May mesenchymal stem cell transplantation be a solution for COVID-19 induced cytokine storm?

Hüseyin Sütlüoğlu, Öner Özdemir

Abstract

The recently emergent disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), transmitted by droplets and aerosols, was named coronavirus disease 2019 (COVID-19) by World Health Organization. Predominantly, the disease progress is asymptomatic or mild, but one-fifth of the patients advance to severe or critical illness. In severe COVID-19 patients, type-2 T helper cells release numerous cytokines; this excessive immune response is named as cytokine storm. The cytokine storm, which is the hallmark of the COVID-19 induced by the disease and aggravates due to lack of proper immune response, similar to SARS and Middle East respiratory syndrome (MERS), and the disease status may progress forward to acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome, multi-organ dysfunction syndrome, and death. Mesenchymal stromal cell transplantation is up-and-coming in treating many diseases such as HIV, hepatitis B, influenza, coronavirus diseases (SARS, MERS), lung injuries, and ARDS. Upon closer inspection on respiratory diseases, COVID-19, influenza, SARS, and MERS have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for the treatment of COVID-19.

Key Words: Mesenchymal stem cell; Mesenchymal stromal cell; COVID-19; Cytokine storm; Immunosuppression; Transplantation

Core Tip: Upon closer inspection on respiratory diseases, coronavirus disease 2019 (COVID-19), influenza, severe acute respiratory syndrome, and Middle East
INTRODUCTION TO COVID-19 PATHOGENESIS AND PRESENT THERAPIES

In the eighty percent of the people who have been exposed to the SARS-CoV-2 via droplets and aerosols from an infected person, the disease remains limited in the upper respiratory tract. However, in the rest of the patients, the virus proceeds to the lower respiratory tract, and with pulmonary involvement, it causes more severe respiratory syndrome have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for the treatment of COVID-19. Transplantation of mesenchymal stromal cells provides tissue regeneration and rejuvenation with immunotolerant and immunomodulant properties on damaged tissues by exerting their effects through immune cells.

Citation: Sütlüoğlu H, Özdemir Ö. May mesenchymal stem cell transplantation be a solution for COVID-19 induced cytokine storm? World J Transplant 2021; 11(8): 344-355
URL: https://www.wjgnet.com/2220-3230/full/v11/i8/344.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i8.344
illness. Disease mortality was reported between 0.5 and 2 percent in different studies and changes with obesity, older age, hypertension, and underlying chronic medical conditions[25-27]. The infectious process might occur progressively in a wide range of manifestations with life-threatening cardiovascular, thromboembolic, neurological, and respiratory complications[4,19,28,29]. As compatible with virus-cell invasion pathophysiology, organ involvement is correlated with the expression of host cells’ angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane protease, serine 2 (TMPRSS2) enzyme[30,31]. Unfortunately, the ACE2 receptor is widely distributed on the human cell surface, like lung, intestine, liver, kidney, brain, especially the alveolar type II (AT2) cells, capillary endothelium, and the AT2 cells highly express TMPRSS2[32-34]. On the grounds of that, the primary target of the virus is the lung. Moreover, the maladaptive immune response in severely ill patients damages the airways and causes a terrible cytokine storm characterized by elevated blood cytokine levels as a consequence of hyperactivation of the immune cells and impaired feedback mechanism. However, it leads to excessive infiltration of monocytes, macrophages, and T cells in the lungs. Therefore, disease severity in patients is due to not only the viral infection but also the host response. A notable example of this condition might be multisystem inflammatory syndrome in children and multisystem inflammatory syndrome in adults[35,36]. This uncontrolled hyperinflammatory response catalyzes multi-organ damage leading to multi-organ failure, especially of the cardiac, hepatic, and renal systems[18,29]. These organ failures raise the mortality rate, such as most patients with SARS-CoV-2 infection who developed acute kidney injury or have existing chronic kidney disease eventually died[37]. At present, no curative and effective COVID-19 treatment is available, and the primary approach to patients is supportive care such as oxygen therapy (such as high flow nasal cannula oxygen therapy, mechanic ventilation), antipyretics, or venous thromboembolism prophylaxis[38,39]. Various drugs and supplementary therapies like antivirals (remdesivir, lopinavir/ritonavir, oseltamivir, favipiravir), antibiotics (azithromycin), immunomodulatory drugs (tocilizumab, hydroxychloroquine, convalescent plasma, anakinra, etc.) are being still investigated, but none of the therapies have reliable evidence[17]. To date, the only drug which is evidenced to decrease the mortality rate in severe and critically ill patients is corticosteroids[40]. Also, a specific agent to alleviate the SARS-CoV-2 induced cytokine storm is not developed as yet, and drugs that are aimed at this phenomenon are non-specific. Suppressing the excessive immune response is the key difficulty of the therapy options[41]. It is thought that people who overcome COVID-19 might have long-term sequelae and different organ damages, notably lung and heart[42,43]. Multipotent MSC transplantation could promote lung and other damaged tissue repairs with its differentiation and paracrine secretory properties (exosomes/extracellular vesicles) and may prevent morbidities[44-47].

IMMUNO-PATHOGENESIS OF THE DISEASE AND PATIENT SELECTION FOR MSC TRANSPLANTATION

The virus that reaches the lungs from the upper respiratory tract via the ACE2 receptor infects AT2 cells here. After intracellular replication, it spreads to the parenchyma by exocytosis and causes epithelial and endothelial damage. The alveolar macrophages recognize damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) that arise from infected both AT-1 and AT-2 type dead cells, and the initiation of the inflammation is triggered (Figure 1). Thus, numerous chemokines and cytokines are started to secret excessively by lung and peripheral immune cells[18]. The cytokine storm, which is the hallmark of the COVID-19 induced by the disease and aggravates due to lack of proper immune response, similar to SARS and MERS, and the clinical status may progress forward ARDS, systemic inflammatory response syndrome, MODS, and death[48,49].

