC transplantation reported improvements in clinical outcome, reduced C-reactive protein and IL-6 levels, and no mortality[54,55]. A Phase I clinical trial of UC-MSCs for COVID-19 found no serious adverse events, and lung lesions in four moderate–severe patients completely disappeared within 2 wk after injection[56]. Adipose-tissue-derived MSCs were used to treat 13 severe COVID-19 pneumonia patients, and 70% of patients had clinical improvement and reduced levels of inflammatory factors[57]. Tang *et al*[58] used menstrual-blood-derived MSCs to treat severe COVID-19 patients, and found that bilateral pulmonary exudation had been absorbed and SaO2 and PO2 were also improved. Similar to MSCs, immunity- and matrix-regulatory cells (IMRCs) also have self-renewal and mesenchymal differentiation ability. Following injection of IMRCs, COVID-19 patients recovered and tested negative for the virus, while many inflammatory cytokines such as IFN-α2, IL-3, M-CSF and TNF-α were suppressed[59]. Previous studies have shown that MSC therapy may activate the immune system, stem cells can repair tissues, and then prevent the cytokine storm and release anti-inflammatory mediators. Consequently, this may prevent pulmonary fibrosis caused by SARS-CoV-2 infection. The MSCs were resistant to viral infection due to expression of interferon-stimulated genes [60-62]. The characteristics of included studies are shown in Table 1.

Recent studies have indicated that MSCs are able to secrete immunomodulatory factors that could suppress the cytokine storm, promote tissue regeneration and inhibit tissue fibrosis. Given the previous preclinical and clinical studies, MSC therapy has shown good safety and efficacy in the treatment of respiratory failure or ARDS[63,64]. Therefore, MSC injection showed promising results for therapy of COVID-19 patients[65]. In addition, many clinical trials on MSCs for COVID-19 (NCT04315987, NCT04313322 and NCT04333368) are ongoing worldwide. More clinical data will support this effective therapy. However, the number of patients in these studies is small, and the long-term safety and efficacy of this treatment require further investigation. The consistency of MSC quality cannot be guaranteed, and the dose was also inconsistent in these studies. The heterogeneity, secretory and immunomodulatory capabilities of MSCs are unclear; therefore, the results from different studies are difficult to compare. Further study would develop clinical preparation and treatment standards for MSCs in COVID-19 patients, and larger numbers of patients remain to be included in MSCs studies.

**CONCLUSION**

MSC transplantation has proved to be a promising choice for COVID-19 patients, and more studies need to be completed in the future. This therapy has been shown to have few side effects. MSCs may be a safe and effective therapeutic strategy, or as part of a combination therapy for COVID-19 patients.

**REFERENCES**

1 **World Health Organization.** Laboratory testing of 2019 novel coronavirus (2019-nCoV) in suspected human cases. [cited 25 March 2021]. Available from: https://apps.who.int/iris/handle/10665/330676

2 **World Health Organization.** Novel coronavirus (2019-nCoV) situation report. [cited 25 March 2021]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation reports

3 **Gorbalenya AE,** Baker SC, Baric RG, Raoul DC， Gulyaeva AA, Haagmans BL, Lauber C; Leontovich AM, Neuman, B W, Penzar D; Perlman S, Poon L, Samborskiy D, Sidorov IA, Solá GI, Ziebuhr J. Severe acute respiratory syndrome-related coronavirus–the species and its viruses, a statement of the coronavirus study group. BioRxiv 2020. [DOI:10.1101/2020.02.07.937862]

4 **Zhu N**, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020; **382**: 727-733 [PMID: 31978945 DOI: 10.1056/NEJMoa2001017]

5 **Li Q**, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; **382**: 1199-1207 [PMID: 31995857 DOI: 10.1056/NEJMoa2001316]

6 **Lu R**, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**: 565-574 [PMID: 32007145 DOI: 10.1016/S0140-6736(20)30251-8]

7 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

8 **Chen Y**, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol* 2020; **92**: 2249 [PMID: 32881013 DOI: 10.1002/jmv.26234]

9 **Rice GI**, Thomas DA, Grant PJ, Turner AJ, Hooper NM. Evaluation of angiotensin-converting enzyme (ACE), its homologue ACE2 and neprilysin in angiotensin peptide metabolism. *Biochem J* 2004; **383**: 45-51 [PMID: 15283675 DOI: 10.1042/BJ20040634]

