to eradicate inhibitors and how emicizumab may help to reduce the required FVIII dose, which is associated with enormous cost.[10] The observation that FVIII provides additional prohemostatic effects in the presence of emicizumab in the mouse model is therefore noteworthy.[1] Key for any prohemostatic therapy in hemophilia is how the development of hemophilic arthropathy is affected. Early experimental data in monkeys indicate that emicizumab prevents joint bleeds,[8] but clinical trial data indicate that emicizumab does not reduce joint bleeds to 0 in all patients (and neither does FVIII)[2,5-7]; thus, a better understanding of the effect of emicizumab on the progression and management of hemophilic arthropathy is urgently needed. The emicizumab-adapted hemophilia A mouse model will encompass an important tool to obtain such insights. However, it should be noted that additional modifications are needed, as indicated, before this model is suited for longer-term hemophilic arthropathy studies.[1]

Finally, while it is typical to address bleeding in hemophilia from a clotting-centric perspective, it is equally important not to overlook that bleeding, and especially joint bleeding, has its own contributing mechanisms that in addition to coagulation may include endogenous anticoagulant pathways, fibrinolysis, vascular and bone remodeling pathways, and others. Joint bleeding is the cumulative disbalance of these pathways, and the mouse is arguable the best model to test how the contributions of these pathways are affected by emicizumab. The emicizumab-adapted hemophilia A mouse bleeding model developed by Ferrière et al enables such studies and is likely to stimulate new areas of hemophilia A research focused on emicizumab.

Conflict-of-interest disclosure: The Scripps Research Institute holds intellectual property rights with L.O.M. listed as inventor. L.O.M. is a cofounder and a member of the board of directors of Hematherix, a biotech company that is developing super-FVa therapy for bleeding complications. ■

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Xia et al, page 755

Earlier the better: convalescent plasma

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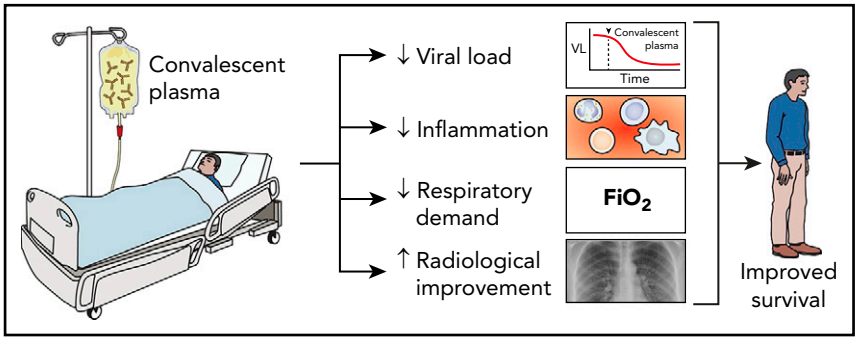
In the current issue of *Blood*, Xia et al evaluate the use of convalescent plasma for the treatment of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease 2019 (COVID-19).[1,2] SARS-CoV-2 has spurred a global crisis. To date, there are limited treatment options for COVID-19 and no proven prophylactic therapies for those who have been exposed to SARS-CoV-2.

Passive antibody administration through transfusion of convalescent plasma offers the best and only short-term strategy to confer immediate immunity to susceptible individuals for COVID-19. Passive antibody therapy has been in use for over a century for both postexposure prophylaxis (eg, rabies, polio) and treatment (eg, SARS-CoV-1, Middle East respiratory syndrome, Ebola).[3]

Limited data suggest a clinical benefit of convalescent plasma for treating patients with COVID-19, including radiological resolution, reduction in viral loads, and improved survival in hospitalized but nonintubated patients.[4,5] In New York City, a propensity score-matched control study demonstrated that convalescent plasma significantly decreased mortality among nonintubated plasma recipients, but convalescent plasma did not appear helpful for the intubated convalescent plasma recipients.[6] Most recently, a randomized control trial of patients with severe disease but not those with critical disease (ie, those receiving mechanical ventilation) who received convalescent plasma showed more frequent and faster clinical improvement compared with controls. However, the trial was terminated early due to lack of eligible patients at the study sites in China because of decreasing cases there.[7] All of these studies combined, however, included <150 patients treated with convalescent plasma. Convalescent plasma may be the best treatment currently available so it is critically important to assess efficacy, safety, and the subpopulations of patients who will benefit most.

