COVID-19 STRATEGIC COMMENTARY

CAN THE COVID-CURED CURE OTHERS?
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By Professor Frank Gannon

It is a simple if not simplistic scenario: A patient with COVID-19 recovers to full health. The virus has evoked an immune response. A blood donation from the cured patient provides the plasma in which the antibodies are present. The plasma is treated to remove any unwanted contaminants (remember the HIV and Hepatitis infections from transfusions?). The plasma is then diluted and transferred to a seriously-ill COVID-19 patient. Based on the assumption that the antibodies not only were a response to COVID-19 but were also the reason the cured person survived, the hope and expectation are that the cured person's donation will provide a cure.

Convalescent Plasma Therapy (CPT), as outlined above, is one member of the very thin armoury of treatments to save lives after COVID-19 infections. It gets less airtime than drugs such as Remdesivir or vaccines that are racing to trials. Perhaps that is because, in one version, there are fewer consequences for the shares of companies and thus, less hype. The technology to prepare CPT is widely available and not very expensive. The treatment could be local and hence there are no problems with a cold chain. As only 2-4% of those infected by COVID die, it follows that there should not be a shortage of supply from the other 90+%. The ethnic biases of blood groups should not be a problem if the source and the recipient are local.

Early attempts

When the infection was pre-pandemic and local in China and South Korea, some clinicians started to use CPT. The results were promising (1-3, for example). Enthusiasm grew for CPT and grants were awarded in the EU and elsewhere to test the effectiveness of the treatment. The difficult step from observations on a small number of patients to a positive outcome from a case-controlled trial had to be taken. This is no different from the trials that are needed for other treatments, even when the general approach of CPT has been used previously and is deemed to be safe.

The results from the first well-designed study have now been reported (4). The paper ends with the dreaded words; *was not statistically significant (see below for a short excerpt from this and other papers).* The irony is that the problem behind the statement is that the trial could not recruit enough patients as the disease came under control in China. The same statistical inadequacy was behind the initial inconclusive trial of Remdesivir in China also. Perhaps, the accusation of under-reporting is not well-founded after all?

When I read the paper by Li et al (4), I thought that was the end of the CPT story. A solution was proposed, the initial studies were promising, but a thorough study was not. However, I was intrigued by an accompanying editorial (5). It highlighted "potentially hopeful signals" and was encouraged that a proper trial was attempted. Building on the glimmer of hope from the trial and having looked at sub-groups in the study, it raised questions about the timing when the treatment might be most effective. That is part of a literature that analyses various aspects of CPT that need to be addressed, rather than simply transfusing available plasma (6-8 for example). The WHO and the FDA have made

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recommendations for trials and set limits on the dilution of plasma that should be used. The EU has established a database for all studies using convalescent plasma. Some are suggesting variations such as therapeutic plasma exchange, where the patient's blood is first removed to dilute the cytokine levels provoked by the virus (9). The authors (2) have responded to that commentary by pointing out some practical consequences (9).

Variations in the pipeline

These discussions move forward the consideration of CPT as a treatment. Another review lists the pros and cons of CPT (10). The many years of use of CPT mean that there is a great depth of knowledge about what to expect. That is a big advantage over new vaccines and drugs. The other related optimistic news is that there is active work on moving to more consistent and powerful treatments based on convalescent plasma. Given its origins and core skills, it is good to see that CSL is part of a global effort to bring the second wave of CP-related products online. Some of these, hyperimmune globulin (H-Ig) are enriched antibodies that are viewed and certified as pharmaceutical products and have the benefit of consistency and reproducibility. Others are moving to make recombinant H-Igs. These appear to me to have great promise and I look forward to results from their use. A terrific review in Nature Biotechnology by Cormac Sheridan (11) covers these developments so well that I will not attempt to paraphrase his work. A further aspect of the H-Ig story is that a number of major companies including Takeda, CSL-Behring and others from around the globe are working together to deliver a non-branded product. This seems like the correct altruistic response to take in face of the global problem of Covid.

Quiet, positive momentum

There is a quiet momentum behind the development of simple and advanced forms of CPT. Its accessibility, positive hints of efficacy and a legacy of information from its use against other pathogens underlie its promise. As the epicentre of the disease moves to South America, the low cost and local availability could make CPT a very credible first line of treatment. Indeed, the paucity of alternatives at present, even in the most advanced economies, is an argument in its favour. As for all of the candidates for a cure, the essential next step is to have reports of efficacy from statistically sound clinical trials. This is a recurrent theme. We have to recognize that it is a source of confusion for the general public to hear one rushed announcement of success being contradicted shortly after by more thorough work. I will return to that theme soon. As is said in Ref 6; now is the time for better science. The cooperative efforts of the clinicians and companies towards building some next generation products together may propel CPT to the default first line of treatment while we await the cavalry of new alternative drugs.

