Review

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(9) 1–12

DOI: 10.1177/0300060520955063
journals.sagepub.com/home/imr
SAGE

Mesenchymal stem cell research progress for the treatment of COVID-19

Dezhi Yao[1], Huanrong Ye[1], Zhirong Huo[1], Lei Wu[1] and Shixiong Wei[2]

Abstract

At the end of 2019, novel coronavirus (COVID-19) infection was detected in Wuhan City, Hubei Province, China. The COVID-19 infection characteristics include a long incubation period, strong infectivity, and high fatality rate, and it negatively affects human health and social development. COVID-19 has become a common problem in the global medical and health system. It is essentially an acute self-limiting disease. Patients with severe COVID-19 infection usually progress to acute respiratory distress syndrome, sepsis, metabolic acidosis that is difficult to correct, coagulation dysfunction, multiple organ failure, and even death within a short period after onset. There remains a lack of effective drugs for such patients clinically. Mesenchymal stem cells (MSCs) are expected to reduce the risk of complications and death in patients because they have strong anti-inflammatory and immunomodulatory capabilities, which can improve the microenvironment, promote neovascularization, and enhance tissue repair capabilities. China is currently conducting several clinical trials on MSCs for the treatment of COVID-19. Here, we review the research progress related to using stem cells to treat patients with COVID-19.

Keywords

Severe Acute Respiratory Syndrome-related Virus 2, mesenchymal stem cells, cytokine storm, immunoregulation, neovascularization, tissue repair

Date received: 15 April 2020; accepted: 10 August 2020

Introduction

At the end of 2019, a novel coronavirus infection was diagnosed for the first time in patients in Wuhan City, Hubei Province. Since the outbreak of the disease, the number of confirmed cases at home and abroad has increased dramatically within a

[1]Department of Respiratory, Songshan Lake Central Hospital, Dongguan, Guangdong Province, China
[2]Department of Cardiovascular Surgery, Chinese PLA General Hospital, Beijing, China

Corresponding author:
Shixiong Wei, Department of Cardiovascular Surgery, Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian Distract, Beijing 100853, China.
Email: wei_shixiong@163.com

short period.[1–3] As of 14 April 2020, the World Health Organization (WHO) has reported more than 1.2 million confirmed cases worldwide, with more than 110,000 deaths, and the death rate of hospitalized patients in China is about 2.3% to 4.3%.[4,5] The International Virus Classification Committee named it Severe Acute Respiratory Syndrome-related Virus 2 (SARS-CoV-2), and the WHO named the novel coronavirus caused by SARS-CoV-2 Coronavirus Pneumonia 2019 (COVID-19). SARS-CoV-2 is similar to Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV) that was first diagnosed in 2003 in China, but SARS-CoV-2 has a longer incubation period and stronger infectivity than SARS-CoV. A study showed that nearly 4.8 million people are at risk of infection in the United States alone, among whom more than 1.9 million patients could need to be admitted to the intensive care unit (ICU), and about 960,000 patients may need mechanical ventilation-assisted respiratory therapy. However, there are less than 100,000 ICU beds and 200,000 ventilators in the United States, and thus, the limited medical resources are facing great challenges.[6] Currently, China has incorporated COVID-19 into Class B infectious diseases as stipulated in the Law of the People's Republic of China on Prevention and Control of Infectious Diseases, and it is being managed in accordance with Class A infectious diseases.[7]

COVID-19 is an acute self-limiting disease. The clinical manifestations of patients are complex and varied from no obvious symptoms to severe respiratory failure that mechanical ventilation support is required. Patients with severe COVID-19 are also prone to acute respiratory distress syndrome (ARDS), coagulation dysfunction, metabolic acidosis difficult to correct, septic shock, and multiple organ failure (MOD).[5,8–11] Huang et al.[12] were the first to report the clinical situation of patients in our country. One-third of 41 patients (n = 13) required admittance to the ICU, and 15% of the patients (n = 6) died. Arentz et al.[13] analyzed 21 critically ill patients with COVID-19 in Washington state, USA. The initial symptoms were chest tightness and shortness of breath (76%), high fever (52%), and cough (48%), and most patients (86%, n = 18) had basic chronic diseases when they were admitted to hospital, mostly with kidney disease or heart failure. Additionally, 81% (n = 17) of patients needed to be transferred to the ICU within 24 hours after admission. All 15 patients with ARDS required mechanical ventilation-assisted respiratory therapy, among whom eight (53%) patients progress to severe ARDS within 72 hours. Medical staff around the world soon realized that there was, and currently is, no specific treatment for COVID-19. The treatment strategy for severe patients was to prevent and treat complications on the basis of symptomatic treatment while actively treating basic diseases and preventing secondary infection. Blood purification, artificial membrane lung, and serum perfusion of convalescent patients lacked sufficient effectiveness for disease treatment, and targeted vaccines cannot be developed in the short term. As a sudden major global public health event, researchers are urgently needed to develop safe and effective treatment methods.[14–18]

