EMERGENCY USE AUTHORIZATION REQUEST
FOR

CONVALESCENT PLASMA FOR THE TREATMENT OF PATIENTS WITH COVID-19

SPONSORED BY:
THE OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

EUA 26382

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1. DESCRIPTION AND ITS INTENDED USE

1.1. Name of Product

COVID-19 convalescent plasma

1.2. Description of Product

COVID-19 convalescent plasma, an unapproved biological product, is human plasma collected by FDA registered or licensed blood establishments from individuals whose plasma contains antibodies to SARS-CoV-2. These individuals must also meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15) and be qualified to donate. COVID-19 convalescent plasma for use under this EUA is collected and manufactured as described in section 8 below.

1.3. Intended Use

Under this Emergency Use Authorization (EUA) request, the Office of the Assistant Secretary for Preparedness and Response (ASPR) is proposing the use of COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. This EUA request is based on: 1) historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, 2) certain preclinical evidence; 3) results from small clinical trials and observational studies of convalescent plasma conducted during the current outbreak; and 4) data obtained from the ongoing National Expanded Access Treatment Protocol (EAP) sponsored by the Mayo Clinic.

Data suggest that use of COVID-19 convalescent plasma with high antibody titer may be effective in reducing mortality in hospitalized patients with COVID-19. COVID-19 convalescent plasma units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by the test used in its manufacture described in section 8.2 are considered Low Titer COVID-19 Convalescent Plasma and must be labeled accordingly. These units are authorized for use. Health care providers can decide whether to use the units based on an individualized assessment of patient benefit:risk. Current evidence suggests benefit is most likely in patients treated early in the course of the disease. FDA will continue to evaluate this authorized use based on additional data that become available.

Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional RCTs are needed. Convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19. Ongoing clinical trials of convalescent plasma should not be amended based on the issuance of the EUA. Providers are encouraged to enroll patients in those ongoing clinical trials.

2. UNMET NEED ADDRESSED BY THE EUA

On February 4, 2020, the Secretary of HHS declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak.

Currently, although there are only a few other products available under EUA, there are no drugs or other therapeutics approved by the FDA to prevent or treat COVID-19 infection that is affecting millions of individuals in the nation. Remdesivir and dexamethasone may have benefit

in specific populations, but the former is in limited supply at this time. Convalescent plasma has been requested for nearly 100,000 individuals as part of the National Expanded Access Treatment Protocol, indicative of the large unmet medical need for safe and effective therapeutic agents against COVID19.

3. APPROVAL/CLEARANCE STATUS

FDA has not approved COVID-19 convalescent plasma for any indication.

4. MANUFACTURING SITE/CGMP STATUS

COVID19 convalescent plasma under this EUA will be obtained from FDA-registered or licensed blood establishments that collect plasma for transfusion according to the blood donor eligibility criteria and donor qualifications described at 21 CFR 630.10 and 21 CFR 630.15. Section 8 details the manufacturing process for the product.

5. ADEQUATE, APPROVED AND ALTERNATIVE PRODUCTS

There are no drugs or other therapeutics approved by the FDA to prevent or treat COVID-19 .

6. SAFETY AND EFFICACY INFORMATION

The sponsor has pointed to four lines of evidence in support of the potential effectiveness of COVID-19 convalescent plasma in the treatment of hospitalized patients with COVID-19: 1) the history of convalescent plasma for respiratory coronaviruses, 2) evidence of preclinical safety and efficacy in animal models, 3) recently published studies of the safety and efficacy of COVID-19 convalescent plasma, and 4) data on safety and efficacy from the U.S. EAP.

6.1. History of Convalescent Plasma in Prior Outbreaks

Published Studies of Convalescent Plasma for Respiratory Infections

A systematic review of passive antibody therapy for SARS coronavirus and severe influenza found a trend towards reduction in mortality, but noted that studies were commonly of low or very low quality, lacked control groups, and were at risk of bias[3].