When the severe patients' laboratory results were analyzed, decreased lymphocyte count, elevated leukocyte count, neutrophils-lymphocytes ratio, a low percentage of monocyte, eosinophils, and basophils have been observed. Besides, Th, T suppressor (Ts), and regulatory T (Treg) cell count were determined as more obviously decreased in severe cases[50]. While studies on the pathophysiology of the disease are continuing, the following substances were found high in patients who suffer from cytokine storm: interleukin (IL)-1β, IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, and IL-17; granulocyte-macrophage colony-stimulating factor (GM-CSF); TNF-α, IFN-γ, and IFN-γ inducible protein 10 (IP10); monocyte chemoattractant protein 1 (MCP-1);...
Figure 1 Summary of coronavirus disease 2019 pathogenesis and mesenchymal stem cells benefits. IL: Interleukin; PAMP: Pathogen-associated molecular patterns; DAMP: Damage-associated molecular patterns; IP-10: Interferon gamma-induced protein 10; IFN: Interferon; MIP1α: Macrophage inflammatory protein-1α; TNF-α: Tumor necrosis factor α; IDO: Indoleamine 2,3-dioxygenase; G-CSF: Granulocyte colony-stimulating factor; PG: Prostaglandin; PD-1: Programmed cell death protein 1; HGF: Hepatocyte growth factor; TGF-β: Transforming growth factor-β; FCN1+: Ficolin-1 (highly inflammatory monocyte-derived macrophage); AT: Adipose tissue; DC: Dendritic cell; T reg: regulatory T lymphocytes; NK cells: Natural killer cells; CXCR: CXC motif chemokine receptors; IV: Intravenous; RAS: Renin-angiotensin system; N/L: Neutrophil/lymphocyte; MSC: Mesenchymal stem cells.

macrophage inflammatory protein 1α (MIP-1α) and MIP-1β; chemokines like CC
chemokine ligand 2 (CCL2), CCL3, and CCL5; and C-X-C motif chemokine ligand 8 (CXCL8), CXCL9, and CXCL10[4,51]. In the detailed clustering analyses of the patients, higher C-reactive-protein (CRP), D-Dimer, ferritin, IP-10 (CXCL10), IL-10, IL-6 were founded to strongly correlated with poor clinical prognosis[52,53].

Together with these results, it is thought immunosuppression might be harmful in the early stages but helpful late stages of the disease. For this reason, the timing of the immunomodulatory therapies is essential[19]. Mortality rate reductive effects of the corticosteroids in patients who are intubated or only taken oxygen support can be explained with their potent anti-inflammatory effects[54]. Immunosuppression is a two-sided sword, and selective application is fundamental. Nevertheless, the ideal candidates for the immunomodulatory therapy in COVID-19 are still unspecified. Even only cytokine-specific therapies like IL-6 inhibitor tocilizumab might cause increasing the risk of sepsis, bacterial pneumonia, gastrointestinal perforation, and hepatotoxicity as a possible consequence of profound immunosuppression[55]. Additionally, indiscriminative and long-lasting immunosuppression has some disadvantages as SARS-CoV-2 progression and secondary infections. Therefore, administration of the short half-live immunosuppressant drugs will be more appropriate management.

There is still no consensus about the biomarkers that can be used for patient selection. However, besides the being need for further studies, it is thought that severe and critically ill patients might benefit from immunomodulatory options including MSC transplantation. Focusing on potential cytokine storm predictors, cytokine level measurement, especially IL-6, is not routine and usually is a "send-out" test. Instead of that, there are more accessible tests such as CRP, D-Dimer, and Ferritin, but their cut-off values vary in different studies. Another disease, hemophagocytic lymphohistocytosis (HLH), which is induced cytokine storm, has a diagnostic score H score, (it assets temperature, organomegaly, number of cytopenias, triglycerides, fibrinogen, ferritin, aspartate aminotransferase, hemophagocytes on bone marrow aspirate, and known immunosuppression), and modified or a redesigned version of the score will be helpful not only in the management of MSC transplantation but, including other immunomodulatory therapies[56]. Further studies, which take these variables into account, need to be undertaken.

**BENEFITS AND MECHANISMS OF MSC TRANSPLANTATION AND LIMITATIONS OF THE STUDIES**

MSCs were firstly described in 1968 by Friedenstein et al[58] with a cluster of cells from bone marrow as colony-forming unit-fibroblasts[57]. Multipotent MSCs were defined by the International Society for Gene & Gene Therapy with three minimal criteria; being plastic adherent, specific surface antigen expression (expressing CD73, CD90, and CD105, lacking the expression of hematopoietic and endothelial markers CD11b, CD14, CD19, CD34, CD45, CD79α, and HLA-DR) and multipotent differentiation potential (capable of in vitro differentiation into adipocyte, chondrocyte and osteoblast lineages)[59]. Recently, The International Society for Cell & Gene Therapy (ISCT) Mesenchymal Stromal Cell (ISCT MSC) committee has advised naming these extraordinary cells as "Mesenchymal Stromal Cells" instead of "Mesenchymal Stem Cells" to clarify nomenclature[60]. In this review, we use the terms as synonyms. These cells derived from limited tissues like adipose, umbilical cord, placenta, synovium, and menstrual blood has such properties as priming, self-renewal, differentiation, immunomodulation & immunoprivilege, angiogenesis & repair, homing mechanism, anti-apoptosis, anti-inflammation & anti-fibrosis, and clinical trials about the benefits on COVID-19 patients continue[61].

MSC transplantation is up-and-coming in treating many diseases such as HIV, Hepatitis B, Influenza, coronaviruses (SARS, MERS), lung injuries, and ARDS. The only treatment of the HLH disease that causes the cytokine storm is stem cell transplantation[62]. Upon closer inspection on respiratory diseases, COVID-19, influenza, SARS, and MERS have similarities in pathogenesis, especially cytokine and immune response profiles. These comparable features in terms of the cytokine storm will provide hints for COVID-19 treatment[56,63]. In influenza A (H5N1) infection-induced lung injury, which acts similar to COVID-19 pro-inflammatory cytokine release, the significant benefits of MSCs in both cytokine profile and alveolar clearance are evidenced[25,64]. Menstrual-blood-derived MSC transplantation has significantly reduced mortality in influenza A (H7N9)-induced ARDS[22]. Mahendiratta et al[65] recently published a systematic review and reported pooled evidence on MSC therapy
benefits in SARS-CoV-2, SARS-CoV, MERS-CoV, and ARDS.

