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Transfusion and Apheresis Science 59 (2020) 102839

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Review

Current treatment approaches for COVID-19 and the clinical value of transfusion-related technologies

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ARTICLE INFO

Keywords:
COVID-19
Convalescent plasma
Plasmapheresis
Mesenchymal stem cell

ABSTRACT

COVID-19 is caused by SARS-CoV-2 which is a new enveloped virus that belongs to the Beta coronavirus genus. As a major health crisis, SARS-CoV-2 has infected over a million people around the world. There is currently no specific treatment available for patients with COVID-19 infection. Numerous potential therapies, including supportive intervention, immunomodulatory agents, antiviral therapy, and convalescent plasma transfusion, have been used in clinical practice. Herein, we summarize the current potential therapeutic approaches for diseases related to COVID-19 infection and discusses the clinical value of blood transfusion-related technologies used in COVID-19 treatment.

1. Introduction

COVID-19 is caused by SARS-CoV-2. SARS-CoV-2 is a new enveloped virus that belongs to the Beta coronavirus genus. SARS-CoV-2 particles are generally polymorphic, with a diameter of 60–140 nm. The genetic characteristics of SARS-CoV-2 vary significantly from those of SARS-CoV and MERS-CoV, with 79 % and 50 % homology, respectively [1]. Lu et al. constructed a structural homology model and found that the receptor-binding domain of SARS-CoV-2 is similar to that of SARS-CoV [2]. Hoffmann et al. showed that angiotensin converting enzyme 2 (ACE2), the receptor for SARS-CoV, is also the cellular receptor for SARS-CoV-2, and that the cellular protease TMPRSS2 is required for SARS-CoV-2 invasion to be completed. SARS-CoV-2 and Bat CoV RaTG13 have 96.3 % homology, which suggests that bats may be the natural host of SARS-CoV-2 [3–5. Since the first confirmed case of infection with SARS-CoV-2 in December 2019, the number of global infections has continued to grow, and the disease is often transmitted to patients' family members and medical staff. Specific and effective antiviral treatment drugs and measures are therefore urgently needed. Therefore, while conducting emergency testing for SARS-CoV-2 in the early stages of the pandemic, we have also followed the progress of antiviral drug development. Although patients with COVID-19 at our hospital are mainly treated by the Department of Infectious Diseases, Respiratory Medicine and Intensive Medicine, the Blood Transfusion department also provides related treatments. This article discusses the blood transfusion-related technologies used in COVID-19 treatment and what this treatment approach may reveal regarding its possible pathogenic mechanisms.

2. Clinical features of COVID-19

Patients with COVID-19 are the main sources of COVID-19 infection because of the long incubation period and asymptomatic nature of SARS-CoV-2 infection. SARS-CoV-2 is spread mainly through contact with viral droplets and items contaminated with viral droplets. Some patients with COVID-19 excrete SARS-CoV-2 in their feces, which suggesting that the virus could be transmitted by the fecal–oral route. People of all genders and ages and from all regions of China appear to be susceptible to SARS-CoV-2 infection.

The incubation period for COVID-19 is 1–14 days, and is most often 3–7 days. The typical clinical manifestations are fever (≥38 °C), fatigue and dry cough, and sometimes nasal congestion, runny nose, sore throat and diarrhea. Elderly individuals and those with underlying diseases such as diabetes, hypertension or cardiovascular disease are seriously affected by infection, while children only exhibit mild effects. Laboratory examinations have shown that the total number of peripheral blood leukocytes in patients infected with SARS-CoV-2 is low or normal, while the number of lymphocytes is low. Most patients' C-reactive protein levels and the erythrocyte sedimentation rate are elevated.

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https://doi.org/10.1016/j.transci.2020.102839
Received 20 May 2020; Accepted 28 May 2020
Available online 03 June 2020
1473-0502/

Computerized tomography examination shows small, patchy shadows and interstitial changes and, at later stages of disease, multiple ground-glass shadows and infiltration shadows. Patients with severe disease exhibit lung consolidation. Chest imaging shows inflammatory infiltration of the lung tissue. In severe cases, dyspnea occurs 1 week after infection, and critically ill patients rapidly progress to acute respiratory distress syndrome, septic shock, metabolic acidosis that is difficult to correct, coagulopathy and multiple organ failure [6].

3. Possible pathogenic mechanisms of COVID-19

3.1. Host cell damage caused by SARS-CoV-2 replication

SARS-CoV-2 mainly replicates in type II alveolar epithelial cells, and the replication process can cause cell and tissue damage and destruction. The main manifestation of cell destruction is apoptosis, which represents a host strategy for inhibiting viral replication and resisting infection. Usually, the damage caused by the virus is related to the viral load in the body.