An uncontrolled study involved the treatment of 80 patients in Hong Kong with SARS-CoV-1[4]. A higher day-22 discharge rate was observed among patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; P<0.001) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; P=0.001). A small retrospective nonrandomized study of patients with progressive SARS after ribavirin and pulse methylprednisolone treatment, the plasma-treated group had a shorter hospital stay and lower mortality than the group that continued treatment with pulse methylprednisolone[5]. These reports followed a single case report of successful convalescent plasma therapy in a 57-year-old woman with SARS in Hong Kong[6]. A case series of three patients with SARS in Taiwan were treated with convalescent plasma, resulting in a reduction in viral load; all three

recipients survived[7]. Treatment with convalescent plasma use was also reported in three patients in South Korea with MERS, but researchers found only a subset of convalescent plasma showed neutralizing activity[8]. A group in Saudi Arabia reported on the feasibility of collecting convalescent plasma for passive immunotherapy of Middle East respiratory syndrome coronavirus (MERS-CoV) infection by using ELISA to screen serum samples from 443 potential plasma donors[9]. They found only a small subset (9 patients) showed neutralization activity and concluded trials would be challenging because of the small pool of donors with sufficiently high titers.

6.2. Preclinical Safety and Efficacy

SARS-CoV-2 replicates efficiently in the lungs of Syrian hamsters and causes severe pathological lesions in the lungs of these animals following intranasal SARS-CoV-2 infection. Micro-CT analysis revealed that severe lung injury occurs in infected hamsters and that the severity of the lung abnormalities is related to the degree of infectious dose. Commonly reported imaging features of COVID-19 patients with pneumonia such as severe, bilateral, peripherally distributed, multilobular ground glass opacity, and regions of lung consolidation were present in all infected animals but not in mock-infected control animals. Computational modeling suggests that ACE2 from Chinese hamster could interact with the S glycoprotein of SARS-CoV-2. SARS-CoV-2–infected hamsters mounted neutralizing antibody responses and were protected against subsequent rechallenge with SARS-CoV-2. Postinfection sera were collected from hamsters that had been infected with the high or low dose of virus and then pooled. The pooled serum was then transferred intraperitoneally to three hamsters on day 1 or 2 after infection with 10^3 PFU of the virus. Normal uninfected hamster serum was injected intraperitoneally into three naïve hamsters as a control. Virus titers in the nasal turbinates and lungs of the animals that received postinfection serum on day 1 postinfection were statistically significantly lower than the virus titers in those organs of animals that received normal serum at the corresponding time point postinfection. Viral titers trended lower in animals administered convalescent plasma on day 2 after infection. These data suggest that earlier administration of convalescent plasma is more effective than later administration.[1]

Mice are resistant to SARS-CoV-2. Providing hACE2 by adenovirus transduction leads to expression of the encoded protein and sensitizes a broad range of immunocompetent and immunodeficient mice for SARS-CoV-2 infection without development of severe disease or extrapulmonary manifestations of disease. When 6-to-8-week-old BALB/c mice were transduced intranasally with 2.5 x 108 PFU Ad5-hACE2, hACE2 expression was observed predominantly in the alveolar epithelium and in occasional airway epithelial cells. Control mice received an Ad5-empty vector. Five days after transduction, mice received 1 x 10^5 PFU of SARS-CoV-2 and were monitored over a 10-day time course. Ad5-hACE2 transduced BALB/c mice infected with SARS-CoV-2 showed ruffled fur, hunching, and difficulty breathing beginning 2 days post infection (d.p.i.). The mice lost up to 20% of their body weight in the first 4–6 days of infection, and virus grew to high titers in lung tissue and gradually declined over the course of the infection. Robust viral antigen was detected in the lungs of mice transduced with Ad5-hACE2 but not Ad5-empty control. Lung tissues demonstrated a variety of lesions including perivascular to interstitial inflammatory cell infiltrates, necrotic cell debris, and alveolar edema. Gross lung specimens from infected Ad5-hACE2-transduced mice revealed increased vascular congestion and hemorrhage, with the most severe changes observed at 5 d.p.i. In experiments of adoptive

plasma transfer, Ad5-hACE2-transduced mice were injected with 150 µL of plasma i.v. from a healthy donor or COVID-19, MERS, or SARS convalescent patients one day prior to infection. Weight and virus titers in lung tissues were monitored and expressed as FFU/g tissue (n = 4 mice per group per time point). Pooled plasma from 3 patients who recovered from SARS-CoV-2 infection (FRNT50 titer = 1:1,000) as well as plasma from a healthy donor, 3 SARS survivors (PRNT50 titer against SARS-CoV = 1:140), and 2 MERS convalescent patients (FRNT50 titer against MERS-CoV = 1:2,183) were evaluated. Administration of 150 µL of SARS-CoV-2 plasma one day prior to SARS-CoV-2 infection prevented weight loss and lung tissue histological changes, and accelerated the rate of virus clearance. More rapid clearance was not observed after treatment with pooled plasma from SARS-CoV-1 survivors or MERS survivors.[2]