While MHC-1 expression of the MSCs provides the escape from Natural killer cells response, minimal MHC-2 expression or absence of this surface protein hampers the CD8+ T cell response. For this reason, they are assumed as hypoimmunogenic[66].

MSCs, provide tissue regeneration and rejuvenation with immunotolerant and immunomodulant properties on damaged tissues by exerting their effects through immune cells[67]. Also, young MSCs might be useful in older adults because aged MSCs contribute to inflammaging and immunosenescence, which may explain the high mortality rate in this population due to COVID-19[68,69]. As well as numerous mechanisms are continuing to be investigated, some of them can be summarized as follows: (1) Inhibition of T cell (significantly cytotoxic CD8+ T cells, Th 1, Th 17)[61,70-72], B cell proliferation to plasma cell (thus MSCs can reduce the secretion of immuno-globulin), Dendritic cell activation, and apoptosis of T cells; (2) Differentiation of the cytokine profile and cell type of T cells and B cells into anti-inflammatory cytokines such as induces the production of IL-10 and regulatory T cell, regulatory B cell[61,67]; (3) Reduction of production in cytokine storm-related inflammatory factors, such as IL-1α, IL-6, IFN-γ, IL-17, TNF-α (Figure 1)[73]; (4) Promoting the transformation of inflammation-related M1 macrophages to regeneration-related M2 macrophages[74, 75]; and (5) MSC products like exosomes and extracellular vesicles that do not contain any cell are thought to have similar effects to MSC transplantation, owing to the soluble mediator profiles they secrete[67,76].

Besides being encouraging and promising, the previous studies had some limitations, and one crucial of them is the small sample size. Also, the outcomes of the studies were not standardized, and most of the outcomes are observatory. Commonly evaluated parameters are CRP, D-dimer, IL-6, IL-10, TNF-α, blood lymphocyte, neutrophil counts, pulmonary involvements in thorax computed tomography, and radiography imaging. Another point is that some studies were assumed as successful, despite having already an ameliorative trend in parameters before transplantation[77, 78]. In almost all of the studies, patients had received antibiotics, antivirals, antipyretics, corticosteroids, and supportive treatments (Table 1).

**ISSUES OF THE MSC TRANSPLANTATION**

Although clinical research is still ongoing, strict ‘Good Manufacturing’ rules are applied in the preparation of MSCs for clinical use[79]. It is seen that these rules are rigorously followed in the studies. The frequently preferred IV MSC dose is 10^6 cells per kilogram, and the infusion rate is 60 min, but the total dose calculation (e.g., 15 × 10^6 cells) and multiple injection choices varied in different studies (Table 1). MSCs reach the lungs about venous vascular anatomy through IV administration and have been shown clearance from injured and inflamed lung tissue within 24-48 h[80]. Most of the studies to date have not contained any information about the ACE2 expression of administered MSCs or supposed as lack of ACE2 expression. Nevertheless, Derkeste et al[81] reported that adult bone marrow, adipose tissue, and umbilical-cord derived MSCs highly express ACE2. The same study has shown that placenta-derived MSCs and human-induced pluripotent stem cells are the best sources for COVID-19 treatment because of very low or absence ACE2 expression. Another significant aspect of MSC products is the contained pro-inflammatory cytokine amount. There are concerns regarding the possibility of worsened the cytokine storm by this situation. Moreover, the inflammatory response within the first two hours was reported due to IV MSC infusion[82]. About that, it has been seen a single shot corticosteroid application before the MSC infusion in previous studies. A recent systematic review from Thompson et al[83] has indicated intravascular (IV) MSC transplantation safety. The study has shown an association with fever but not non-fever acute infusional toxicity, infection, thrombotic/embolic events, or malignancy. However, Möll et al[84] have drawn attention to that MSCs highly express the procoagulant tissue factor and could trigger blood clotting in COVID-19 patients already in a hypercoagulable state. Finally, while cell-based strategies have tremendous benefits, it should be kept in mind that treatment costs are still very high, and the developing countries will have difficulties meeting these therapies[85].
Table 1: Promising mesenchymal stem cells studies

| Ref. | MSC type | Sample size | Dose | Outcome |
|------|----------|-------------|------|---------|
| Leng et al [86] | ACE2: MSC | 10 patients (7 MSC + 3 Placebo) | Single infusion 10^6 cells/kg cells IV, 40 min | A decrease of TNF-α and an increase of anti-inflammatory IL-10 were significant (P < 0.05). Other outcome data consisted of one critically ill patient. Three of the 7 patients who taken MSC discharged in the follow-up period. |
| Zhang et al [77] | Human umbilical cord Wharton’s jelly-derived MSCs (hWJCs) | One critically ill patient | Single infusion 10^6 cells/kg cells IV, 40 min | The patient was discharged 6 d after the administration. They suggested that remarkable amelioration in imaging, laboratory, and clinical test outcomes. |
| Sanchez-Guijo et al [87] | Adipose tissue-derived MSC (AT-MSC) | 13 severe ill patients | More than 1 infusion approximately 10^6 cells/kg cells IV | Two patients died during the follow-up period. They detected a decrease in inflammatory parameters and an increase in total lymphocyte counts 5 d after administration. |
| Sengupta et al [88] | Bone marrow MSCs derived exosomes | 24 patients | Single infusion 15 ml ExoFloTM IV | The study’s survival rate is 83%, and 71% of the patients were recovered in the study interval. The outcome of the study is a clinical improvement with an average PaO2/FiO2 rate increase of 192% (P < 0.001) |
| Peng et al [89] | UC-MSCs and CP | 1 severe ill patient | Two times infusion plasma volume 400 mL (Total) (1:160 titer SARS-CoV-2 specific IgG) 3 times infusion 10^6 cells/kg (Total) IV 30-40 min | Lack of response to CP treatment, MSCs were administrated to the patient. After the clinical improvement, the patient was discharged. |
| Liang et al [78] | UC-MSCs | 1 critically ill patient | 3 times infusion 5 × 10^6 cell (each time) with thymosin-a1 IV | Clinical and laboratory improvement had been seen. The patient was discharged 17 d after the first MSC infusion. |
| Tang et al [90] | Menstrual blood-derived MSCs | 2 patients | 3 times infusion 10^6/kg cells | Imaging and laboratory improvement had been seen. |
| Shu et al [91] | UC-MSCs | 41 severe ill patients (12 MSC treatment + 29 Placebo) | Single infusion 2 × 10^6 cells/kg IV 60 min | In treatment arm progression from severe to critical illness and 28-d mortality rate were 0, while 4 patients deteriorated to critical condition and 3 of them died, 28 d mortality rate was 10.34%. The treatment arm’s clinical and laboratory improvements were significantly faster than the placebo group. |
| Tao et al [92] | Human umbilical cord blood-derived MSCs | 1 critically ill patient | 5-times infusion 1.5 × 10^6 cells/kg (each time) IV 60-80 min | After the MSC treatment, related to the clinical condition, the patient had undergone lung transplantation. The patient died 6 d after the transplantation because of the rejection. |
| Feng et al [93] | UC-MSCs | 16 severe and critically ill patients | 4 times with one-day intervals 1 × 10^6 cells once 90 min | The primary outcome was oxygenation index on day 14, and it has improved after UC-MSCs transplantation. On day 28, there is no significant difference between severe and critical types’ mortality rates (6.25%) |
| Guo et al [94] | UC-MSCs | 31 severe and critically ill patients | 10^6/kg cells in 100 mL saline 200 mL (median volume) for each infusion | They reported a significant increase in lymphocyte count, PaO2/FiO2, and decrease CRP, D-Dimer, IL-6, procalcitonin |