3.2. Damage caused by the immune response

Viruses that enter the body activate the body's innate and adaptive immune responses. The virus activates immune cells to produce cytokines, which activate more immune cells. This reaction is generally regulated and controlled to avoid producing excessive cytokines, so that viral killing can be achieved without causing severe cell damage to the host's own tissues. However, the regulatory mechanism sometimes malfunctions, which results in uncontrolled mass production of cytokines, which creates a cytokine storm [7]. This is a severe inflammatory reaction that causes serious damage to tissues and organs, and can manifest as acute lung injury and respiratory distress syndrome [8]. Additionally, cytokine storms can also damage other tissues and organs such as the blood vessels, liver, kidney and heart, leading to bleeding, impaired coagulation, liver and kidney dysfunction and acid–base balance disorders [9]. Patients with severe cases of cytokine storm ultimately die of respiratory failure, hypoxia, cardiac arrest, shock, and so on. The magnitude of the immune response is closely related to the severity of COVID-19 [10].

3.3. Damage caused by free radicals

Viral invasion of tissues and organs can create hypoxic state, in which energy metabolism is impaired and cytochrome oxidase cannot reduce oxygen to water. Oxygen molecules are therefore deprived of an electron, which results in the conversion of harmless oxygen into lethal, active oxygen free radicals. Lipid peroxidation mediated by oxygen free radicals destroys the structure and function of various membranes, destroys mitochondria, abolishes the cell's energy supply, destroys lysosomes and induces cell autolysis [11,12]. Free radicals can cause acute lung injury through various mechanisms. They can also seriously damage the myocardial cell membrane. The production of large amounts of ions by myocardial cells can disrupt the electrical signal that controls the heartbeat and cause ventricular fibrillation, resulting in death. Free radical accumulation in the body also causes tumors and aging.

COVID-19 is likely the result of all three pathogenic mechanisms described above. It is possible that the each mechanism plays a leading role in different patients, different disease stages and different clinical disease types. For example, critically ill patients in the ICU have higher cytokine levels than patients with milder forms of the disease.

4. Progress in treatment of COVID-19

The current treatment principles for SARS-CoV-2 infection cases mainly include the protection and support of internal organs, treatment of underlying diseases, relief of symptoms and reduction of complications. Patient needs include strengthening supportive treatment, paying attention to the water–electrolyte balance and maintaining homeostasis. Oxygen therapy is required for patients with hypoxemia. Mechanical ventilation is often required for patients who do not respond to oxygen therapy and experience respiratory distress. High-flow nasal catheters and non-invasive ventilation are both useful options and invasive mechanical ventilation and extracorporeal membrane oxygenation may be required [13]. Antibacterial drugs are used to prevent and treat secondary bacterial infections. Attention should be paid to avoiding blind use or misuse of antibacterial drugs, especially in combination with broad-spectrum antibacterial drugs. Bacteriological monitoring should be strengthened for elderly, immunocompromised and severely affected patients. Hormone use is currently controversial, and improper use will increase patient mortality. According to COVID-19 diagnosis and treatment guidelines, glucocorticoids can be used for a short time in patients with severe disease, depending on their condition. No drug that specifically treats SARS-CoV-2 infection is currently available. Immunotherapy, including convalescent plasma therapy and the administration of human monoclonal antibodies or polyclonal antibodies, is an important part of comprehensive therapy. However, the available evidence for COVID-19 is limited, and the safety and effectiveness of immunotherapy for COVID-19 treatment still need basic and clinical testing. The development of a vaccine is one of the main measures needed to control the spread of the COVID-19 pandemic. Several domestic and foreign companies are using various technologies to develop SARS-CoV-2 vaccines to control the spread of SARS-CoV-2 as soon as possible.

5. Transfusion-related treatments used in patients with COVID-19

The pathogenic mechanism of SARS-CoV-2 is complex and a multidisciplinary, comprehensive treatment approach should be used to account for the different pathogenic mechanisms. Infection with SARS-CoV-2 can induce adaptive humoral and cellular immune responses, and patients exhibit stronger immunity after recovery. As the epidemic is still ongoing, little information is available regarding the status of the immune system after 2019-nCoV infection. Antibodies have been detected in the serum of some patients in the late stage of SARS-CoV-2 infection, and serum IL-2, IL-7, IL-10, GCSF, MCP-1, MIP1A and TNF-α levels are higher in patients with severe disease than in patients with mild disease. SARS-CoV-2 isolated from one patient with severe COVID-19 can be neutralized by serum from several other patients with COVID-19. The current transfusion-related technologies that can be applied to COVID-19 therapy include convalescent plasma therapy, plasmapheresis and mesenchymal stem cell therapy.