10 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

11 **Huang CL,** Wang YM, Li XW, Ren LL, Zhao JP, Hu Y, Zhang L, Fan GH, Xu JY, Gu XY, Cheng ZS, Yu Ting, Xia JA, Wei Y, Wu WJ, Xie XL, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie JG, Wang GF, Jiang RM, Gao ZC, Jin Q, Wang JW, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**: 497-506 [DOI: 10.1016/S0140-6736(20)30183-5]

12 **Merad M,** Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 2020; **20**: 355-362 [PMID: 32376901 DOI: 10.1038/s41577-020-0331-4]

13 **Tang B**, Bragazzi NL, Li Q, Tang S, Xiao Y, Wu J. An updated estimation of the risk of transmission of the novel coronavirus (2019-nCov). *Infect Dis Model* 2020; **5**: 248-255 [PMID: 32099934 DOI: 10.1016/j.idm.2020.02.001]

14 **Leng Z**, Zhu R, Hou W, Feng Y, Yang Y, Han Q, Shan G, Meng F, Du D, Wang S, Fan J, Wang W, Deng L, Shi H, Li H, Hu Z, Zhang F, Gao J, Liu H, Li X, Zhao Y, Yin K, He X, Gao Z, Wang Y, Yang B, Jin R, Stambler I, Lim LW, Su H, Moskalev A, Cano A, Chakrabarti S, Min KJ, Ellison-Hughes G, Caruso C, Jin K, Zhao RC. Transplantation of ACE2- Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. *Aging Dis* 2020; **11**: 216-228 [PMID: 32257537 DOI: 10.14336/AD.2020.0228]

15 **Hoffmann M,** KleineWeber H, Krüger N, Müller M, Drosten C, Pöhlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. BioRxiv 2020. [DOI: 10.1101/2020.01.31.929042]

16 **Chang**, Lin M, Wei L, Xie L, Zhu G, Dela Cruz CS, Sharma L. Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China. *JAMA* 2020; **323**: 1092-1093 [PMID: 32031568 DOI: 10.1001/jama.2020.1623]

17 **Xu Z**, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; **8**: 420-422 [PMID: 32085846 DOI: 10.1016/S2213-2600(20)30076-X]

18 **Chan JF,** Yip CC, To KK, Tang TH, Wong SC, Leung KH, Fung AY, Ng AC, Zou Z, Tsoi HW, Choi GK, Tam AR, Cheng VC, Chan KH, Tsang OT, Yuen KY. Improved Molecular Diagnosis of COVID-19 by the Novel, Highly Sensitive and Specific COVID-19-RdRp/Hel Real-Time Reverse Transcription-PCR Assay Validated In Vitro and with Clinical Specimens. *J Clin Microbiol* 2020; **58**: e00310-20 [PMID: 32132196 DOI: 10.1128/JCM.00310-20]

19 **Zhang B**, Zhou X, Zhu C, Song Y, Feng F, Qiu Y, Feng J, Jia Q, Song Q, Zhu B, Wang J. Immune Phenotyping Based on the Neutrophil-to-Lymphocyte Ratio and IgG Level Predicts Disease Severity and Outcome for Patients With COVID-19. *Front Mol Biosci* 2020; **7**: 157 [PMID: 32719810 DOI: 10.3389/fmolb.2020.00157]

20 **Zhao J**, Yuan Q, Wang H, Liu W, Liao X, Su Y, Wang X, Yuan J, Li T, Li J, Qian S, Hong C, Wang F, Liu Y, Wang Z, He Q, Li Z, He B, Zhang T, Fu Y, Ge S, Liu L, Zhang J, Xia N, Zhang Z. Antibody Responses to SARS-CoV-2 in Patients With Novel Coronavirus Disease 2019. *Clin Infect Dis* 2020; **71**: 2027-2034 [PMID: 32221519 DOI: 10.1093/cid/ciaa344]

21 **Weiss DJ**, Kolls JK, Ortiz LA, Panoskaltsis-Mortari A, Prockop DJ. Stem cells and cell therapies in lung biology and lung diseases. *Proc Am Thorac Soc* 2008; **5**: 637-667 [PMID: 18625757 DOI: 10.1513/pats.200804-037DW]