UC: Umbilical cord; MSC: Mesenchymal stem cell; AT: Adipose Tissue; CP: Convalescent plasma; IL: Interleukin; PaO2: Partial pressure of oxygen; FiO2: Fraction of inspired oxygen; CRP: C reactive protein.

CONCLUSION

Despite to be seen the benefits of MSC and its products in COVID-19, the mechanisms still need to be elucidated. Therefore, the need for the results of ongoing clinical trials and meta-analyses of randomized controlled trials continues. We think that if the costs, ethical, and storage problems of treatments are resolved over time, they might prevent COVID-19 related morbidity and mortality. We foresee that most of these problems will get over with advanced researches on MSC products. However, it should not be overlooked that MSC and MSC-based treatments are still experimental and have pros and cons.

REFERENCES

1. Ge XY, Li JL, Yang XL, Chmura AA, Zhu G, Epstein JH, Mazet JK, Hu B, Zhang W, Peng C, Zhang YJ, Luo CM, Tan B, Wang N, Zhu Y, Cramer G, Zhang SY, Wang LF, Dazuk P, Shi ZL. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013; 503: 535-538 [PMID: 24172901 DOI: 10.1038/nature12711]
2. Menachery VD, Yount BL Jr, Debink K, Agnihotram S, Gralinski LE, Plante JA, Graham RL,
Sütlüoğlu H et al. Mesenchymal stem cell transplantation for COVID-19

Scobey T, Ge XY, Donaldson EF, Randell SH, Lanzavecchia A, Marasco WA, Shi ZL, Baric RS. A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence. *Nat Med* 2015; 21: 1508-1513 [PMID: 26520088 DOI: 10.1038/nm.3985]

Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet* 2020; 395: 514-523 [PMID: 31986261 DOI: 10.1016/S0140-6736(20)30154-9]

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497-506 [PMID: 31862664 DOI: 10.1016/S0140-6736(20)30183-5]

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zha 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]

Tang X, Wu C, Li X, Song Y, Yao X, Wu X, Duan Y, Zhang H, Wang Y, Qian Z, Cui J, Lu J. On the origin and continuing evolution of SARS-CoV-2. *Nat Sci Rev* 2020; 7: 1012-1023 [DOI: 10.1093/nrs/nraa046]

Le 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]

van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI, Lloyd-Smith JO, de Wit E, Munster VJ. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med* 2020; 382: 1564-1567 [PMID: 32182409 DOI: 10.1056/NEJMcm2004973]

World Health Organization. WHO Director-General’s opening remarks at the media briefing on COVID-19. 11 March 2020. [cited 10 February 2021]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

Tolksdorf K, Buda S, Schuler E, Wieler LH, Haas W. Influenza-associated pneumonia as reference to assess seriousness of coronavirus disease (COVID-19). *Euro Surveill* 2020; 25 [PMID: 32186278 DOI: 10.2807/1560-7917.ES.2020.25.11.2000258]

World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. [cited 10 February 2021]. Available from: https://covid19.who.int

Green A, Li Wenliang. *The Lancet* 2020; 395: 682 [DOI: 10.1016/S0140-6736(20)30382-2]

Oliver SE, Gargano JW, Marin M, Wallace M, Curran KG, Chamberland M, McClung N, Campos-Outcalt D, Morgan RL, Mbaeyi S, Romero JR, Talbot HK, Lee GM, Bell BP, Dooling K. The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Moderna COVID-19 Vaccine - United States, December 2020. *MMWR Morb Moral Wkly Rep* 2021; 69: 1653-1656 [PMID: 33382675 DOI: 10.15585/mmwr.mm695152e1]

Ledford H. Moderna COVID vaccine becomes second to get US authorization. *Nature* 2020 [PMID: 33340017 DOI: 10.1038/d41586-020-03593-7]

Mahase E. Covid-19: What have we learnt about the new variant in the UK? *BMJ* 2020; 371: m4944 [PMID: 33361120 DOI: 10.1136/bmj.m4944]

Parums V. Editorial: Revised World Health Organization (WHO) Terminology for Variants of Concern and Variants of Interest of SARS-CoV-2. *Med Sci Monit* 2021; 27: e933622 [PMID: 34149046 DOI: 10.12659/MSM.933622]

Parasher A. COVID-19: Current understanding of its Pathophysiology, Clinical presentation and Treatment. *Postgrad Med J* 2021; 97: 312-320 [PMID: 32978337 DOI: 10.1136/postgradmedj-2020-138577]

Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020; 20: 363-374 [PMID: 32346093 DOI: 10.1038/s41577-020-0311-8]