Currently, cell-based therapy has been formally incorporated into the diagnosis and treatment guidelines or consensus for diseases including lung, cardiovascular, liver, and kidney diseases,[19,20] and there are also multi-center successful clinical cases of umbilical cord stem cell therapy for critically ill patients in China.[3,21] On 15 February 2020, Professor Zhang Xinmin, director of the China Biological Center of the Ministry of Science and Technology, held a press conference at the joint defense and control mechanism of the State Council. He reported that

mesenchymal stem cell (MSC) technology can improve microcirculation, promote endogenous repair, and relieve ARDS symptoms by inhibiting the over-activation of immune system in patients with COVID-19, and he affirmed its effect in the treatment of severe patients.[22] This article reviews the research progress on the mechanism of COVID-19 virus at home and abroad, and the clinical research status of MSC technology in the treatment of patients with COVID-19 to provide reference for frontline clinical and scientific researchers.

SARS-CoV-2 pathogenesis

Some studies have shown that SARS-CoV-2 pathogenesis occurs through the specific recognition of its spike protein (S protein) and angiotensin I converting enzyme-2 receptor (ACE-2). Cells with positive ACE-2 expression are more susceptible (such as SARS-2003 virus, but its affinity for ACE-2 is only 5% to 10% of SARS-CoV-2).[23–25] Another study from Germany showed that the intracellular serine protease TMPRSS2 has the ability to specifically recognize and bind with the S protein of SARS-CoV-2, which plays an important role in the process of virus infection and transmission.[26,27] ACE-2 is widely distributed on the surface of human cells except for bone marrow, lymph nodes, thymus, spleen, and immune cells, while TMPRSS2 is highly expressed in alveolar type II epithelial cells and capillary endothelial cells.[28] Therefore, COVID-19 pathogens entering the patient's blood circulation can be widely spread within a short period and lead to organ damage in addition to the lung such as acute kidney injury, myocardial injury, shock, and MOD.

Research progress on COVID-19 therapy

Both chloroquine and hydroxychloroquine have been shown to have certain effects on the treatment of patients with COVID-19. A study showed that hydroxychloroquine has better effects in the early treatment of severe patients (<5 days).[15,29–34] Some scholars claimed that remdesivir (RDV), which is an antiviral nucleoside analogue drug, can add virus RNA-dependent RNA polymerase (RdRp) through competitive inhibition of natural nucleoside triphosphate (NTP) to prevent virus RNA synthesis and, thus, inhibit virus replication. RDV has shown good anti-MERS-CoV, SARS-CoV, and SARS-CoV-2 activity in *in vitro* studies and animal models, indicating that RDV can be used as a potential anti-COVID-19 drug, but its safety and effectiveness still need to be verified by phase II and phase III clinical trials.[1,13,15,16,35,36]

Pharmaceutical companies and epidemic prevention agencies worldwide have begun to develop a COVID-19 vaccine, but because the vaccine must have a sufficient scientific basis and sufficient safety, its research and development cycle may take months to years. On the basis of the drug research and development experience of MERS-CoV and SARS-CoV, searching for new potential drugs using existing drugs has become the current main strategy owing to its low research cost and short research and development cycle. A recombinant protein vaccine has just been approved to start clinical trials, an inactivated vaccine is in the stage of establishing animal infection models, a nucleic acid vaccine has undergone clinical trials (NCT04283461), a recombinant virus vector vaccine is undergoing adenovirus vector vaccine clinical trials (NCT04313127), and two other lentivirus vector vaccine clinical trials (NCT04299724, NCT04276896) are being conducted. However, owing to the lack of animal models that can effectively evaluate *in vivo* efficacy and the diversity and mutability of coronaviruses, there are still challenges in the research and development of vaccines and new drugs.[37]