References

(1) **Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma.**
Chenguang Shen, PhD; Zhaoqin Wang, PhD; Fang Zhao, PhD; Yang Yang, MD; Jinxiu Li, MD; Jing Yuan, MD; Fuxiang Wang, MD; Delin Li, PhD; Minghui Yang, PhD; Li Xing, MM; Jinli Wei, MM; Haixia Xiao, PhD; Yan Yang, MM; Jiuxin Qu, MD; Ling Qing, MM; Li Chen, MD; Zhixiang Xu, MM; Ling Peng, MM; Yanjie Li, MM; Haixia Zheng, MM; Feng Chen, MM; Kun Huang, MM; Yujing Jiang, MM; Dongjing Liu, MD; Zheng Zhang, MD; Yingxia Liu, MD; Lei Liu, MD
JAMA. 2020; 323(16):1582-1589. doi: 10.1001/jama.2020.4783

"…In this uncontrolled case series of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS), administration of convalescent plasma containing neutralizing antibody was followed by an improvement in clinical status…"

(2) **Effectiveness of convalescent plasma therapy in severe COVID-19 patients.**

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Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X.
Proc Natl Acad Sci U S A. 2020 Apr 28;117(17):9490-9496. doi: 10.1073/pnas.2004168117. Epub 2020 Apr 6. PMID: 32253318

"…The viral load was undetectable after transfusion in seven patients who had previous viremia. No severe adverse effects were observed. This study showed CP therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia in severe COVID-19 cases…
In conclusion, this pilot study on CP therapy shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. One dose of CP with a high concentration of neutralizing antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. The optimal dose and treatment time point, as well as the definite clinical benefits of CP therapy, need to be further investigated in randomized clinical studies."

(3) Treatment with convalescent plasma for COVID-19 patients in Wuhan, China.
Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, Xia X, Lv T.Ye M, et al.
J Med Virol. 2020 Apr 15:10.1002/jmv.25882. doi: 10.1002/jmv.25882. Online ahead of print. PMID: 32293713

"… laboratory confirmed COVID-19 patients were enrolled and received the transfusion of ABO-compatible convalescent plasma
…This study indicates that convalescent plasma therapy is effective and specific for COVID-19."

(4) Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19A RANDOMIZED CLINICAL TRIAL.
Ling Li, MD, PhD[1,2]; Wei Zhang, MD[3,4]; Yu Hu, MD, PhD[5]; et al Xunliang Tong, MD, PhD[6]; Shangen Zheng, MD[7]; Juntao Yang, PhD[8]; Yujie Kong, MD[1,2]; Lili Ren, PhD[9,10]; Qing Wei, MD[11]; Heng Mei, MD, PhD[5]; Caiying Hu, MD[12]; Cuihua Tao, MD[13,14]; Ru Yang, MD[15]; Jue Wang, MD[1,2]; Yongpei Yu, PhD[16]; Yong Guo, PhD[17]; Xiaoxiong Wu, MD[18]; Zhihua Xu, MD[12,19]; Li Zeng, MD[3,20]; Nian Xiong, MD[12,21]; Lifeng Chen, MD[22]; Juan Wang, MD[11]; Ning Man, MD[23]; Yu Liu, PhD[1]; Haixia Xu, MD[1,2]; E. Deng, MS[1]; Xuejun Zhang, MS[1]; Chenyue Li, MD[1,2]; Conghui Wang, PhD[9]; Shisheng Su, PhD[17]; Linqi Zhang, PhD[24]; Jianwei Wang, PhD[9,10]; Yanyun Wu, MD, PhD[25]; Zhong Liu, MD, PhD[1,2]
JAMA. Published online June 3, 2020. doi:10.1001/jama.2020.10044

"…In this randomized clinical trial that included 103 patients and was terminated early, the hazard ratio for time to clinical improvement within 28 days in the convalescent plasma group vs the standard treatment group was 1.40 and was not statistically significant"

(5) A Randomized Trial of Convalescent Plasma for COVID-19—Potentially Hopeful Signals.
Arturo Casadevall, MD, PhD[1]; Michael J. Joyner, MD[2]; Liise-Anne Pirofski, MD[3]
JAMA. Published online June 3, 2020. doi:10.1001/jama.2020.10218
"…In their article in JAMA, Li et al[8] present findings from the first randomized clinical trial of convalescent plasma therapy for patients with COVID-19 conducted in China It was an important accomplishment to conduct a carefully controlled trial during a pandemic with an entirely new highly contagious disease that stressed health systems in an unprecedented way.

… the first randomized clinical trial of convalescent plasma in COVID-19, reported by Li et al in JAMA, showed no statistically significant benefit in clinical improvement at 28 days or mortality among all randomized patients, but does provide an important signal of possible benefit in the subgroup of severely ill patients and suggests that high titer antibody against SARS-CoV-2 may have antiviral efficacy. …suggest that future studies should focus on determining efficacy in less severely ill patients.

If the efficacy of convalescent plasma is established by future studies, the ratio of donor to patients is favorable because individuals who recover from COVID-19 can donate 2 or 3 units of plasma, which could be used to treat more than 1 person with COVID-19 disease."