Fajgenbaum DC, June CH. Cytokine Storm. *N Engl J Med* 2020; 383: 2255-2273 [PMID: 32364543 DOI: 10.1056/NEJMra2026131]

Sanz-Baro R, García-Arranz M, Guadalajara H, de la Quintana P, Herreros MD, García-Olmo D. First-in-Human Case Study: Pregnancy in Women With Crohn’s Perianal Fistula Treated With Adipose-Derived Stem Cells: A Safety Study. *Stem Cells Transl Med* 2015; 4: 598-602 [PMID: 25925838 DOI: 10.5966/sctm.2014-0255]

Le Blanc K, Frassoni F, Bull L, Locatelli F, Roelofs H, Lewis I, Lanneo E, Sundberg B, Bernardo ME, Rembarzer M, Dini G, Egeler RM, Bacigalupo A, Fibbe W, Ringden O. Developmental Committee of the European Group for Blood and Marrow Transplantation. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. *Lancet* 2008; 371: 1579-1586 [PMID: 18468541 DOI: 10.1016/S0140-6736(08)60690-X]
Sütlüoğlu H et al. Mesenchymal stem cell transplantation for COVID-19

22 Chen J, Hu C, Chen L, Tang L, Zhu Y, Xu X, 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: 32926227 DOI: 10.1016/j.eng.2020.02.006]

23 Lay H, Kuok DIT, Hui KPY, Choi MHL, Yuen W, Nicholls JM, Peiris JSM, Chan MCW. Therapeutic Implications of Human Umbilical Cord Mesenchymal Stromal Cells in Attenuating Influenza A(H5N1) Virus-Associated Acute Lung Injury. J Infect Dis 2019; 219: 186-196 [PMID: 30805072 DOI: 10.1093/infdis/jiy478]

24 Hu S, Li J, Xu X, Liu A, He H, Xu J, Chen Q, Liu S, Liu L, Qiu H, Yang Y. The hepatocyte growth factor-expressing character is required for mesenchymal stem cells to protect the lung injured by lipopolysaccharide in vivo. Stem Cell Res Ther 2016; 7: 66 [PMID: 27129877 DOI: 10.1186/s13287-016-0203-5]

25 Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. Int J Infect Dis 2020; 101: 138-148 [PMID: 33007452 DOI: 10.1016/j.ijid.2020.09.1464]

26 Jehi L, Ji X, Milinovich A, Erzurum S, Merlino A, Gordon S, Young JB, Kattan MW. Development and validation of a model for individualized prediction of hospitalization risk in 4,536 patients with COVID-19. PLoS One 2020; 15: e0237419 [PMID: 32780765 DOI: 10.1371/journal.pone.0237419]

27 Garg S, Kim L, Whitaker M, O'Halloran A, Cummings C, Holstein R, Prill M, Choi SJ, Kirley PD, Alden NB, Kawasaki B, Yousef-Hindes K, Niccolai L, Anderson EJ, Opko PN, Weigel A, Monroe NL, Ryan P, Henderson J, Kim S, Como-Sabetti K, Lynfield R, Sosin D, Torres S, Muse A, Bennett NM, Billing L, Sutton M, West N, Schaffner W, Talbot HK, Aquino C, George L, Klotz A, Bresnahan L, Langley G, Hall AJ, Fry A. Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 - COVID-NET, 14 States, March 1-30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 458-464 [PMID: 32298251 DOI: 10.15585/mmwr.mm6915e3]

28 Wu Z, McGooian 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]

29 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]

30 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]

31 Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020; 110: 102433 [PMID: 32113704 DOI: 10.1016/j.jaut.2020.102433]

32 Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M, Nagata N. TMPRSS2 Contributes to Virus Spread and Immunopathology in the Airways of Murine Models after Coronavirus Infection. J Virol 2019; 93 [PMID: 30626688 DOI: 11.1128/JVI.01815-18]

33 Stokes KE, Zambrano LD, Anderson KN, Marder EP, Kaz M, El Burai Felix S, Tie Y, Fullerton KE. Coronavirus Disease 2019 Case Surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 759-765 [PMID: 32555134 DOI: 10.15585/mmwr.mm6924e2]

34 Hamming I, Timens W, Bulthuis ML, Lely AJ, Navis G, van Goor H. Tissue distribution of ACE2, an ACE homologue, in murine tissues. J Pathol 2004; 203: 631-637 [PMID: 15141377 DOI: 10.1002/path.1570]

35 Rowley AH. Understanding SARS-CoV-2-related multisystem inflammatory syndrome in children. Nat Rev Immunol 2020; 20: 453-454 [PMID: 32546853 DOI: 10.1038/s41577-020-0367-5]

36 Morris SB, Schwartz NG, Patel P, Abbo L, Beauchamps L, Balan S, Lee EH, Paneth-Pollak R, Geevarghese A, Lash MK, Dorsett P, Baren J, Smith SE, Robin M, Robinson S, Stoughton P, Lim S, Fox SE, Richardson G, Band J, Oliver NT, Kofman A, Bryant B, Ende Z, Datta D, Belay E, Godfred-Cato S. Case Series of Multisystem Inflammatory Syndrome in Adults Associated with SARS-CoV-2 Infection - United Kingdom and United States, March-August 2020. MMWR Morb Mortal Wkly Rep 2020; 69: 1450-1456 [PMID: 33031361 DOI: 10.15585/mmwr.mm6940e1]

37 Russo E, Esposito P, Taramasso L, Magnasco L, Saio M, Briano F, Russo C, Dettori S, Vena A, Di Biagio A, Garibotto G, Bassetti M, Viazzio F. GECOVID working group. Kidney disease and all-cause mortality in patients with COVID-19 hospitalized in Genoa, Northern Italy. J Nephrol 2021; 34: 173-183 [PMID: 33025516 DOI: 10.1007/s41577-020-00875-1]

38 Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients. Clin Microbiol Infect 2020; 26: 1259.e5-1259.e7 [PMID: 32535147 DOI: 10.1016/j.cmi.2020.06.003]

39 Thacil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, Clark C, Iba T. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost 2020; 18: 1023-1026 [PMID: 32338827 DOI: 10.1111/jth.14810]