MSC therapy for COVID-19

Stem cell therapy usually refers to the process of extracorporeal separation, culture, subculture, proliferation, and differentiation of exogenously obtained stem cells, which are then transplanted into patients for immune regulation and microenvironment repair. Currently, MSCs and natural killer (NK) cells are mainly divided into two types on the basis of their cell types, among which the former is widely used because it has advantages of a widely available source, convenient material acquisition, strong immune regulation, and microenvironment effects. The safety and effectiveness of MSCs have been shown in a number of basic studies and clinical trials. MSCs have been widely used in the treatment of inflammatory diseases in the field of immunology, such as in graft versus host disease (GVHD) and systemic lupus erythematosus (SLE). Some studies have shown that MSCs have definite efficacy in improving cardiovascular, kidney, liver, and other diseases.[38–41]

Potential mechanism of MSCs therapy for COVID-19

MSC regulation of the immune system. Previous studies have shown that MSCs can regulate immune cells and inflammatory factors when exposed to an inflammatory environment, which can eventually affect specific or nonspecific immune responses in the human body. This regulation is related to exosomes or various cytokines that are secreted by MSCs, such as prostaglandin (PG)E-2, interleukin (IL)-10, and transforming growth factor (TGF)-β.[42,43] MSCs regulate T cell function in many ways, including T cell proliferation, which is controlled by inflammatory stimulation. A study on cell cycle analysis revealed that T cell subsets can be blocked at the G0/G1 phase. Additionally, MSCs can regulate T cell function through cytokines, such as up-regulating the FoxP3 gene by releasing TGF-β, inhibiting the immune activity of Th17 cells, inducing their transformation into T regulatory cell (Treg) cells, or secreting hepatocyte growth factor (HGF) to regulate the Th17/Treg cell balance.[44] MSCs also play a regulatory role in the proliferation, differentiation, and antibody secretion of B cells. MSCs can affect the G0/G1 phase transition of B cells and regulate the antibody secretion ability of B cells through various transcription pathways.[45] For cell phenotype, MSCs increase the number of regulatory B cells that express IL-10 by producing EBI3, and MSCs also activate T cells to release interferon. Suppression of activated B cells in follicular and marginal areas indirectly regulates the immune function of B cells, and MSCs can also affect innate immune cells (such as macrophages and dendritic cells) to realize immune regulation. Under inflammatory conditions, MSCs regulate macrophage function in a negative feedback manner.[46] When macrophages of the pro-inflammatory type (M1) release inflammatory factors, activated MSCs can up-regulate the cyclooxygenase (COX)-2 signal and increase PGE2 secretion, thereby promoting the transformation of macrophages from classic activated pro-inflammatory type to selectively activated anti-inflammatory type (M2). MSCs secreting the anti-inflammatory factor TSG-6 combined with CD44 of macrophages will destroy the interaction between CD44 and toll-like receptor (TLR)2, inhibit the nuclear factor (NF)-κB signal downstream, and reduce the inflammatory response.[47] For dendritic cells, MSCs can secrete HGF under endotoxin stimulation to induce differentiation into regulatory dendritic cells and alleviate acute lung injury.[48]

MSCs inhibit cytokine storm in severe patients. Cytokine storm in patients with severe COVID-19 can lead to the release of nitric oxide, which affects the normal systolic and

diastolic function of blood vessels, thereby causing hypotension and multi-organ hypoxia.[49] Research has found that there are a large number of inflammatory factors in blood of patients with COVID-19, such as interferon (INF)-γ, interferon-inducible protein-10 (IP-10), and monocyte chemoattractant protein 1 (MCP-1). Research has also shown that the concentration of granulocyte colony-stimulating factor (G-CSF), MCP-1, tumor necrosis factor (TNF)-α, and other inflammatory factors in ICU patients is significantly higher than that in non-ICU patients. The severity of cytokine storm is positively correlated with the clinical manifestations of COVID-19.[50]

COVID-19 can change from a mild disease to a severe disease. Although this partially results from complications, cytokine storm also has certain damaging effects. IL-6 levels in severe patients are ten-times higher than those in non-severe patients. In addition, the IL-6 level is closely related to the serum SARS-CoV-2 virus content and vital signs of patients with COVID-19. Some scholars have now shown that sufficient use of tozumab (anti-IL-6 receptor) can prevent worsening of the disease.[51] MSCs that are derived from the human umbilical cord can also inhibit monocyte activation and IL-6 production to inhibit the development of cytokine storm and improve the patient's prognosis. Under stimulation by high IL-6 levels, MSCs can adaptively produce cytokines and exosomes that are enriched with mirR-455-3p, thus relieving cytokine storm and treating acute inflammatory liver injury. However, the effect of MSCs on cytokine storm in patients with COVID-19 still needs further research and confirmation.[52]