5.1. Convalescent plasma therapy

There is currently no specific effective drug against COVID-19. Some drugs that are believed to have virus-inhibiting effects are currently being tested in clinical trials. Convalescent plasma from patients who recovered from COVID-19 contains specific antibodies that can effectively treat SARS-CoV-2 infection. The premise of convalescent plasma treatment is that it is most effective in patients with a high viral titer, so it is suitable for patients with rapid disease progression or who are severely or critically ill. Convalescent plasma may aggravate lung injury in patients with multiple organ failure, and they may experience severe adverse reactions to blood transfusion, so they should not be infused. Patients should be infused with convalescent plasma early in the course of the disease when the body has not yet produced IgG antibodies. After infusion, the body obtains high levels of IgG antibodies that neutralize the virus, decrease repeated stimulation of the immune system by killer T cells, improve the humoral immune response, prevent cytokine storms and shorten the course of disease.

COVID-19 is not the first viral infection to be treated with

convalescent plasma. SARS-CoV, MERS-CoV, Ebola virus and H1N1 infections have all been treated with convalescent plasma [14–17]. In 2009, a study in Hong Kong, China showed that treating patients with severe H1N1 infection with convalescent plasma containing antibody titers ≥1:160 can significantly reduce respiratory viral load and mortality [18]. During the Ebola outbreak, convalescent plasma was used to treat two infected American medical personnel [19]. Ko et al. showed that convalescent plasma containing antibody titers ≥1:80 is effective in treating MERS-CoV infection [20]. A retrospective meta-analysis of 32 cases of SARS-CoV infection showed that early use of convalescent plasma therapy after symptom onset can reduce mortality [21].

Convalescent plasma treatment of COVID-19 requires attention to plasma donation standards, timing of infusion and evaluation of efficacy. Convalescent plasma donation standards are as follows: (1) The donor must have recovered completely and have no residual SARS-CoV-2 in the body; pharyngeal swabs, sputum, alveolar lavage fluid, blood and stools must all be negative by nucleic acid test; (2) Donors have produced high titers of protective antibodies, namely SARS-CoV-2–specific IgG antibodies. Convalescent plasma with an antibody titer≥1:160 or ≥1:320, if possible, has the best effect. The presence of IgM antibodies indicates recent viral infection, viral replication or residual virus, so convalescent plasma that is strongly positive for or has high titers of IgM antibodies should not be used for clinical infusion; (3) The donor's physical condition must meet basic blood donation standards and tests for hepatitis B surface antigen, hepatitis C antibodies, AIDS antibodies and *Treponema pallidum* antigens must be negative; (4) Donors must provide informed consent indicating that they are willing to donate plasma.

After being stimulated by viral antigens, the body mounts an initial immune response, with an incubation period of about 10 days, and then produces low-affinity IgM and IgG antibodies. When the immune insult is repeated, high-affinity IgG antibodies are quickly produced. Theoretically, the best time to infuse patients with convalescent plasma is in the early stage of the disease, when IgG antibodies have not been produced, the nucleic acid test is strongly positive, and the viral load is high. Given that the antigen-antibody reaction time is approximately 24 h, 24–48 h after infusion of convalescent plasma is likely the best time to evaluate treatment efficacy. The indicators used to evaluate efficacy include clinical symptoms, laboratory indicators, lung imaging, and nucleic acid detection.

5.2. Plasmapheresis

Plasmapheresis involves using a blood component separator to separate the plasma from the patient's whole blood. The plasma, which contains the pathogenic substances, is discarded, and the other blood components are returned to the patient, supplemented with replacement fluids such as fresh frozen plasma or human blood albumin. SARS and MERS were treated with plasmapheresis therapy [22–24]. Using plasmapheresis to treat patients with COVID-19 removes excessive cytokines and prevents the "cytokine storm," thereby reducing damage to the body. Additionally, plasmapheresis plays an important role in blocking and reducing free radical damage. Plasmapheresis is a routine procedure conducted by blood transfusion departments [25–27]; therefore, blood transfusion departments have a technical advantage in treating patients with COVID-19.

5.3. Mesenchymal stem cell therapy

Mesenchymal stem cells have immunomodulatory effects in that they prevent uncontrolled mass production of cytokines or inflammatory factors, inhibit excessive immune responses, and reduce immune damage to tissues and organs. Mesenchymal stem cells not only play a role in suppressing immune injury through immunomodulation, but also replace and repair damaged tissue and inhibit lung fibrosis. Treating COVID-19 with mesenchymal stem cells has achieved good results [28]. Stem cell therapy can suppress excessive activation of the immune system, promote endogenous repair by improving the microenvironment, slow the progression of acute lung inflammation and relieve the symptoms of respiratory distress. Initial reports show that this is a safe and effective treatment for patients with COVID-19.

