COVID-19 convalescent plasma: phase 2

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As transfusion medicine specialists we understood the potential that convalescent plasma (CCP) could play early in the management of patients with COVID-19. However, with no guidance from the US Food and Drug Administration (FDA), we could not begin to establish a program for coronavirus disease 2019 (COVID-19) CCP. That changed on March 24, 2020, when the FDA issued its first guidance on this topic. The rules were clear: identify subjects with molecularly confirmed COVID-19, and after they have been asymptomatic for 14 days, test them to confirm they are no longer infectious and that they are eligible to donate CCP. With a small hospital-based donor center, an academic medical center that had implemented molecular testing for COVID-19, and an established clinical research unit, we realized we were set to establish and implement a program quickly. In addition, Iowa City, Iowa, was an initial "hot spot" for patients, as a number of local people had been infected on an Egyptian cruise the first week of March. The purpose of this commentary is to briefly summarize our initial experience establishing the CCP program and propose ideas for how to move this treatment forward to the next phase.

With the FDA guidance document on March 24, 2020, we put together an institutional review board (IRB) application to screen subjects for eligibility, obtain their consent to participate in our "study," and test them to confirm they were negative and likely eligible to donate. This application was submitted to the IRB on Friday, March 27, and was approved on April 1. By April 6, we had screened our first donor, who had been asymptomatic for 14 days (this 14-day period delayed screening for many subjects we were following), and the donor was confirmed to be negative for the virus and donated on April 9. Meanwhile, we worked with our infectious disease specialist to adopt the "Mayo" protocol, which is likely being widely used across the country as the Biomedical Advanced Research and Development Authority (BARDA)–supported expanded access protocol. This protocol became available to us on Saturday, April 4, and was approved by our IRB on April 10. We treated our first patient on April 13, 20 days after the FDA guidance document was released. As we all now realize, processes that typically take months have been compressed to weeks or even days to get CCP treatment to patients with COVID-19.

As it is now more than 1 month since the original FDA guidance document was released, we can begin to review the results to date and consider implementing plans that may improve on this therapy and eventually help us determine whether the therapy has been effective. We have treated 20 patients to date with CCP and screened more than 50 subjects to be CCP donors. On the donor side, we have tested 36 subjects who had previously tested positive for COVID-19. Of these, four patients tested viral positive, most near the 14-day window for resolution of symptoms. This finding suggests the FDA was wise to confirm that subjects in this window are tested before donation to ensure the safety of donor personnel. We also have severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody results back on 31 of our subjects. There is no standard for testing for antibodies, and we anticipate that a wide array of tests will be used at least initially. For us, we worked with our state hygienic lab to validate an enzyme-linked immunoassay (EUROIMMUN) that detects IgG antibodies against SARS-CoV-2. They are testing samples from our subjects to determine their IgG levels. The cutoff for a positive test with this assay is greater than 1.1 (ratio of optical density of patient sample to optical density of comparator) and found that 5 of our 31 (16%) subjects with molecularly confirmed COVID-19 had antibody levels below the cutoff. While the plasma from these subjects may still contain protective antibodies (IgA, IgM, neutralizing antibodies), we have made the decision to not use plasma from these donors for our patients at this time. Of the 26 remaining subjects with positive antibody results, the SARS-CoV-2 IgG ratio ranged from 1.3 to 10.7 with a mean of 5.6 and a median of 5.2. At this stage, we have

ABBREVIATIONS: CCP = convalescent plasma; COVID-19 = coronavirus disease 2019; FDA = US Food and Drug Administration; IRB = institutional review board; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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decided to ask donors with a value above 3.0 to continue to donate, while donors with a value below that will not be asked back unless we are unable to keep up with demand for that plasma or if they have a blood type we are in particular need of (AB).

The original Mayo protocol has now been revised to allow for transfusion of 1 or 2 units of plasma. Can we use this initial data to decide who should get 2 units versus just 1? We propose a protocol that would ensure all or nearly all patients get a minimal dose of CCP. First, we believe that patient weight should be factored into the dosing. Does it make sense for us to treat a 50-kg patient the same as a 150-kg patient? For nonmedical personnel, does it make sense for Kareem Abdul Jabbar to receive the same dose as Nadia Comaneci? (For the younger generation, should Lebron James get the same treatment as Simone Biles?) We propose dosing CCP like intravenous immunoglobulin, using weight-based dosing. How would we do that for CCP since we have no standard approach to measuring antibody levels? We propose using whatever antibody test you are using with your donors to help ensure that our patients at least receive "an average" therapeutic dose if given just 1 unit. For the analysis, we propose using the average antibody level (approx. 5.0) from the donors/subjects we have tested to date. Thus, an average 70-kg patient receiving a "standard" dose of plasma (210 mL) from an average CCP donor (5.0 ratio) would be getting the equivalent of 15 "units"/kg ($210 \times 5.0 / 70$). Using this equation, we reviewed the dose from the first 19 subjects (ranging in weight from 51 kg to 167 kg) who received antibody-positive CCP at our institution: nine of them received the minimum "standard dose," and 10 did not. Under our revised treatment plan, these 10 patients would have been eligible for a second unit. As we selectively recruit donors with high antibody levels to return to donate, we anticipate the percentage of patients who need more than 1 unit to reach the minimal dose will drop. This approach may help us balance preserving this precious inventory (at least for now) while doing our best to ensure that nearly all of our patients receive a minimal dose of CCP.

An additional change we would like to see in the protocol relates to ABO compatibility of the plasma. We have yet to identify a type AB donor to allow us to treat patients of blood type AB, as the current protocol requires ABO compatible plasma. We have screened our donors for low levels of ABO antibodies and have identified A/B donors with low (<1:32) anti-A/Bs. Given our experience using low-titer O whole blood and type A plasma in emergency situations, we would like to advocate for use of low-titer minor incompatible plasma when ABO-compatible plasma cannot be identified.

While randomized controlled studies are being developed to help determine whether this therapy is effective, we should also think about processes that will help us assess the effectiveness of this therapy in future analyses. We are regularly collecting and freezing serum samples from our donors at each visit. These samples may help us determine how rapidly antibody levels change over time with these donors. While the Mayo protocol consent form does not include obtaining consent to study blood samples from our transfused patients, we are working with our hospital clinical laboratories to obtain and freeze samples from each of these subjects before and after their transfusions. These stored samples will allow us to look at whether these patients had SARS-CoV-2 antibodies before receiving CCP. In addition, we may be able to determine whether the transfusion of CCP leads to detectable increases in SARS-CoV-2 antibodies in the patient. These data would allow a more careful and comprehensive assessment of these patients when the results are analyzed in the future. For example, will patients without antibodies at the time of treatment be more likely to benefit from this therapy? Can we do these studies without patient consent? We believe it is important to maintain identifiers with these samples, so patient consent will be important. Our plan is to collect the samples now and obtain consent later (postcollection consent). Postcollection consenting is a well-accepted process in the tissue collection world and applies to biospecimens that would otherwise be discarded, such as hospital blood samples. After this study is approved, we will contact these subjects to obtain consent (likely by phone/mail). If the subjects decline to participate, we will discard the samples, but if they consent to this study, we will be able to initiate the post hoc studies (and others) described above. The more facilities able to initiate these processes, the more likely it is that we will be able to determine whether CCP has been an effective therapy for COVID-19.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.