MSCs inhibit pulmonary fibrosis and ARDS aggravation. Studies have shown that after intravenous MSC infusion, MSCs can return to the lungs and improve the microenvironment of the lungs, protect alveolar epithelial cells, promote neovascularization, and prevent pulmonary fibrosis.[3,38–40] MSCs achieve their repair function through a variety of cytokines, especially keratinocyte growth factor (KGF).[48] KGF promotes alveolar fluid clearance and alleviates acute lung injury that is induced by endotoxin by up-regulating α1 subunit of ACE-2.[49] KGF can also up-regulate the activity of sodium potassium ATP enzyme in alveolar cells, improve alveolar fluid transport, and play a therapeutic role in ARDS and lung injury that is induced by bacterial pneumonia.[53]

The role of MSCs in bacteriostasis. Previously, some scholars questioned whether the virus could cause MSCs to lose their function when the MSCs are invaded by bacteria. However, a clinical trial in Beijing, which included seven patients with severe COVID-19 and three controls, showed that the COVID-19 virus could not infect umbilical cord MSCs that were infused intravenously.[3] Current research has confirmed that MSCs can exert their anti-COVID-19 virus effect through direct and indirect mechanisms. MSCs can produce a direct anti-virus effect by secreting antibacterial peptides and proteins (AMPs), indoleamine 2,3-dioxygenase (IDO), IL-17, and other molecules, and unlike somatic cells that produce interferon during virus invasion and then activate hundreds of genes that resist virus infection, MSCs can continuously activate a large number of anti-virus genes independent of interferon, such as the IFITM gene, which can encode protein structures that prevent viruses from invading cells.[31] MSCs can also exert an indirect antiviral effect by regulating the dynamic coordination of pro-inflammatory and anti-inflammatory elements of the patient's immune system and promoting the activity of phagocytes.[54–61] Researchers have also confirmed the immunoregulation and antibacterial and antiviral values of MSCs

using an *in vitro* sepsis model, ARDS model, and alveolar epithelial fibrosis model.[60,61] MSCs have been found to secrete at least four AMPs, which are antibacterial peptide LL-37 (Cathelicidin LL-37), human defensin 2 (Human defensin-2), hepcidin, and lipocalin-2. These AMPs mediate the cell killing process by killing cells, inhibiting the synthesis of essential proteins, DNA, and RNA of infected cells, interacting with certain targets in infected cells, and playing an active regulatory role in the infection and inflammatory progress of patients with COVID-19.[54]

MDC clinical studies

The results of two recent clinical trials showed that MSCs have a curative effect in the treatment of COVID-19. In the first clinical trial, human umbilical cord MSCs were used in three intravenous infusions that were administered to patients with COVID-19. After the second intravenous infusion, the neutrophil levels in the subjects decreased significantly, lymphocytes increased, CD4+ T and CD8+ T cells returned to normal level, and most vital signs were improved.[62] The second clinical trial showed that transplantation of MSCs can improve the prognosis of patients with COVID-19. This clinical trial recruited seven patients with COVID-19 (two mild cases, four severe cases, and one critical case) to receive one intravenous MSC transplantation each. Two to 4 days after MSC transplantation, the patient's regulatory dendritic cell population increased, the level of the pro-inflammatory factor TNF-α decreased, and the level of anti-inflammatory factor IL-10 increased.[63] The above evidence shows the beneficial effect of MSCs on the treatment of severe patients. However, more clinical data are still needed to confirm its effectiveness.

Selection of different MSC sources

In accordance with the current US Food and Drug Administration (FDA) regulations, autologous bone marrow MSCs are widely used for clinical treatment of pain that is caused by an abnormal musculoskeletal system in patients. This approach was shown to be safe and effective by many groups.[64–67] The content of MSC in adult bone marrow is relatively low, and it can be injected into joints, the spine, and other places, but it is not enough for patients with systemic diseases caused by COVID-19. Other MSCs that are available for clinical use include adipose MSC, amniotic membrane MSCs, and umbilical cord MSCs, among which umbilical cord MSCs have the best clinical promotion value for the reasons that are described below.