Xia et al present the most extensive study to date among COVID-19 patients in the largest hospital in Wuhan, China. There



Convalescent plasma improves patient outcomes. Studies have demonstrated when convalescent plasma is given prior to the onset of critical disease in COVID-19 patients, it decreases patient's viral load, inflammatory state, and respiratory demand and improves their outcomes with fewer fatalities. VL, viral load.

were 138 patients who received convalescent plasma and 1430 control patients. Although the patients who received convalescent plasma were older and had more severe disease, convalescent plasma therapy led to a decrease in viral load, decrease in C-reactive protein concentration, radiologic improvements, and >50% decrease in mortality compared with controls (see figure). Convalescent plasma therapy did not help the sickest patients (ie, those requiring extracorporeal membrane oxygenation and mechanical ventilation). In addition, convalescent plasma only appeared beneficial to those patients who received convalescent plasma within the first 7 weeks of diagnosis but not in those who received it later.

The US Food and Drug Administration published guidance for 3 pathways to access convalescent plasma. The primary pathway is a government-led initiative that set up the Expanded Access Program (EAP) for participating institutions under one Investigational New Drug approval and a master treatment protocol. Through the EAP, convalescent plasma has been requested for >30 000 patients in the United States, and >23 000 patients have been transfused to date.[8] In response to the EAP and substantial demand for convalescent plasma, the New York Blood Center Enterprises developed a system and scaled up to collecting to >5000 units of convalescent plasma per week.[9] A large analysis of the first of 5000 convalescent plasma transfusions through the EAP found virtually no adverse events attributable to the convalescent plasma treatment.[10]

Most recently, the outcomes of the first 20 000 patients who had been transfused 1 to 2 convalescent plasma units were reported. The 7-day mortality rate was 8.6% and higher in intensive care unit (10.5% vs 6.0%), ventilated (12.1% vs 6.2%), and septic or multiorgan failure (14.0% vs 7.6%) patients.[11] Although these data further support earlier use of convalescent plasma in the disease course, it remains unknown if convalescent plasma improves outcomes compared with other treatment options.

Also, in this issue of *Blood* (and discussed in another Blood Commentary), Hegerova et al present a case series of 20 patients who received convalescent plasma under the EAP compared with 20 matched control patients.[2] Patients who received convalescent plasma had a decrease in their body temperature, C-reactive protein concentration, and FiO_2. None of the patients who received convalescent plasma within the first 7 days of hospitalization died. In the future, it is hoped, more efficacy information will be available from the thousands of patients receiving convalescent plasma through the EAP; currently the correlation between convalescent plasma antibody levels and patient outcomes is being investigated. This information is urgently needed to ensure COVID-19 patients are being best served.

The study by Xia et al, and also Hegerova et al, provides a dramatic improvement in the evidence supporting the use of convalescent plasma for patients infected with SARS-CoV-2. Similar to other infections, passive antibody therapy appears to be most effective when administered early after the onset of symptoms. Convalescent plasma also appears to be safe based on few adverse events associated with the transfusion. Limitations to these studies, however, include not fully matched cases and controls. Furthermore, the studies were confounded by patients simultaneously receiving other therapies (ie, antiviral therapy, hydroxychloroquine, traditional Chinese medicine, anticoagulation, etc) Last, data on neutralizing antibody titer were not available, and antibody titers were widely variable of the transfused convalescent plasma. Consequently, well-conducted randomized controlled trails are urgently required. The clinical trials are needed to assess the subpopulations who may or may not benefit from convalescent plasma. There are a number of different protocols for various patient populations, including (1) postexposure prophylaxis to prevent infection, (2) early treatment to prevent hospitalization, (3) treatment just after hospitalization for those requiring oxygen but not yet intubated (ie, green zone), (4) severely ill patients who are already intubated, and (5) pediatric patients. As of 1 June 2020, on ClinicalTrials.gov, there are currently >80 convalescent plasma trials for COVID-19. In this time of public health crisis, institutions should collaborate and form multicenter trials to quickly determine the best treatments.

Convalescent plasma is one of the best therapies currently available to treat COVID-19. However, critical questions on timing of treatment in the disease course and dose (volume and antibody titer levels) need to be answered. These answers will also help prepare us for other passive antibody treatments (eg, hyperimmune globulin made from convalescent plasma and monoclonal antibodies). The medical community must work together to battle this deadly disease in order to determine the best therapies and reduce mortality.