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(6) **COVID-19 Convalescent Plasma: Now Is the Time for Better Science.**
Sunny Dzik
Transfus Med Rev. 2020 Apr 23 PMCID: PMC7177063PMID: 32359789

"…Although the absence of randomized controlled data is to be expected for rare and orphan diseases, there is no excuse for their absence in illnesses with thousands of patients. In fact, the sheer numbers of individuals afflicted with and dying from COVID-19 present a clear ethical as well as scientific requirement that the health care system seek truth regarding treatments. We all hope that CCP will be a beneficial treatment, and a preliminary report by Duan et al of its uncontrolled use in 10 patients in China might be seen as encouraging [2]. Although bypassing randomized controlled investigation of CCP may be tempting given the sense of urgency to "just do something," a mistake repeated is a decision taken. Failure to "study first before wide-scale implementation" risks doing harm to both patients and the health care system."

(7) **Convalescent Plasma to Treat COVID-19Possibilities and Challenges.**
John D. Roback, MD, PhD[1]; Jeannette Guarner, MD[2]
JAMA. 2020;323(16):1561-1562. doi:10.1001/jama.2020.4940

"…Both academic[4] and industry groups are beginning to investigate the efficacy of passive antibody therapies for COVID-19 infection. If substantial, robust evidence from rigorously conducted clinical trials clearly establishes effectiveness, and if tests could identify patients who could benefit from passive immunity, the US and other countries could consider a national campaign to provide such treatment. Although a logistical challenge, this may be one approach to protect high-risk populations and could synergize with parallel efforts to develop vaccines and antiviral drugs. However, just as executive direction was critical for rapid implementation of COVID-19 tests, so it will be important to accelerate this effort. Specifically, guidance would be needed to direct blood centers and plasma fractionators to begin prioritizing collections from COVID-19-convalescent donors; expedite the availability of these products for therapeutic use; create a data collection, analysis, and regulatory infrastructure to identify factors that predict therapeutic efficacy and to inform the relative levels of convalescent plasma vs H-Ig production; and remove regulatory barriers that, for example, currently limit the use of pathogen reduction technology for convalescent plasma collections or that require several-month inventory holds on H-Ig pharmaceuticals."

(8) **Deployment of convalescent plasma for the prevention and treatment of COVID-19.**
Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JP, Pekosz A, Lau B, Wesolowski A, Katz L, Shan H, Auwaerter PG, Thomas D, Sullivan DJ, Paneth N, Gehrie E, Spitalnik S, Hod EA, Pollack L, Nicholson WT, Pirofski LA, Bailey JA, Tobian AA.Bloch EM, et al. J Clin Invest. 2020 Jun 1;130(6):2757-2765. doi: 10.1172/JCI138745.J Clin Invest. 2020. PMID: 32254064

"…Nonetheless, there are nuanced challenges, both regulatory and logistical, spanning donor eligibility, donor recruitment, collections, and transfusion itself."

(9) **Get rid of the bad first: Therapeutic plasma exchange with convalescent plasma for severe COVID-19.**
Selman Kesici, Sinan Yavuz, and Benan Bayrakci
PNAS first published May 12, 2020 https://doi.org/10.1073/pnas.2006691117

"…However, only 3 of 10 patients' respiratory status, together with laboratory parameters, improved after CP transfusion {SEE REF 2 above}
*Performing TPE (Therapeutic Plasma Exchange) with CP will provide removal of chaotic proinflammatory cytokines as well as the positive effects of CP transfusion. It is obvious that more CP will be needed for this procedure than the conventional CP transfusion but we think that this will not be a problem because there are 319,064 recovered people worldwide as of 8 April 2020 (**7**). Nonetheless, more CP may accelerate the healing process.*
RESPONSE (Duan et al): In our study, 200 mL CP containing neutralized antibody above 1:640 rapidly cleared the viremia and achieved clinical improvement. Considering the accessibility of plasma donors, using CP as replacement fluid for the therapeutic plasma exchange may be not feasible.

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(10) **Convalescent Plasma: Therapeutic Hope or Hopeless Strategy in the SARS-CoV-2 Pandemic.**
H. Cliff Sullivan John D.Roback
Transfusion Medicine Reviews. Available online 23 April 2020

"…The pros would include possible clinical efficacy, immediate availability from a large donor pool, relative ease of procuring plasma through current approved methods, and potential cost advantages over some of the more experimental antivirals.
The cons of convalescent plasma include basic administrative and logistical barriers of identifying, consenting, collecting, and testing donors.
…the current lack of widely available and validated SARS-CoV-2 antibody assays, particularly assays detecting neutralizing antibodies, may hamper identification of ideal donors
…potential viral antibody dependent enhancement (ADE), a process in which plasma antibodies exacerbate disease by enhancing viral cell entry and viral replication by various mechanisms, some of which have been described in MERS infectious model.

…the administration of passive antibodies can suppress the recipient's humoral immune system from generating pathogen-specific antibodies thereby leaving an individual susceptible to reinfection.
…risks include transfusion reactions such as transfusion related acute lung injury, transfusion associated dyspnea, transfusion circulatory overload, and serve allergic reactions with associated bronchospasm."

(11) **Convalescent serum lines up as first-choice treatment for coronavirus.**
Nature Biotechnology 38 , 655–658, Cormac Sheridan

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