40 Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Iczovich A, Kum E, Pardo-Hernandez H, Qasim A,
Martinez JPD, Rochwerger B, Lamontagne F, Han MA, Liu Q, Agarwal A, Agoritsas T, Chu DK, Couban R, Cusano E, Darzi A, Devji T, Fang B, Fang C, Flottorp SA, Foroutan F, Ghadimi M, Heels-Ansdell D, Honarmand K, Hou L, Hou X, Ibrahim Q, Khamis A, Lam B, Loeb M, Marucci C, McLeod SL, Motaghi S, Murthy S, Mustafa RA, Neary JD, Rada G, Rizai IB, Sadeghirad B, Sekercioglu N, Sheng L, Sreekantia A, Switzer C, Tendal B, Thabane L, Tomlinson G, Turner T, Vardivk PO, Vermeij RW, Viteri-Garcia A, Wang Y, Yao L, Ye Z, Guyatt GH, Brignardello-Petersen R. Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020; 370: m2980 [PMID: 32732190 DOI: 10.1136/bmj.m2980]

41 Li J, Wang X, Li N, Jiang Y, Huang H, Wang T, Lin Z. Xiong N. Feasibility of Mesenchymal Stem Cell Therapy for COVID-19: A Mini Review. Curr Gene Ther 2020; 20: 285-288 [PMID: 32867652 DOI: 10.2174/156652322099920208172829]

42 Marshall M. The lasting misery of coronavirus long-haulers. Nature 2020; 585: 339-341 [PMID: 32929257 DOI: 10.1038/d41586-020-02598-6]

43 Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebollode PA, Cuapio A, Villapol S. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. medRxiv 2021 [PMID: 33532785 DOI: 10.21203/rs.3.rs.3-266574/v1]

44 Chen S, Cui G, Peng C, Lavin MF, Sun X, Zhang E, Yang Y, Guan Y, Du Z, Shao H. Transplantation of adipose-derived mesenchymal stem cells attenuates pulmonary fibrosis of silicosis via anti-inflammatory and anti-apoptosis effects in rats. Stem Cell Res Ther 2018; 9: 110 [PMID: 29673394 DOI: 10.1186/s13287-018-0846-9]

45 Fu X, Liu G, Halim A, Ju Y, Luo Q, Song AG. Mesenchymal Stem Cell Migration and Tissue Repair. Cells 2019; 8 [PMID: 31357692 DOI: 10.3390/cells8080784]

46 Liu D, Kong F, Yuan Y, Seth P, Xu W, Wang H, Xiao F, Wang L, Zhang Q, Yang Y. Decorin-Modified Umbilical Cord Mesenchymal Stem Cells (MSCs) Attenuate Radiation-Induced Lung Injuries via Regulating Inflammation, Fibrotic Factors, and Immune Responses. Int J Radiat Oncol Biol Phys 2018; 101: 945-956 [PMID: 29975070 DOI: 10.1016/j.ijrobp.2018.04.007]

47 Yang Y, Hu S, Xu X, Li J, Liu A, Han J, Liu S, Liu L, Qiu H. The Vascular Endothelial Growth Factors-Expressing Character of Mesenchymal Stem Cells Plays a Positive Role in Treatment of Acute Lung Injury In Vivo. Mediators Inflamm 2016; 2016: 2347938 [PMID: 27313398 DOI: 10.1155/2016/2347938]

48 Wong CK, Lam CW, Wu AK, Ip WK, Lee NL, Chan IH, Lit LC, Hui DS, Chan MH, Chung SS, Sung JJ. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004; 136: 95-103 [PMID: 15030519 DOI: 10.1111/j.1365-2249.2004.02415.x]

49 Mahallawi WH, Khabour OF, Zhang Q, Mahdoul HM, Suliman BA. MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile. Cytokine 2018; 104: 8-13 [PMID: 29414327 DOI: 10.1016/j.cyto.2018.01.025]

50 Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, Xie C, Ma K, Shang K, Wang W, Tian DS. Dysregulation of Immune Response in Patients With Coronavirus 2019 (COVID-19) in Wuhan, China. Clin Infect Dis 2020; 71: 762-768 [PMID: 32619490 DOI: 10.1093/cid/ciaa248]

51 Samaddar A, Grover M, Nag VL. Pathophysiology and Potential Therapeutic Candidates for COVID-19: A Poorly Understood Arena. Front Pharmacol 2020; 11: 585888 [PMID: 33041830 DOI: 10.3389/fphar.2020.585888]

52 Lucas C, Wong P, Klein J, Castro TBR, Silva J, Sundaram M, Ellingson MK, Mao T, Oh JE, Israelow B, Takahashi T, Tokuyama M, Lu P, Venkataraman A, Park A, Mohanty S, Wang H, Wyllie AL, Vogels CBF, Earnest R, Lupidas S, Ott IM, Moore AJ, Muenker MC, Fournier JB, Campbell M, Odio CD, Casanovas-Massana A; Yale IMPACT Team, Herbst R, Shaw AC, Medzhitov R, Schulz WL, Grubaud NA, Dela Cruz C, Farhadian S, Ko AI, Omer SB, Iwasaki A. Longitudinal analyses reveal immunological misfiring in severe COVID-19. Nature 2020; 584: 463-469 [PMID: 32717743 DOI: 10.1038/s41420-020-02588-y]

53 Laing AG, Lorenc A, Del Molino Del Barrio I, Das A, Fish M, Monin L, Muñoz-Ruiz M, McKenzie DR, Hayday TS, Frances-Quijorna I, Kamdar S, Joseph M, Davies D, Davis R, Jennings A, Zlatareva I, Vantourout P, Wu Y, Sofra V, Cano F, Greco M, Theodoridis E, Freedman JD, Gee S, Chan JNE, Ryan S, Bugallo-Blanco E, Peterson K, Pisman K, Haljasmägi L, Chadi L, Moingeon P, Martinez L, Merrick B, Bisnauthsing K, Brooks K, Ibrahim MAA, Mason J, Lopez Gomez F, Babaloba K, Abdullah Jawad S, Cason J, Mant C, Seow J, Graham C, Dorees KJ, Di Rosa F, Edgeworth J, Shankar-Hari M, Hayday AC. A dynamic COVID-19 immune signature includes associations with poor prognosis. Nat Med 2020; 26: 1623-1635 [PMID: 32070934 DOI: 10.1038/s41591-020-1039-6]