6.3. Clinical Trials Conducted Using COVID-19 Convalescent Plasma

Early data on the use of convalescent plasma came in the form of two case series from the initial outbreak in China[10] [11]. These studies in patients with very severe illness found that patients showed improved viral load, symptoms, and radiographic findings. The case series studies suggested COVID-19 Convalescent Plasma may be helpful but were limited by their small size and lack of controls. A large number of clinical trials have been initiated, but most have not yet reported results. Available data generally fall into one of four categories: randomized controlled trials, controlled trials based on availability of plasma but not truly randomized, retrospective matched cohorts (e.g., propensity score matched), and case series. Several reports remain in pre-print status and have not been peer-reviewed at the time of this submission.

Randomized controlled trials

The two randomized controlled trials reported to date were both stopped early, resulting in trials that may have been underpowered to detect clinically meaningful differences. The first study by Li et al. in Wuhan, China[12], was in patients with severe to life-threatening COVID-19 who were transfused with 4-13 mL/kg COVID-19 Convalescent Plasma with ELISA titer >1:640. The primary outcome was time to clinical improvement within 28 days and the study found clinical improvement in 27/52 (51.9%) in the COVID-19 Convalescent Plasma arm, and 22/51 (43.1%) in the control arm (p=0.26). When examining subgroups by disease severity they found that in severe disease 21/23 (91.3%) in the COVID-19 Convalescent Plasma arm and 15/22 (68.2%) in the control arm [p=0.03] showed clinical improvement. In life-threatening disease, 6/29 (20.7%) in COVID-19 Convalescent Plasma and 7/29 (24.1%) in control (p=0.83) showed clinical improvement. However, there was a non-significant test for interaction (p=0.17), so the results in the subgroups should not be interpreted differently. Of note, the median duration of symptoms at the time of transfusion was 30 days. The study was stopped early due to low enrollment as a result of improved case rates in the Wuhan region.

The second RCT by Gharbharan et al. in the Netherlands[13] examined patients with clinical COVID-19 as determined by a positive test in the previous 96 hours (most patients met criteria for severe disease, median of 10 days of symptoms at transfusion) who were treated with 300 mL of plasma with a neutralization titer of at least 1:80. The primary outcome was overall mortality until discharge. The trial was stopped early because they observed that antibody titers in the recipients were already high at the time of transfusion, and therefore, they made a decision to halt and redesign the trial because the presumed benefit would be in patients earlier in disease. At the time of study stopping, 6 of 43 COVID-19 Convalescent Plasma patients (14%) had died

and 11 of 43 control patients (26%) had died. The prespecified comparison of adjusted mortality showed no difference (aOR 0.95 [0.2-4.67]), but the study was underpowered to detect clinically meaningful differences at study stopping.

Controlled trials

In addition to the randomized controlled trials, two studies from the Middle East[14] [15] reported prospective trials in which the control patients were those who were not transfused due to a lack of plasma availability[14] or "As a result of ABO compatibility and limited plasma…randomly chosen to take CP"[15].

The study by Rasheed et al[15] examined COVID-19 Convalescent Plasma transfusion in patients admitted to the ICU for less than 3 days (mean of 14-16 days of symptoms) and found that 1 of 21 COVID-19 Convalescent Plasma patients (4.8%) died within the observation period, and 8 of 28 (28.6%) control patients died within the observation period, with only one patient experiencing a mild allergic reaction. This study is limited by the lack of formal reporting of statistical approaches.