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Hegerova et al, page 759

Convalescent plasma to treat COVID-19

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In this issue of *Blood*, Hegerova et al report on a study of 20 hospitalized patients with severe or critical coronavirus disease 2019 (COVID-19) who were transfused with convalescent plasma (CP); the authors suggest a favorable, albeit modest, benefit as compared with 20 matched (ie, nontransfused) controls, particularly when transfusion was undertaken within the first 7 days of hospitalization.[1]

CP that has been collected from individuals who have recovered from COVID-19 (ie, COVID-19 convalescent plasma [CCP]) has emerged as a leading treatment of COVID-19. Early studies in China reported benefits of CCP transfusion in patients with COVID-19, including viral clearance, radiological resolution of pulmonary disease, improved oxygenation, and survival.[2,3] This spurred efforts by the US Food and Drug Administration (FDA) and the US blood-banking community to collect and transfuse CCP on an unprecedented scale.[4] To date, over 26 000 patients have been transfused with CCP in the United States alone, primarily through a government-led expanded access program.[5] Data gleaned from this program have shown CCP to be well tolerated, with comparable risk to standard (ie, nonimmune) plasma.[6]

Hegerova et al add to a growing number of observational studies that have reported on the use of CCP to treat COVID-19. The outcomes of the collective studies span dramatic examples of recovery to the absence of demonstrable effect,[2,3,7,8] highlighting the challenges of CP in general. Like many infectious diseases for which CP has been applied, clinical trial data are lacking. CP is typically deployed in times of emergency when the design and execution of randomized clinical trials is most complex. Beyond the administrative, regulatory, and logistical barriers of initiating trials in times of crisis, timing is critical: once epidemics wane, enrollment goals risk going unfulfilled. There is already at least 1 example of this with COVID-19: in a clinical trial in China, critically ill patients with COVID-19 were randomized to CCP with standard therapy vs standard therapy alone.[9] Despite encouraging signals of benefit in earlier—severe rather than life-threatening disease, the trial failed to show a significant difference in clinical improvement 28 days following randomization, its primary outcome. With only 103 of its targeted 200 subjects enrolled, the study was ultimately underpowered.

Currently, we are reliant on observational data of CCP to guide practice.[2,3,7,8] Observational studies have proven invaluable to the CCP initiative but they share a host of methodologic limitations. Some are constrained by small sample sizes and lack of controls. All have selected for severe COVID-19 in which most patients have received other therapies, in addition to CCP, such as steroids, antibiotics, and antivirals, blurring interpretation of the findings. Hegerova et al acknowledged this as a limitation in their study in which one-half of their control group had received remdesivir, an investigational antiviral that could well have masked the differential effect of CCP if indeed one were present. Beyond concomitant therapies, the investigators highlight 2 other elements that have not been standardized across studies: dosage and titering. Dosing of CCP has been gleaned from studies of severe acute respiratory syndrome; the pharmacokinetics of CP in the context of COVID-19 are not well understood. Most studies of COVID-19 have reported use of 1 to 2 U (~200-500 mL) of CCP to treat COVID-19; while practical, this fails to account for differences in the volumes of distribution or acuity of disease. Furthermore, the approaches that have been used to qualify donors and/or the transfused units of CCP have varied enormously, from qualitative assessments of immunoglobulin G to formal viral neutralization assays and associated titers.[4]

Independent of the study design, the patient population that is being targeted for CCP use may be suboptimal. An enduring finding across studies of CP is the need for early intervention.[1,4,7,9] Yet, the overwhelming majority, if not all, CCP to date has been transfused to patients with advanced COVID-19. At inception, the US expanded access program required severe or life-threatening COVID-19 for enrollment.[6] Although the desire to help those who are most sick is intuitive, this is the population for which evidence of benefit from CP is weakest. Late intervention also fails to abrogate the societal burden of disease. In short, intervention likely needs to occur earlier in the disease process.[4]

In conclusion, observational studies and compassionate use programs have been instrumental in the mobilization of CCP to contend with a global health emergency. Although safety has been addressed, efficacy data are critically needed to transition CCP's status from an investigational product to a standard therapy. The latter has practical ramifications, offering a formal mechanism for reimbursement and