54 RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Webb M, Bell J, Linsell L, Staplin N, Brightling EC, Ustianowski A, Elman A, Prudon B, Greaves DR, Fallow T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffrey K, Montgomery A, Rowan K, Juszczak E, Bailleil JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with COVID-19. N Engl J Med 2021; 384: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2102436]

55 Romani L, Tomino C, Puccetti P, Garaci E. Off-label therapy targeting pathogenic processes in COVID-19. Cell Death Dis 2020; 6: 49 [PMID: 32457788 DOI: 10.1038/s41420-020-0283-2]

56 Ryabkova VA, Churilov LP, Shoenefeld Y. Influenza infection, SARS, MERS and COVID-19: Cytokine storm - The common denominator and the lessons to be learned. Clin Immunol 2021; 223: 108652 [PMID: 33333256 DOI: 10.1016/j.clim.2020.108652]

57 Bianco P, Robey PG, Simmons PJ. Mesenchymal stem cells: revisiting history, concepts, and assays. Cell Stem Cell 2008; 2: 313-319 [PMID: 18397751 DOI: 10.1016/j.stem.2008.03.002]
Sütlüoğlu H et al. Mesenchymal stem cell transplantation for COVID-19

58 Friedenstein AJ, Petrikova KV, Kurolesova AI, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation 1968; 6: 230-247 [PMID: 5654088]

59 Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop DJ, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006; 8: 315-317 [PMID: 16923606 DOI: 10.1080/14653240600585905]

60 Viswanathan S, Shi Y, Galipeau J, Krampera M, Leblanc K, Martin I, Nolta J, Phinney DG, Senebe L. Mesenchymal stem versus stromal cells: International Society for Cell & Gene Therapy (ISCT®) Mesenchymal Stromal Cell committee position statement on nomenclature. Cytotherapy 2019; 21: 1019-1024 [PMID: 31526643 DOI: 10.1016/j.jcyt.2019.08.002]

61 Jeyaraman M, John A, Koshy S, Ranjan R, Anudeep TC, Jain R, Swati K, Jha NK, Sharma A, Kesarla KK, Prakash A, Nand P, Jha SK, Reddy PH. Fostering mesenchymal stem cell therapy to halt cytokine storm in COVID-19. Biochim Biophys Acta Mol Basis Dis 2021; 1867: 166014 [PMID: 33232817 DOI: 10.1016/j.bbadis.2020.166014]

62 Ishii E. Hemophagocytic Lymphohistiocytosis in Children: Pathogenesis and Treatment. Front Pediatr 2016; 4: 47 [PMID: 27242976 DOI: 10.3389/fped.2016.00047]

63 Latreille E, Lee WL. Interactions of Influenza and SARS-CoV-2 with the Lung Endothelium: Similarities, Differences, and Implications for Therapy. Viruses 2021; 13 [PMID: 33499234 DOI: 10.3390/v13020161]

64 Chan MC, Kuok DI, Leung CY, Hui KP, Valkenbury 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 vivo. Proc Natl Acad Sci U S A 2016; 113: 3621-3626 [PMID: 26975697 DOI: 10.1073/pnas.1601911113]

65 Mahendiratta S, Bansal S, Sarma P, Kumar H, Choodythary G, Kumar S, Prakash A, Sehgal R, Medhi B. Stem cell therapy in COVID-19: Pooled evidence from SARS-CoV-2, SARS-CoV, MERS-CoV and ARDS: A systematic review. Biomed Pharmacother 2021; 137: 111300 [PMID: 33529944 DOI: 10.1016/j.biopha.2021.111300]

66 Ryan JM, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. J Inflamm (Lond) 2005; 2: 8 [PMID: 16045800 DOI: 10.1186/1476-9255-2-8]

67 Weiss ARR, Dhahile MH. Immunomodulation by Mesenchymal Stem Cells (MSCs): Mechanisms of Action of Living, Apoptotic, and Dead MSCs. Front Immunol 2019; 10: 1191 [PMID: 31214172 DOI: 10.3389/fimmu.2019.01191]

68 Omarjee L, Perrot F, Meilhac O, Mahe G, Bousquet G, Janin A. Immunometabolism at the cornerstone of inflamming, immunosenescence, and autoimmunity in COVID-19. Aging (Albany NY) 2020; 12: 26263-26278 [PMID: 33361522 DOI: 10.18632/aging.202422]

69 Lee BC, Yu KR. Impact of mesenchymal stem cell senescence on inflamming. BMB Rep 2020; 53: 65-73 [PMID: 31964472 DOI: 10.5483/BMBRep.2020.53.3.291]

70 Abraham A, Krasnodembskaya A. Mesenchymal stem cell-derived extracellular vesicles for the treatment of acute respiratory distress syndrome. Stem Cells Transl Med 2020; 9: 28-38 [PMID: 31647191 DOI: 10.1002/sctm.19-0205]

71 Bartholomew A, Sturgeon C, Siatksas M, Ferrer K, McIntosh K, Devine S, Ucker D, Deans R, Moseley A, Hoffman R. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 2002; 30: 42-48 [PMID: 11823036 DOI: 10.1016/s0301-472x(01)00769-x]

72 Pfnusa J, Chaporet L, Richard MJ, Molens JP, Bensa JC, Favor M. Mesenchymal stem cells induce apoptosis of activated T cells. Leukemia 2005; 19: 1597-1604 [PMID: 16049516 DOI: 10.1038/sj.leu.2403871]

73 Wang Y, Chen X, Cao W, Shi Y. Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications. Nat Immunol 2014; 15: 1009-1016 [PMID: 25329189 DOI: 10.1038/ni.3002]

74 Morrison TJ, Jackson MV, Cunningham EK, Kissinpfennig A, McAuley DF, O’Kane CM, Krasnodembskaya AD. Mesenchymal Stromal Cells Medulate Macrophages in Clinically Relevant Lung Injury Models by Extracellular Vesicles Mitochondrial Transfer. Am J Respir Crit Care Med 2017; 196: 1275-1286 [PMID: 28592224 DOI: 10.1164/rrccm.201701-0170oc]