Compared with bone marrow, the umbilical cord has a wider source and a higher concentration of MSCs.[67,68] Systemic multi-system injury of patients with COVID-19 is serious, the demand for MSCs infusion is large, and the expansion speed of umbilical cord MSCs is extremely fast, which can efficiently complete this process under laboratory conditions.[68] Umbilical cord MSCs can be extracted using a non-invasive method, unlike bone marrow or fat MSCs. Compared with bone marrow or adipose MSCs, umbilical cord MSCs have a gene profile that is similar to embryonic MSCs, which means that it has a faster amplification speed, stronger plasticity, and no tumorigenic effect, and thus, it has better clinical efficacy. However, in contrast to the value of embryonic MSCs, umbilical cord MSCs are a type of tissue that is formed after birth that was previously considered to have no effect. Extraction of umbilical cord MSCs will not cause damage to the human body.[69] In addition, although allogeneic umbilical cord MSCs are mainly being used clinically, they have low major histocompatibility

complex (MHC) class I molecule expression, and their cell surface expresses few MHC class II molecules, and thus, it has good immune escape.[70] For these reasons, MSCs that were derived from the umbilical cord have also been used in the clinical trials of MSC therapy for patients with COVID-19 in China.

Route of administration

To date, research results have shown that intravenous infusion is still the most preferred route of administration that has been used in the current relevant studies in China. Compared with arterial infusion and intra-tissue injection, intravenous infusion has the characteristics of less trauma, safety, and reliability. Most MSCs will eventually settle in lung tissue after systemic circulation, and the lung happens to be one of the target organs that is most seriously infected by COVID-19. Previous studies also showed that MSCs that settled in lung can act on distant damaged organs through direct secretion or in a paracrine manner.[3] Some studies have shown that MSC administration to tracheal intubation patients via the airway also has certain clinical effects.[61,71,72]

Safety of MSC treatment

The most important thing is the quality of the MSCs, which should be obtained from authorized laboratories that meet the standards of China's Health and Safety Commission. Researchers should strictly screen umbilical cord MSC donors and ensure sterility at every step from the collection of umbilical cord tissue to the final preparation of reagents for clinical application. The quality assurance staff should analyze cell activity, and they must meet the clinical requirements. Clinically, sufficient preventive measures should be taken for possible complications such as pulmonary embolism when MSCs are infused into patients. Because most of the injected MSCs come from allogeneic tissues, we should always be alert for allergic reactions in patients. There have been reports of serious complications that were caused by improper administration of MSCs in the past.[73,74] First-line doctors should formulate individualized treatment plans based on the patient's situation, such as cell dosage, cell suspension concentration, and infusion speed, to ensure the maximum curative effect.

Discussion

COVID-19 enters host cells[2,3] by binding S protein on its surface via ACE-2 that are located on the surface of human cells. ACE-2 is widely expressed in human lungs, heart, liver, kidney, and various digestive organs. Almost all endothelial cells and smooth muscle cells in the human body express some ACE-2.[24,26] Therefore, once the COVID-19 virus enters the blood circulation, it will rapidly spread to multiple organs and tissues, which can also explain why ICU patients often have complications such as acute myocardial injury, arrhythmia, acute kidney injury, shock, MOD, and other complications besides ARDS.[66]

Epidemiological data show that COVID-19 has a greater impact on elderly men who have underlying diseases, and they are more prone to fatal respiratory diseases such as ARDS.[75] The current treatment and rehabilitation for critically ill patients still mainly depends on the patient's own immune mechanism. When an overactivated immune system kills virus pathogens, it also produces a large number of inflammatory factors. Some patients progress into life-threatening inflammatory factor storms, while the elderly are more affected by the decline of the immune system.[5] Abnormal activated immune cells

cause a large amount of cytokines to be released, leading to endothelial cell dysfunction, capillary leakage, accumulation of mucus in the lungs, and eventually respiratory failure in patients. Cao et al.[12] reported that serum IL-2, IL-7, G-CSF, IP10, MCP-1, MIP-1A, and TNF-α levels in ICU patients were higher than those in ward patients. A study showed that MSCs can secrete anti-inflammatory factors to inhibit the progression of the disease.[3] Flow cytometric analysis results showed that COVID-19 virus causes the failure of lymphocytes and whole immune system function through infection. MSCs can regulate or even reverse this process by inducing mature dendritic cells to enter the Jagged-2-dependent dendritic cell population, prevent monocyte migration to the lung, and up-regulate IL-10 and vascular endothelial growth factor (VEGF) expression and that other factors to promote lung repair. Therefore, MSCs have some therapeutic value for severe COVID-19 patients.[76,77]