6. Outlook

The clinical treatment plan for COVID-19 continues to improve. At least 28 interventional, preventive and observational studies on COVID-19 have been registered with the National Clinical Trial Registration Center. To control the spread of COVID-19, reliable diagnostic methods are needed to diagnose patients and track the spread of the epidemic, and it is necessary to develop vaccines and antiviral drugs to prevent and cure this disease. Multidisciplinary collaboration within the academic community is needed to investigate basic and clinical questions related to SARS-CoV-2 to help develop effective antiviral drugs and vaccines.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

Acknowledgments

The study was supported by the National Natural Science Foundation of China (Grant No.81802888); the Key Research and Development Project of Shandong Province (Grant No.2018GSF118088).

References

[1] Lu RJ, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395(10224):565–74.
[2] Lu J, du Plessis L, Liu Z, et al. Genomic epidemiology of SARS-CoV-2 in Guangdong Province, China. Cell 2020. pii: S0092-8674(20)30486-4.
[3] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181(2):271–280.e8.
[4] Hoffmann M, Kleine-Weber H, Pöhlmann S. A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. Mol Cell 2020. pii: S1097-2765(20)30264-1.
[5] Hoffmann M, Schroeder S, Kleine-Weber H, et al. Nafamostat mesylate blocks activation of SARS-CoV-2: new treatment option for COVID-19. Antimicrob Agents Chemother 2020. pii: AAC.00754-20.
[6] Luo Y, Yuan X, Xue Y, et al. Using the diagnostic model based on routine laboratory tests to distinguish patients infected with SARS-CoV-2 from those infected with influenza virus. Int J Infect Dis 2020. pii: S1201-9712(20)30295-2.
[7] Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017;39(5):529–39.
[8] Huang KJ, Su IJ, Theron M, et al. An interferon-Gamma-related cytokine storm in SARS patients. J Med Virol 2005;75(2):185–94.
[9] Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020. pii: ciaa248.
[10] Liu J, Zheng X, Tong QX, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 2020;92(5):491–4.
[11] Sun MS, Jin H, Sun X, et al. Free radical damage in ischemia-reperfusion injury: an obstacle in acute ischemic stroke after revascularization therapy. Oxid Med Cell Longev 2018. 3804979.
[12] Oda T, Akaike T, Hamamoto T, et al. Oxygen radicals in influenza-induced pathogenesis and treatment with pyran polymer-conjugated SOD. Science 1989;244(4907):974–6.
[13] Valdenassi L, Franzini M, Ricevuti G, et al. Potential mechanisms by which the oxygen-ozone (O2-O3) therapy could contribute to the treatment against the coronavirus COVID-19. Eur Rev Med Pharmacol Sci 2020;24(8):4059–61.
[14] Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24(1):44–6.
[15] Zhou BP, Zhong NS, Guan Y. Treatment with convalescent plasma for influenza A (H5N 1) infection. N Engl J Med 2007;357(14):1450–1.
[16] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe

acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211(1):80–90.
[17] Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14(2):152–7.
[18] Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A(H1N1)2009 virus infection. Clin Infect Dis 2011;52(4):447–56.
[19] Kraft CS, Hewlett AL, Koepsell S, et al. The use of TKM-100802 and convalescent plasma in 2 patients with ebola virus disease in the United States. Clin Infect Dis 2015;61(4):496–502.
[20] Ko JH, Seok H, Cho SY, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single center experience. Antivir Ther 2018;23(7):617–22.
[21] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211(1):80–90.
[22] Tsang K, Zhong NS. SARS: pharmacotherapy. Respirology 2003;8(Suppl):S25–30.
[23] Koch B, Schult-Dietrich P, Büttner S, et al. Lectin affinity plasmapheresis for middle east respiratory syndrome-coronavirus and Marburg virus glycoprotein elimination. Blood Purif 2018;46(2):126–33.
[24] Arabi YM, Al-Enezi F, Longuere KS, et al. Feasibility of a randomized controlled trial to assess treatment of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection in Saudi Arabia: a survey of physicians. BMC Anesthesiol 2016;16(1):36.
[25] Li ZJ, Teng BX, Luo J, et al. Clinical application of therapeutic plasma exchange in the Three Gorges Area. Transfus Apher Sci 2010;43(3):305–8.
[26] Luo MC, Wang WF, Yin WF, et al. Clinical efficacy and mechanism of lymphoplasma exchange in the treatment of Guillain-Barre syndrome. Cell Mol Biol (Noisy-le-grand) 2017;63(10):106–15.
[27] Sivakumaran P, Vo AA, Villicana R, et al. Therapeutic plasma exchange for desensitization prior to transplantation in ABO-incompatible renal allografts. J Clin Apher 2009;24(4):155–60.
[28] Leng Z, Zhu R, Hou W, et al. Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia. Aging Dis 2020;11(2):216–28.