75 Ren G, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, Zhao RC, Shi Y. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell 2008; 2: 141-150 [PMID: 18371435 DOI: 10.1016/j.stem.2007.11.014]

76 Deffune E, Prudencianti A, Moraz A. Mesenchymal stem cell (MSC) secretome: A possible therapeutic strategy for intensive-care COVID-19 patients. Med Hypotheses 2020; 142: 109769 [PMID: 32371362 DOI: 10.1016/j.mehy.2020.109769]

77 Zhang Y, Ding J, Ren S, Wang W, Yang Y, Li S, Meng M, Wu T, Liu D, Tian S, Tian H, Chen S, Zhou C. Intravenous infusion of human umbilical cord Wharton’s jelly-derived mesenchymal stem cells as a potential treatment for patients with COVID-19 pneumonia. Stem Cell Res Ther 2020; 11: 207 [PMID: 32460839 DOI: 10.1186/s13287-020-01725-4]

78 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.00000000000021429]
Sensèbe L, Bourin P, Tarte K. Good manufacturing practices production of mesenchymal stem/stromal cells. *Hum Gene Ther* 2011; 22: 19-26 [PMID: 21028982 DOI: 10.1089/hum.2010.197]

Armitage J, Tan DBA, Troedson R, Young P, Lam KV, Shaw K, Sturm M, Weiss DJ, Moodley YP. Mesenchymal stromal cell infusion modulates systemic immunological responses in stable COPD patients: a phase I pilot study. *Eur Respir J* 2018; 51 [PMID: 29348155 DOI: 10.1183/13993003.02369-2017]

Desterke C, Griscelli F, Imeri J, Marcoux P, Lemonnier T, Latsis T, Turhan AG, Bennaceur-Griscelli A. Molecular investigation of adequate sources of mesenchymal stem cells for cell therapy of COVID-19-associated organ failure. *Stem Cells Transl Med* 2021; 10: 568-571 [PMID: 33273619 DOI: 10.1002/sctm.20-01819]

Hoogduijn MJ, Roemeling-van Rhijn M, Engela AU, Korevaar SS, Mensah FK, Franquena M, de Bruin RW, Betjes MG, Weimar W, Baan CC. Mesenchymal stem cells induce an inflammatory response after intravascular infusion. *Stem Cells Dev* 2013; 22: 2825-2835 [PMID: 23767885 DOI: 10.1089/scd.2013.0193]

Thompson M, Mei SH, Wolfe D, Champagne J, Ferguson D, Stewart DJ, Sullivan KJ, Doxtator E, Lalu M, English SW, Granton J, Hutton B, Marshall J, Maybee A, Walley KR, Santos CD, Weinstock B, McIntyre L. Cell therapy with intravascular administration of mesenchymal stromal cells continues to appear safe: An updated systematic review and meta-analysis. *E Clinical Medicine* 2020; 19: 100249 [PMID: 31989101 DOI: 10.1016/eclinm.2019.100249]

Moll G, Drzeniek N, Kamnieh-Milz J, Geissler S, Volk HD, Reinke P. MSC Therapies for COVID-19: Importance of Patient Coagulopathy, Thromboprophylaxis, Cell Product Quality and Mode of Delivery for Treatment Safety and Efficacy. *Front Immunol* 2020; 11: 1091 [PMID: 32574263 DOI: 10.3389/fimmu.2020.01091]

Golchin A. Cell-Based Therapy for Severe COVID-19 Patients: Clinical Trials and Cost-Utility. *Stem Cell Rev Rep* 2021; 17: 56-62 [PMID: 33009982 DOI: 10.1007/s12015-020-10046-1]

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]

Sánchez-Guijo F, García-Arranz M, López-Parra M, Monedero P, Mata-Martínez C, Santos A, Sagredo V, Alvarez-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, Prösser F. Adipose tissue-derived mesenchymal stromal cells for the treatment of patients with severe SARS-CoV-2 pneumonia requiring mechanical ventilation. A proof of concept study. *E Clinical Medicine* 2020; 25: 100454 [PMID: 32833232 DOI: 10.1016/eclinm.2020.100454]

Sengupta V, Songupta S, Lazo A, Woods P, Nolan A, Bremer N. Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19. *Stem Cells Dev* 2020; 29: 747-754 [PMID: 32232505 DOI: 10.1089/scd.2020.0088]

Peng H, Gong T, Huang X, Sun X, Luo H, Wang W, Luo J, Luo B, Chen Y, Wang X, Long H, Mei H, Li C, Dai Y, Li H. A synergistic role of convalescent plasma and mesenchymal stem cells in the treatment of severely ill COVID-19 patients: a clinical case report. *Stem Cell Res Ther* 2020; 11: 291 [PMID: 32678017 DOI: 10.1186/s12880-020-01802-8]

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]

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 umbilical cord mesenchymal stem cells. *Stem Cell Res Ther* 2020; 11: 361 [PMID: 32811531 DOI: 10.1186/s12880-020-01875-5]

Tao J, Nie Y, Wu H, Cheng L, Qiu Y, Fu J, Jiang X. Umbilical cord blood-derived mesenchymal stem cells in treating a critically ill COVID-19 patient. *J Infect Dev Ctries* 2020; 14: 1138-1145 [PMID: 33175709 DOI: 10.3855/jidc.13081]

Feng Y, Huang J, Wu J, Xu Y, Chen B, Jiang L, Xiang H, Peng Z, Wang X. Safety and feasibility of umbilical cord mesenchymal stem cells in patients with COVID-19 pneumonia: A pilot study. *Cell Proef* 2020; 53: e12947 [PMID: 33205469 DOI: 10.1111/cpr.12947]

Guo Z, Chen Y, Luo X, He X, Zhang Y, Wang J. Administration of umbilical cord mesenchymal stem cells in patients with severe COVID-19 pneumonia. *Crit Care* 2020; 24: 420 [PMID: 32653043 DOI: 10.1186/s13054-020-03142-8]
