Update on newer approaches to prevent or treat COVID-19 infection: What we all need the most right now!!

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ABSTRACT

COVID-19 convalescent plasma (CCP) therapy involves the use of circulating antibodies administration from recovered COVID 19 patients as a practical strategy to provide immediate passive immunity in susceptible recipients in need. Global concern over the potential for "second" or "third" waves of infection to occur before effective vaccines or drug therapies are available has many looking at other biological sources for large-scale production of neutralizing SARS-CoV-2 antibodies. This report summarizes some of the novel strategies for developing alternative safe sources of therapeutic autologous antibodies from COVID -19 infected patients, and provides some original thoughts on how to rapidly implement a safe passive immunity in those COVID-19 patients who are most in need of intervention. COVID-19 antibodies can be isolated or delivered using a number of other techniques including: plasmapheresis, plasma cryoprecipitate reduced (cryosupernatant), antibody hyperconcentrates and advanced cell-based delivery systems. While these proposed technological options may, in some cases, be theoretical, the growing concern over the rapid spread of the SARS-CoV-2 virus has prompted many to pursue innovative and creative solutions to reduce the mortality and morbidity resulting from the current global pandemic. A comparative analysis of various strategies currently in use deserved exploring and this highlighted separately as the essential part of this concise theme.

1. Introduction

The COVID-19 pandemic is a new critical emerging human disease, where no vaccines, or monoclonal antibodies (mAbs), or drugs are currently available for preventative measures or therapy. Active vaccination, as the first choice, requires the induction of an immune response against a given agent by a susceptible individual for the purpose of preventing or treating the disease. Development of an effective vaccine can take time to be fully validated for use. The duration of effectiveness of a vaccine must be established, so is its capability and effectiveness as a public health tool can be established. Moreover, to develop an effective and appropriate of vaccine to the SARS-CoV-2 virus, it is advisable to target the spiky crown of the virus to prevent viral propagation via entry of the virus into the cell and to target the viral development machinery. Trials underway in the UK indicate that there is promising progress with the development of an effective vaccine. In addition, the use of available drug therapies, such as dexamethasone to treat lung inflammation or the antiviral Remdesivir, can reduce mortality. More data are expected in the future with the use of other relevant drugs.

COVID-19 convalescent plasma (CCP) therapy involves the use of circulating antibodies (Abs) administration from recovered COVID 19 patients, in particular after 2−4 weeks recovery, as a practical strategy to provide immediate passive immunity in susceptible recipients in need. The success of therapeutic use of convalescent plasma in Ebola cases is well established [1,2] and this has led many investigators worldwide to pursue developing COVID-19 convalescent plasma programs for compassionate and emergency use [3–10].

Currently, to respond to the COVID-19 pandemic crisis many countries have adopted widespread public health initiatives for the testing, tracking, tracing, and isolation of those that are at risk of transmitting the SARS-CoV-2 virus. Through these initiatives, it has become possible to identify recovered COVID-19 individuals who can participate in large CCP programs. Currently in the USA and other countries, multiple randomized control trials are underway to evaluate the efficacy of CCP

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therapy. Such programs are highly complex undertakings and have required rigorous risk assessments, and detailed planning in order to ensure that there are the required resources and staff available to perform the targeted donor recruitment, plasma collection, testing, and product inventory management required [3]. Establishing appropriate SARS-CoV-2 antibody titres for donor selection, evaluating concerns over residual levels of virus antigen in asymptomatic individuals and the need to adopt pathogen inactivation processes as part of standardizing apheresis collections are some of the additional challenges facing the rapid establishment of CCP programs.

At the time of preparing this article, more than 53,000 people in the United States have received COVID-19 convalescent plasma (www. uscovidplasma.org) and controlled clinical trials of CCP are underway around the world. Given the lack of other therapies available, many countries are making available CCP under "Expanded Access" or compassionate use programs, while at the same time conducting the clinical trials that will establish if CCP has any clinical benefit in patients affected by the disease. While limited studies have reported on the effectiveness of CCP in treating patients with severe disease [7,11], these studies have served in guiding important decisions around donor selection and appropriate source and dose of neutralizing antibodies in CCP products. Importantly, as evidence emerges from large multi-site clinical trials, new indications for the collection, production and use of CCP will emerge which will allow for more targeted use of this product.

Global concern over the potential for "second" or "third" waves of infection to occur before effective vaccines or drug therapies are available has many looking at other biological sources for large-scale production of neutralizing SARS-CoV-2 antibodies. This report summarizes some of the novel strategies for developing alternative safe sources of therapeutic autologous antibodies from COVID-19 infected patients, and provides some original thoughts on how to rapidly implement a safe passive immunity in those COVID-19 patients who are most in need of intervention.