22 **Pittenger MF**, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. *NPJ Regen Med* 2019; **4**: 22 [PMID: 31815001 DOI: 10.1038/s41536-019-0083-6]

23 **Wilson JG**, Liu KD, Zhuo H, Caballero L, McMillan M, Fang X, Cosgrove K, Vojnik R, Calfee CS, Lee JW, Rogers AJ, Levitt J, Wiener-Kronish J, Bajwa EK, Leavitt A, McKenna D, Thompson BT, Matthay MA. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *Lancet Respir Med* 2015; **3**: 24-32 [PMID: 25529339 DOI: 10.1016/S2213-2600(14)70291-7]

24 **Prockop DJ**. The exciting prospects of new therapies with mesenchymal stromal cells. *Cytotherapy* 2017; **19**: 1-8 [PMID: 27769637 DOI: 10.1016/j.jcyt.2016.09.008]

25 **Hashmi S**, Ahmed M, Murad MH, Litzow MR, Adams RH, Ball LM, Prasad VK, Kebriaei P, Ringden O. Survival after mesenchymal stromal cell therapy in steroid-refractory acute graft-versus-host disease: systematic review and meta-analysis. *Lancet Haematol* 2016; **3**: e45-e52 [PMID: 26765648 DOI: 10.1016/S2352-3026(15)00224-0]

26 **Kamen DL,** Nietert PJ, Wang HJ, Duke T, Cloud C, Robinson A, Gilkeson GS. CT-04 safety and efficacy of allogeneic umbilical cord-derived mesenchymal stem cells (MSCs) in patients with systemic lupus erythematosus: results of an open-label phase I study. *Lupus Sci Med* 2018; **5**: 46-47 [DOI: 10.1136/lupus-2018-lsm.76]

27 **Chan MC**, Kuok DI, Leung CY, Hui KP, Valkenburg SA, Lau EH, Nicholls JM, Fang X, Guan Y, Lee JW, Chan RW, Webster RG, Matthay MA, Peiris JS. Human mesenchymal stromal cells reduce influenza A H5N1-associated acute lung injury in vitro and in vivo. *Proc Natl Acad Sci U S A* 2016; **113**: 3621-3626 [PMID: 26976597 DOI: 10.1073/pnas.1601911113]

28 **Chen J,** Hu C, Chen L, Tang L, Zhu Y, Xu X, Chen L, Gao H, Lu X, Yu L, Dai X, Xiang C, Li L. Clinical Study of Mesenchymal Stem Cell Treatment for Acute Respiratory Distress Syndrome Induced by Epidemic Influenza A (H7N9) Infection: A Hint for COVID-19 Treatment. *Engineering (Beijing)* 2020; **6**: 1153-1161 [PMID: 32292627 DOI: 10.1016/j.eng.2020.02.006]

29 **Golchin A**, Farahany TZ, Khojasteh A, Soleimanifar F, Ardeshirylajimi A. The Clinical Trials of Mesenchymal Stem Cell Therapy in Skin Diseases: An Update and Concise Review. *Curr Stem Cell Res Ther* 2019; **14**: 22-33 [PMID: 30210006 DOI: 10.2174/1574888X13666180913123424]

30 **Ðokić JM**, Tomić SZ, Čolić MJ. Cross-Talk Between Mesenchymal Stem/Stromal Cells and Dendritic Cells. *Curr Stem Cell Res Ther* 2016; **11**: 51-65 [PMID: 26337378 DOI: 10.2174/1574888X10666150904114035]

31 **Ling TY**, Kuo MD, Li CL, Yu AL, Huang YH, Wu TJ, Lin YC, Chen SH, Yu J. Identification of pulmonary Oct-4+ stem/progenitor cells and demonstration of their susceptibility to SARS coronavirus (SARS-CoV) infection in vitro. *Proc Natl Acad Sci U S A* 2006; **103**: 9530-9535 [PMID: 16772384 DOI: 10.1073/pnas.0510232103]

32 **Vellingiri B**, Jayaramayya K, Iyer M, Narayanasamy A, Govindasamy V, Giridharan B, Ganesan S, Venugopal A, Venkatesan D, Ganesan H, Rajagopalan K, Rahman PKSM, Cho SG, Kumar NS, Subramaniam MD. COVID-19: A promising cure for the global panic. *Sci Total Environ* 2020; **725**: 138277 [PMID: 32278175 DOI: 10.1016/j.scitotenv.2020.138277]