Conclusion and future prospects

COVID-19 has become a common problem that is facing the global medical system. It is characterized by a long incubation period, strong infectivity, and high mortality rate, which seriously endangers human health and social development. However, there is still a lack of effective treatment for severe patients. SARS-CoV-2 can cause inflammatory factor storm through the patient's excessive immune response, which can lead to ARDS, sepsis, MOD, and even death. MSCs have obvious two-way immunoregulation ability. On the one hand, MSCs regulate the balance of patients' immune system by secreting factors that inhibit inflammation. On the other hand, MSCs accumulate in damaged tissues by homing, and MSCs also have direct antiviral ability by secreting various growth factors to improve the microenvironment, repair damaged cells, and stimulate cardiovascular formation. Studies have shown that intravenous infusion of the umbilical cord MSCs can reduce lung injury and prevent or reduce ARDS and other serious complications that have occurred in patients. MSCs also show efficacy in reducing the mortality rate of COVID-19 patients. Currently, China is conducting several clinical trials related to MSC treatment of COVID-19 at different stages, which have initially shown the safety and effectiveness of MSCs, but the complete mechanism of action requires further research.

Authors' contributions

Dr. Wei Shixiong collected data and wrote the first draft of the article. All authors read and approved the final manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Shixiong Wei https://orcid.org/0000-0002-1370-7967

References

1. Kruse RL. Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China. *F1000Res* 2020; 9: 72.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382: 727–733.
3. Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2 mesenchymal stem cells improves the outcomes of patients

with COVID-19 pneumonia. *Aging Dis* 2020; 11: 216–228.
4. World Health Organization (WHO). Confirmed coronavirus cases worldwide tops 125,000 in 118 countries – 4,613 deaths. SciTechDaily, April 14, 2020.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020 [Epub ahead of print].
6. Holly R. Over-capacity challenges loom large as US COVID-19 hospitalizations projected to reach 4.8M. Home Health Care News, March 12, 2020.
7. Cavazzana M, Bushman FD, Miccio A, et al. Gene therapy targeting haematopoietic stem cells for inherited diseases: progress and challenges. *Nat Rev Drug Discov* 2019; 18: 447–462.
8. Wu Z and McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020 Feb 24.
9. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; Jan 29.
10. Del Rio C and Malani PN. 2019 novel coronavirus –important information for clinicians. *JAMA* 2020 [Epub ahead of print].
11. Centers for Disease Control and Prevention. Coronavirus Disease 2019 (COVID-19), if you are at high risk. www.cdc.gov/coronavirus/2019-ncov/specific-groups/high-riskcomplications.html
12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395: 497–506.
13. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA* 2020; 323: 1612–1614.
14. Cascella M, Rajnik M, Cuomo A, et al. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls. Treasure Island (FL): StatPearls Publishing, 2020 August 10.
15. Li H, Wang YM, Xu JY, et al. Potential antiviral therapeutics for 2019 novel coronavirus. *Zhonghua Jie He Hu Xi Za Zhi* 2020; 43: 170–172.
16. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; 30: 269–271.
17. Mire CE, Geisbert JB, Agans KN, et al. Passive immunotherapy: assessment of convalescent serum against Ebola virus Makona infection in nonhuman primates. *J Infect Dis* 2016; 214: S367–S374.
18. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus* 2016; 14: 152–157.
19. Behnke J, Kremer S, Shahzad T, et al. MSC-based therapies-new perspectives for the injured lung. *J Clin Med* 2020; 3: 9.
20. Manchikanti L, Centeno CJ, Atluri S, et al. Bone marrow concentrate (BMC) therapy in musculoskeletal disorders: evidence-based policy position statement of American Society of Interventional Pain Physicians (ASIPP). *Pain Physician* 2020; 23: E83–E129.
21. Liang B, Chen J, Li T, et al. Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells. *ChinaXiv* 2020; 202002.00084.
22. Knoepfler P. 'We cannot stick to the rules': claims of stem cells saving COVID-19 patients. The Niche, March 3, 2020.
23. Xu X, Chen P, Wang J, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. *Sci China Life Sci* 2020; 63: 457–460.
24. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; 395: 565–574.
25. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; 579: 270–273.
26. Kuba K, Imai Y, Rao SA, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med* 2005; 11: 875–879.