2. Alternative sources of COVID-19 antibodies for clinical use

To support the development of guidelines for COVID-19 management, systematic reviews and meta- analyses on the use of convalescent plasma in COVID-19 and other severe respiratory viral infections, including influenza and Ebola viral infections, have been performed [6–9]. Intriguingly, in one meta-analysis the quality of evidence was very low for all efficacy outcome and raises the possibility that convalescence plasma has minimal or no benefit in the treatment of COVID-19. This highlights that there is an urgent need for optimizing the products to be used, more carefully establishing antibody titers, dose, and at what stage of disease such preventative or therapeutic modality can provide the most favorable clinical outcome to recipients.

In general, convalescent plasma is collected from eligible donors who have previously been confirmed positive for COVID-19 by a laboratory test but have recovered and are symptom-free for 14–28 d. Leukodepleted CCP from whole blood donation can be stored fresh as liquid plasma for up to 40 d or frozen for up to 12 months prior to use. However, COVID-19 antibodies can be isolated or delivered using a number of other techniques including:

i) **Plasmapheresis**: Standardisation of plasma collection using modern mobile apheresis procedures can be used to collect single or double doses of CCP from an individual donor. As plasmapheresis infrastructure is well established and readily accessible to a large percentage of the population, this method of collecting large numbers of CCP has been adopted by many of the regional and national programs that have been launched to support ongoing clinical trials and compassionate / emergency access programs.

ii) **Plasma Cryoprecipitate Reduced (Cryosupernatant)** - Recently we have proposed the use of Plasma Cryoprecipitate Reduced (US) or Plasma, Fresh Frozen Cryoprecipitate Depleted (Europe) instead of apheresis plasma from recovered COVID-19 patients as a source of neutralizing SARS-CoV-2 antibodies [5]. Since originally proposed by Judith Pool in 1964 [12], most blood manufacturers are able to produce cryoprecipitate supernatant from rapidly frozen plasma. The plasma containing the neutralizing SARS-CoV-2 antibodies is rapidly frozen to less than – 70 °C, in liquid nitrogen or a deep freezer and the cryoprecipitate, containing FVIII, fibrinogen and fibronectin is isolated after thawing overnight at 4 °C using a cold centrifuge and the cryosupernatant containing all immunoglobulins is transferred to a new bag and store in the refrigerator for up to 5 days if required before freezing. This cryosupernatant has found a unique place in therapeutic exchanges of thrombotic thrombocytopenic purpura (TTP) patients with enormous success, as it lacks the high molecular substances in plasma. Our suggestion is that leukocyte-depleted and virally inactivated cryosupernatant would remove the residual risk of SARS-CoV-2 infection and provide a safer product due to the depletion of large molecular weight plasma proteins than whole blood-derived and apheresis CCP.

iii) **Affinity Column Preparation of Antibody Hyperconcentrate** – Affinity columns can be used to remove either the COVID-19 viral antigen or its antibodies from COVID-19 patients, blood products or the circulation of recovered COVID-19 donors to produce a hyperconcentrate for therapeutic use. Such procedures, purposely designed by some manufacturers of affinity columns to removal FIX antibodies, have been already developed and used with success in Malmo, Sweden and can be easily adopted to COVID-19 antibody removal. In fact, a capture ELISA, with a plate coated with recombinant ACE-2, or its complexes with S-Protein or its S1 subunit, as a specific receptor, have been designed for capturing allo- or autoantibodies present in COVID 19 patients; especially useful for those with delayed severe complications. This would allow measurement of the kinetics of these antibodies during disease evolution. If present, these antibodies are expected to be alloantibodies, induced by the association of the viral protein. A similar design could be constructed on an affinity column matrix to capture antibodies or antigens as required either in the circulation or from FFP from COVID-19 plasma. To enhance the safety of the antibody hyperconcentrate, the final products should be pathogen inactivated or UVC sterilized.

iv) **Other Therapeutic Alternatives** - Several other protocols might be helpful to consider including platelet exchange instead of plasma exchange from COVID-19 patients to combat severe viral infection of the lungs. Platelet therapy or viral-inactivated platelet lysates which contain all of the active components in a platelet product are a routine procedure in many establishments and may be a new mode of therapy for COVID-19 patients.