33 **World Health Organization.** Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. [cited 25 March 2021]. Available from: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

34 **Wang M**, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; **30**: 269-271 [PMID: 32020029 DOI: 10.1038/s41422-020-0282-0]

35 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

36 **Elfiky AA**. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sci* 2020; **248**: 117477 [PMID: 32119961 DOI: 10.1016/j.lfs.2020.117477]

37 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

38 **Lim J**, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, Choe KW, Kang YM, Lee B, Park SJ. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *J Korean Med Sci* 2020; **35**: e79 [PMID: 32056407 DOI: 10.3346/jkms.2020.35.e79]

39 **Stebbing J,** Phelan A, Griffifin I, Tucker C, Oechsle O, Smith D, Richardson P. COVID-19: combining antiviral and anti-inflflammatory treatments. *Lancet Infect Dis* 2020; **20**: 400-402 [DOI: 10.1016/S1473-3099(20)30132-8]

40 **Zheng M**, Song L. Novel antibody epitopes dominate the antigenicity of spike glycoprotein in SARS-CoV-2 compared to SARS-CoV. *Cell Mol Immunol* 2020; **17**: 536-538 [PMID: 32132669 DOI: 10.1038/s41423-020-0385-z]

41 **Wang Z**, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. *Biosci Trends* 2020; **14**: 64-68 [PMID: 32037389 DOI:10.5582/bst.2020.01030]

42 **Bamba C**, Singh SP, Choudhury S. Can mesenchymal stem cell therapy be the interim management of COVID-19? *Drug Discov Ther* 2020; **14**: 139-142 [PMID: 32554953 DOI: 10.5582/ddt.2020.03032]

43 **Hamizi K**, Aouidane S, Belaaloui G. Etoposide-based therapy for severe forms of COVID-19. *Med Hypotheses* 2020; **142**: 109826 [PMID: 32416415 DOI: 10.1016/j.mehy.2020.109826]

44 **Zheng G**, Huang L, Tong H, Shu Q, Hu Y, Ge M, Deng K, Zhang L, Zou B, Cheng B, Xu J. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. *Respir Res* 2014; **15**: 39 [PMID: 24708472 DOI: 10.1186/1465-9921-15-39]

45 **Asmussen S**, Ito H, Traber DL, Lee JW, Cox RA, Hawkins HK, McAuley DF, McKenna DH, Traber LD, Zhuo H, Wilson J, Herndon DN, Prough DS, Liu KD, Matthay MA, Enkhbaatar P. Human mesenchymal stem cells reduce the severity of acute lung injury in a sheep model of bacterial pneumonia. *Thorax* 2014; **69**: 819-825 [PMID: 24891325 DOI: 10.1136/thoraxjnl-2013-204980]

46 **Khoury M**, Alcayaga-Miranda F, Illanes SE, Figueroa FE. The promising potential of menstrual stem cells for antenatal diagnosis and cell therapy. *Front Immunol* 2014; **5**: 205 [PMID: 24904569 DOI: 10.3389/fimmu.2014.00205]

47 **Chen L**, Qu J, Xiang C. The multi-functional roles of menstrual blood-derived stem cells in regenerative medicine. *Stem Cell Res Ther* 2019; **10**: 1 [PMID: 30606242 DOI: 10.1186/s13287-018-1105-9]

48 **Amati E**, Perbellini O, Rotta G, Bernardi M, Chieregato K, Sella S, Rodeghiero F, Ruggeri M, Astori G. High-throughput immunophenotypic characterization of bone marrow- and cord blood-derived mesenchymal stromal cells reveals common and differentially expressed markers: identification of angiotensin-converting enzyme (CD143) as a marker differentially expressed between adult and perinatal tissue sources. *Stem Cell Res Ther* 2018; **9**: 10 [PMID: 29338788 DOI: 10.1186/s13287-017-0755-3]

49 **Bao W**, Min D, Twigg SM, Shackel NA, Warner FJ, Yue DK, McLennan SV. Monocyte CD147 is induced by advanced glycation end products and high glucose concentration: possible role in diabetic complications. *Am J Physiol Cell Physiol* 2010; **299**: C1212-C1219 [PMID: 20810913 DOI: 10.1152/ajpcell.00228.2010]