27. Ge XY, Li JL, Yang XL, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. *Nature* 2013; 503: 535–538.
28. Hamming I, Timens W, Bulthuis MLC, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol* 2004; 203: 631–637.
29. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal [published correction appears in BMJ. 2020 Jun 3;369:m2204]. *BMJ* 2020; 369: m1328. doi:10.1136/bmj.m1328.
30. Walter J, Ware LB, Matthay MA. Mesenchymal stem cells: mechanisms of potential therapeutic benefit in ARDS and sepsis. *Lancet Respir Med* 2014; 2: 1016–1026. doi:10.1016/S2213-2600(14)70217-6.
31. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome [published correction appears in Lancet Respir Med. 2020 Feb 25]. *Lancet Respir Med* 2020; 8: 420–422. doi:10.1016/S2213-2600(20)30076-X.
32. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020; 71: 732–739.
33. Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jie He Hu Xi Za Zhi* 2020; 43: 185–188.
34. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020; 14: 72–73.
35. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; 11: 222.
36. Zhang S, Li L, Shen A, et al. Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. *Clin Drug Investig* 2020; 40: 511–518. doi:10.1007/s40261-020-00917-3.
37. Wang J, Wang BJ, Yang JC, et al. Research advances in the mechanism of pulmonary fibrosis induced by coronavirus disease 2019 and the corresponding therapeutic measures [In Chinese]. *Zhonghua Shao Shang Za Zhi* 2020; 36: 691–697. doi:10.3760/cma.j.cn501120-20200307-00132.
38. Cruz FF and Rocco PRM. The potential of mesenchymal stem cell therapy for chronic lung disease. *Expert Rev Respir Med* 2020; 14: 31–39.
39. Li D, Liu Q, Qi L, Dai X, Liu H, Wang Y. Low levels of TGF-β1 enhance human umbilical cord-derived mesenchymal stem cell fibronectin production and extend survival time in a rat model of lipopolysaccharide-induced acute lung injury. *Mol Med Rep* 2016; 14: 1681–1692.
40. Iyer SS, Co C and Rojas M. Mesenchymal stem cells and inflammatory lung diseases. *Panminerva Med* 2009; 51: 5–16.
41. Abraham A and Krasnodembskaya A. Mesenchymal stem cell-derived extracellular vesicles for the treatment of acute respiratory distress syndrome. *Stem Cells Transl Med* 2020; 9: 28–38.
42. Shi Y, Wang Y, Li Q, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. *Nat Rev Nephrol* 2018; 14: 493–507.
43. Willis G R, Fernandez-Gonzalez A, Anastas J, et al. Mesenchymal stromal cell exosomes ameliorate experimental bronchopulmonary dysplasia and restore lung function through macrophage immunomodulation. *Am J Respir Crit Care Med* 2018; 197: 104–116.
44. Chen QH, Wu F, Liu L, et al. Mesenchymal stem cells regulate the Th17/Treg cell balance partly through hepatocyte growth factor in vitro. *Stem Cell Res Ther* 2020; 11: 91.
45. Corcione A, Benvenuto F, Ferretti E, et al. Human mesenchymal stem cells modulate B-cell functions. *Blood* 2006; 107: 367–372.