v) **Advanced Cell-Based Delivery Systems** - Instead of passive immune therapy through plasma exchange, local delivery of hyperconcentrated COVID-19 antibodies using engineered RBCs or other carriers may be a future consideration. RBC are considered to be the best natural drug delivery system due to their abundance, long circulation half-life and their well-established immune-biocompatibility and biodegradability. With well-established protocols for their safe collection, processing and storage this makes RBCs readily available to be used as delivery systems. The emergence of stem-cell derived RBCs provides further opportunities for developing customized antibody delivery systems for immune therapy [13]. Currently, several drug-loading techniques such as encapsulation and surface conjugation have been used for the effective treatment of

infections, cancer, and chronic autoimmune diseases [13]. More recently, there is progressive evolution in the use of inhalable drug delivery systems for lung cancer therapy. Inhalation offers many advantages as it is a non-invasive method of drug administration as well as provides for localized delivery of anti-cancer drugs to lung tumors. Currently various inhalable colloidal systems exist for tumor-targeted drug delivery including polymeric, lipid, hybrid and inorganic nanocarriers. These approaches for enhanced delivery of nanocarriers to lung cancer cells were illustrated by the recent advances of inhalable microparticles-based drug delivery systems for lung cancer therapy including: large porous, solid lipid and drug-complex microparticles [14]. Despite enormous progress in this field, nevertheless,s little is done in the direction of the potential application of RBC-based DDS in transfusion therapy in particular hypoxia that appears to be a common feature of COVID-19 patients even in the preclinical stages. Hence, deserved to be explored further by investigators with appropriate know how as a research protocol.

3. Conclusions

In countries without access to advanced blood-processing technologies, choices may initially be restricted to convalescent plasmapheresis using modern apheresis tools that provide leukoreduced plasma for the treatment of COVID-19 patients. As ongoing clinical trials establish the optimal conditions for CCP therapy, data on effective neutralizing antibody concentrations and dose will help inform the development of more efficient plasmapheresis protocols. The use of two units of plasma, or plasma from two different individuals and /or even preparation of pools of immunoglobulins containing antibodies from various individuals may emerge as the most effective therapy. Cryosupernatant plasma or pools of cryosupernatant plasma may also be considered as evidence on the effectiveness of these protocols is collected. In technologically more advanced countries, additional options for pathogen inactivated and sterilized convalescent plasma or blood products such as immunoglobulins to SARS-CoV-2, including virally inactivated minipool plasma may be considered.

This commentary has introduced various alternatives to the current use of COVID-19 convalescent plasma to treat COVID-19 patients. While the proposed technological options may, in some cases, be theoretical, the growing concern over the rapid spread of the SARS-CoV-2 virus has prompted many to pursue innovative and creative solutions to reduce the mortality and morbidity resulting from the current global pandemic.

References

[1] Burnouf T, Seghatchian J. Ebola virus convalescent blood products: where we are now and where we may need to go. Transfus Apher Sci 2014;51(2):120–5.

[2] World Health Organization. Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion as an empirical treatment during outbreaks. 2014 (Accessed Feb 20, 2020). September, http://apps.who.int/iris/rest/bitstreams/604045/.

[3] Brown BL, McCullough J. Treatment for emerging viruses: convalescents plasma and COVID-19. Transfus Apher Sci 2020;59(3):102790.

[4] Amiral J, Vissac AM, Seghatchian J. Covid-19, induced activation of hemostasis, and immune reactions: Can an auto-immune reaction contribute to the delayed severe complications observed in some patients? Transfus Apher Sci 2020;59(3): 102804.

[5] Seghatchian J, Lanza F. Convalescent plasma, an apheresis research project targeting and motivating the fully recovered COVID 19 patients: a rousing message of clinical benefit to both donors and recipients alike. Transfus Apher Sci 2020;59 (3):102794.

[6] Dholaria B, Savani BN. How do we plan hematopoietic cell transplant and cellular therapy with the looming COVID-19 threat? Br J Haematol 2020;189(2):239–40.

[7] Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020;323(16):1582–9.

[8] Lanza F, Seghatchian J. Reflection on passive immunotherapy in those who need most: some novel strategic arguments for obtaining safer therapeutic plasma or autologous antibodies from recovered COVID -19 infected patients. Br J Haematol 2020;190(1):e27–9.

[9] Li G, Fan Y, Lai Y, Han T, Li Z, et al. Coronavirus infections and immune responses. J Med Virol 2020;92(4):424–32.

[10] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, et al. Research and development of therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci 2020;6(3):315–31.

[11] Duan K, Liu B, Li C, Zhang H, Yu T, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA 2020;117(17): 9490–6.

[12] Pool JG, Hershgold EJ, Pappenhagen AR. High-potency antihaemophilic factor concentrate prepared from cryoglobulin precipitate. Nature 1964;203:312.

[13] Villa CH, Seghatchian J, Muzykantov V. Drug delivery by erythrocytes: "Premium non nocere. Transfus Apher Sci 2016;55(3):275–80.

[14] Rossi L, Fraternale A, Bianchi M, Magnani M. Red cell membrane processing for biomedical applications. Front Physiol 2019;10:1070.