50 **Jun D**, Garat C, West J, Thorn N, Chow K, Cleaver T, Sullivan T, Torchia EC, Childs C, Shade T, Tadjali M, Lara A, Nozik-Grayck E, Malkoski S, Sorrentino B, Meyrick B, Klemm D, Rojas M, Wagner DH Jr, Majka SM. The pathology of bleomycin-induced fibrosis is associated with loss of resident lung mesenchymal stem cells that regulate effector T-cell proliferation. *Stem Cells* 2011; **29**: 725-735 [PMID: 21312316 DOI: 10.1002/stem.604]

51 **Ulrich H,** Pillat MM. CD147 as a Target for COVID-19 Treatment: Suggested Effects of Azithromycin and Stem Cell Engagement. *Stem Cell Rev Rep* 2020; **16**: 434-440 [PMID: 32307653 DOI: 10.1007/s12015-020-09976-7]

52 **Chen X**, Shan Y, Wen Y, Sun J, Du H. Mesenchymal stem cell therapy in severe COVID-19: A retrospective study of short-term treatment efficacy and side effects. *J Infect* 2020; **81**: 647-679 [PMID: 32422152 DOI: 10.1016/j.jinf.2020.05.020]

53 **Liang B**, Chen J, Li T, Wu H, Yang W, Li Y, Li J, Yu C, Nie F, Ma Z, Yang M, Xiao M, Nie P, Gao Y, Qian C, Hu M. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells: A case report. *Medicine (Baltimore)* 2020; **99**: e21429 [PMID: 32756149 DOI: 10.1097/MD.0000000000021429]

54 **Zhao RC**. Stem Cell-Based Therapy for Coronavirus Disease 2019. *Stem Cells Dev* 2020; **29**: 679-681 [PMID: 32292113 DOI: 10.1089/scd.2020.0071]

55 **Shu L**, Niu C, Li R, Huang T, Wang Y, Huang M, Ji N, Zheng Y, Chen X, Shi L, Wu M, Deng K, Wei J, Wang X, Cao Y, Yan J, Feng G. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. *Stem Cell Res Ther* 2020; **11**: 361 [PMID: 32811531 DOI: 10.1186/s13287-020-01875-5]

56 **Meng F**, Xu R, Wang S, Xu Z, Zhang C, Li Y, Yang T, Shi L, Fu J, Jiang T, Huang L, Zhao P, Yuan X, Fan X, Zhang JY, Song J, Zhang D, Jiao Y, Liu L, Zhou C, Maeurer M, Zumla A, Shi M, Wang FS. Human umbilical cord-derived mesenchymal stem cell therapy in patients with COVID-19: a phase 1 clinical trial. *Signal Transduct Target Ther* 2020; **5**: 172 [PMID: 32855385 DOI: 10.1038/s41392-020-00286-5]

57 **Sánchez-Guijo F**, García-Arranz M, López-Parra M, Monedero P, Mata-Martínez C, Santos A, Sagredo V, Álvarez-Avello JM, Guerrero JE, Pérez-Calvo C, Sánchez-Hernández MV, Del-Pozo JL, Andreu EJ, Fernández-Santos ME, Soria-Juan B, Hernández-Blasco LM, Andreu E, Sempere JM, Zapata AG, Moraleda JM, Soria B, Fernández-Avilés F, García-Olmo D, Prósper F. Adipose-derived mesenchymal stromal cells for the treatment of patients with severe SARS-CoV-2 pneumonia requiring mechanical ventilation. A proof of concept study. *EClinicalMedicine* 2020; **25**: 100454 [PMID: 32838232 DOI: 10.1016/j.eclinm.2020.100454]

58 **Tang L**, Jiang Y, Zhu M, Chen L, Zhou X, Zhou C, Ye P, Chen X, Wang B, Xu Z, Zhang Q, Xu X, Gao H, Wu X, Li D, Jiang W, Qu J, Xiang C, Li L. Clinical study using mesenchymal stem cells for the treatment of patients with severe COVID-19. *Front Med* 2020; **14**: 664-673 [PMID: 32761491 DOI:10.1007/s11684-020-0810-9]

59 **Li Z**, Niu S, Guo B, Gao T, Wang L, Wang Y, Wang L, Tan Y, Wu J, Hao J. Stem cell therapy for COVID-19, ARDS and pulmonary fibrosis. *Cell Prolif* 2020; **53**: e12939 [PMID: 33098357 DOI: 10.1111/cpr.12939]