46. De Witte SFH, Luk F, Sierra Parraga JM, et al. Immunomodulation by therapeutic mesenchymal stromal cells (MSC) is triggered through phagocytosis of MSC by monocytic cells. *Stem Cells* 2018; 36: 602–615.
47. Prockop DJ. Concise review: two negative feedback loops place mesenchymal stem/stromal cells at the center of early regulators of inflammation. *Stem Cells* 2013; 31: 2042–2046.
48. Lu Z, Chang W, Meng S, et al. Mesenchymal stem cells induce dendritic cell immune tolerance via paracrine hepatocyte growth factor to alleviate acute lung injury. *Stem Cell Res Ther* 2019; 10: 372.
49. Chousterman BG, Swirski FK and Weber GF. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol* 2017; 39: 517–528.
50. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. *EBio Medicine* 2020; 55: 102763.
51. Chen X, Zhao B, Qu Y, et al. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely correlated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. *Clin Infect Dis* 2020; ciaa449.
52. Shao M, Xu Q, Wu Z, et al. Exosomes derived from human umbilical cord mesenchymal stem cells ameliorate IL-6-induced acute liver injury through miR-455-3p. *Stem Cell Res Ther* 2020; 11: 37.
53. Monsel A, Zhu Y, Gennai S, et al. Therapeutic effects of human mesenchymal stem cell-derived microvesicles in severe pneumonia in mice. *Am J Respir Crit Care Med* 2015; 192: 324–336.
54. Alcayaga-Miranda F, Cuenca J and Khoury M. Antimicrobial activity of mesenchymal stem cells: current status and new perspectives of antimicrobial peptide-based therapies. *Front Immunol* 2017; 8: 339.
55. Predictive technology group addresses use of mesenchymal stem cells in treatment of secondary issues related to coronavirus. GlobeNewswire, March 17, 2020. https://finance.yahoo.com/news/predictive-technology-group-addressesmesenchymal-154552966.html
56. Frew L and Stock SJ. Antimicrobial peptides and pregnancy. *Reproduction* 2011; 141: 725–735.
57. Zanetti M. Cathelicidins, multifunctional peptides of the innate immunity. *J Leukoc Biol* 2004; 75: 39–48.
58. Bals R, Weiner DJ, Moscioni AD, et al. Augmentation of innate host defense by expression of a cathelicidin antimicrobial peptide. *Infect Immun* 1999; 67: 6084–6089.
59. Schneider JJ, Unholzer A, Schaller M, et al. Human defensins. *J Mol Med (Berl)* 2005; 83: 587–595.
60. Krasnodembskaya A, Song Y, Fang X, et al. Antibacterial effect of human mesenchymal stem cells is mediated in part from secretion of the antimicrobial peptide LL-37. *Stem Cells* 2010; 28: 2229–2238.
61. Sutton MT, Fletcher D, Ghosh SK, et al. Antimicrobial properties of mesenchymal stem cells: therapeutic potential for cystic fibrosis infection and treatment. *Stem Cells Int* 2016; 2016: 12.
62. Liang B, Chen J, Li T, et al. 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. doi:10.1097/MD.0000000000021429.
63. Leng Z, Zhu R and Hou W. Transplantation of ACE2− mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. *Aging Dis* 2020; 11: 216–228.
64. Navani A, Manchikanti L, Albers SL, et al. Responsible, safe, and effective use of biologics in the management of low back pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2019; 22: S1–S74.
65. Sanapati J, Manchikanti L, Atluri S, et al. Do regenerative medicine therapies provide long-term relief in chronic low back pain: a systematic review and metaanalysis. *Pain Physician* 2018; 21: 515–540.
66. Hernigou P, Trousselier M, Roubineau F, et al. Stem cell therapy for the treatment of hip osteonecrosis: a 30-year review of progress. *Clin Orthop Surg* 2016; 8: 1–8.

67. Arutyunyan I, Elchaninov A, Makarov A, et al. Umbilical cord as prospective source for mesenchymal stem cell-based therapy. *Stem Cells Int* 2016; 2016: 6901286.
68. Weiss ML and Trover DL. Stem cells in the umbilical cord. *Stem Cell Rev* 2006; 2: 155–162.
69. Nagamura-Inoue T and He H. Umbilical cord-derived mesenchymal stem cells: their advantages and potential clinical utility. *World J Stem Cells* 2014; 6: 195–202.
70. Tipnis S, Viswanathan C and Majumdar AS. Immunosuppressive properties of human umbilical cord-derived mesenchymal stem cells: role of B7-H1 and IDO. *Immunol Cell Biol* 2010; 88: 795–806.
71. Wilson JG, Liu KD, Zhou H, et al. Mesenchymal stem (stromal) cells for treatment of ARDS: a phase 1 clinical trial. *Lancet Respir Med* 2015; 3: 24–32.
72. Ahn SY, Chang YS, Kim JH, et al. Two-tear follow-up outcomes of premature infants enrolled in the Phase I trial of mesenchymal stem cells transplantation for bronchopulmonary dysplasia. *J Pediatr* 2017; 185: 49–54.
73. Centers for Disease Control and Prevention. Coronavirus pandemic update 37: the ACE-2 receptor - The doorway to COVID-19 (ACE Inhibitors & ARBs). Accessed date 3/18/2020.
74. Bauer G, Elsallab M and Abou-El-Enein M. Concise review: a comprehensive analysis of reported adverse events in patients receiving unproven stem cell-based interventions. *Stem Cells Transl Med* 2018; 7: 676–685.
75. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; 395: 507–513.
76. Chen L, Zhang W, Yue H, et al. Effects of human mesenchymal stem cells on the differentiation of dendritic cells from CD34(+) cells. *Stem Cells Dev* 2007; 16: 719–731.
77. Zhang B, Liu R, Shi D, et al. Mesenchymal stem cells induce mature dendritic cells into a novel Jagged-2-dependent regulatory dendritic cell population. *Blood* 2009; 113: 46–57.