60 **Glenn JD**, Whartenby KA. Mesenchymal stem cells: Emerging mechanisms of immunomodulation and therapy. *World J Stem Cells* 2014; **6**: 526-539 [PMID: 25426250 DOI: 10.4252/wjsc.v6.i5.526]

61 **Hu S**, Park J, Liu A, Lee J, Zhang X, Hao Q, Lee JW. Mesenchymal Stem Cell Microvesicles Restore Protein Permeability Across Primary Cultures of Injured Human Lung Microvascular Endothelial Cells. *Stem Cells Transl Med* 2018; **7**: 615-624 [PMID: 29737632 DOI: 10.1002/sctm.17-0278]

62 **Wu X**, Dao Thi VL, Huang Y, Billerbeck E, Saha D, Hoffmann HH, Wang Y, Silva LAV, Sarbanes S, Sun T, Andrus L, Yu Y, Quirk C, Li M, MacDonald MR, Schneider WM, An X, Rosenberg BR, Rice CM. Intrinsic Immunity Shapes Viral Resistance of Stem Cells. *Cell* 2018; **172**: 423-438.e25 [PMID: 29249360 DOI: 10.1016/j.cell.2017.11.018]

63 **Sadeghi S**, Soudi S, Shafiee A, Hashemi SM. Mesenchymal stem cell therapies for COVID-19: Current status and mechanism of action. *Life Sci* 2020; **262**: 118493 [PMID: 32979360 DOI: 10.1016/j.lfs.2020.118493]

64 **Xiong J**, Bao L, Qi H, Feng Z, Shi Y. Mesenchymal Stem Cell-Based Therapy for COVID-19: Possibility and Potential. *Curr Stem Cell Res Ther* 2021; **16**: 105-108 [PMID: 32479246 DOI: 10.2174/1574888X15666200601152832]

65 **Kumar P**, Sah AK, Tripathi G, Kashyap A, Tripathi A, Rao R, Mishra PC, Mallick K, Husain A, Kashyap MK. Role of ACE2 receptor and the landscape of treatment options from convalescent plasma therapy to the drug repurposing in COVID-19. *Mol Cell Biochem* 2021; **476**: 553-574 [PMID: 33029696 DOI: 10.1007/s11010-020-03924-2]

**Footnotes**

**Conflict-of-interest statement:** The author declared there are no conflicts of interest to this work.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** March 26, 2021

**First decision:** May 12, 2021

**Article in press:**

**Specialty type:** Infectious diseases

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Kashyap MK **S-Editor:** Wu YXJ **L-Editor:** Kerr C **P-Editor:**

**Table 1 Characteristics of included stem cell studies of COVID-19**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Refs** | **Disease** | **Treatment** | ***n*** | **Results** |
| Leng *et al*[14], 2020 | COVID-19 pneumonia | MSCs | 7 | Improve outcome without adverse effects |
| Chen *et al*[52], 2020 | Severe COVID-19 pneumonia | MSCs | 25 | All patients gained clinical improvement and 64% gained chest CT improvement. |
| Liang *et al*[53], 2020 | Severe COVID-19 pneumonia | UC-MSCs | 1 | Most of the laboratory indexes and CT images showed remission without side effects. |
| Shu *et al*[55], 2020 | Severe COVID-19 pneumonia | UC-MSCs | 12 | The UC-MSC treatment group had shorter clinical improvement time, reduced CRP and IL-6 levels, and no mortality. |
| Meng *et al*[56], 2020 | Moderate and serve COVID-19 pneumonia | UC-MSCs | 9 | No serious adverse events were observed and all the patients recovered and were discharged. |
| Sánchez-Guijo*et al*[57], 2020 | Severe COVID-19 pneumonia | AD-MSCs | 13 | 70% of patients had clinical improvement and no adverse events were related to the therapy. |
| Tang *et al*[58], 2020 | Severe COVID-19 pneumonia | MB-MSCs | 2 | Bilateral pulmonary exudation had been absorbed and SaO2 and PO2 were also improved |

COVID-19: Coronavirus disease 2019; MSCs: Mesenchymal stem cells; UC-MSCs: Umbilical cord-derived MSCs; AD-MSCs: Adipose tissue-derived MSCs; MB-MSCs: Menstrual blood-derived MSCs; CT: Computed tomography.