A study by Abolghasemi et al[14] likewise compared COVID-19 Convalescent Plasma transfused patients to controls who were not transfused due to plasma availability within 3 days of enrollment. Patients had severe disease and were enrolled if they were within 7 days of illness onset. Patients were transfused with 500-1000 mL of plasma confirmed anti-SARS-CoV-2 by semi-quantitative ELISA. The primary outcomes were described as survival and hospital length of stay. All-cause mortality was 17/115 (14.8%) in the COVID-19 Convalescent Plasma arm versus 18/74 (24.3%) in the control arm [p=0.09]. The mean hospital length of stay was 9.5 days in COVID-19 Convalescent Plasma arm versus 12.9 in the control [p=0.002]. 107 (93%) COVID-19 Convalescent Plasma patients were discharged versus 59 (79.7%) in the control [p=0.006].

These studies provide encouraging signs of effectiveness but are limited due to their nonrandomized design, and in the case of Rasheed et al[15], low quality of the methods and report.

Retrospective matched cohort studies

Several reports of retrospective matched cohort studies of COVID-19 Convalescent Plasma have been made publicly available [16] [17] [18].

In severe to life-threatening COVID-19 Liu et al[18] found that convalescent plasma transfusion was significantly associated with improved survival in non-intubated patients (hazard ratios: 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not in intubated patients. Convalescent plasma recipients were more likely than controls to remain the same or have improvements in supplemental oxygen requirements at day 14 (OR 0.86, p =0.028).

Using a propensity score matching algorithm, Salazar et al[16] found 28-day mortality was 3.7% in 136 COVID-19 Convalescent Plasma transfused subjects with severe COVID-19 versus 7.6% in 543 non-transfused controls, although the difference was not significant in the overall population (p=0.13). In those transfused within 72 hours of admission and with high-titer units, there was a significant difference in 28-day mortality (1.2% in COVID-19 Convalescent Plasma vs 7.0% in control). The authors concluded that transfusion of high anti-RBD IgG titer COVID-19 convalescent plasma early in hospitalization reduces mortality.

In smaller studies, Perotti et al and Hegerova et al found similar trends toward benefit but noted that trends would need confirmation in well-controlled randomized trials[17] [19].

Case Series

Several investigators have reported case series ranging in size from 5 to 20,000 patients and across several countries [10] [11] [20] [21] [22] [23]. This includes the early reports described above in the early pandemic in China[10] [11]. The largest series are those reported out of the Expanded Access Program by Joyner et al. [21] [22]. These data demonstrated a low rate of adverse events observed with COVID-19 Convalescent Plasma transfusion, with 7-day mortality rate of 8.6% overall (12.1% in non-ventilated subjects, 6.2% in ventilated subjects). The authors concluded that COVID-19 Convalescent Plasma is safe in hospitalized patients with COVID-19. Additional case series similarly showed that most patients improved following COVID-19 Convalescent Plasma but were of limited interpretability in the absence of controls[20] [23] [24]

6.4. Clinical Safety and Efficacy

Protocol 20-003312, Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19

The National Expanded Access Treatment Protocol, sponsored by the Mayo Clinic, was initiated in early April 2020 to provide broad access to convalescent plasma. This expanded access program provided access to investigational convalescent plasma for patients in acute care facilities infected with SARS-CoV-2 who had severe or life-threatening COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening disease. The protocol had a single arm with sites across the US. COVID-19 convalescent plasma was obtained from the American Red Cross or America's Blood Centers. The study design included capture of demographics and endpoints of safety, -day-7- and 30-day survival. As a tertiary objective exploring efficacy, dose response by titer or the plasma administered was explored.

Objective

The primary objective of the expanded access program was to make COVID-19 convalescent plasma broadly available. The secondary objective was to assess the safety of patient transfusion with COVID-19 convalescent plasma. Tertiary endpoints included the assessment of healthcare outcomes at 7 and 28 days after treatment as well as the retrospective determination of COVID-19 neutralizing antibody titers in transfused units and their correlation with clinical outcomes.

Patients and Methods

As of August 4, 2020, there were 85,719 patients enrolled and 56,472 patients reported to have been treated at 2738 clinical sites enrolled in the EAP located across all 50 states and the District of Columbia. For the purposes of the safety analysis, a convenience sample drawn from 20,000 consecutive patients enrolled in the EAP from April 3 to June 2, 2020, was used. Exploratory efficacy analyses correlating neutralizing antibody titers to observed clinical outcomes have been undertaken on 4330 patients administered convalescent plasma. Different assays were used for determination of these antibodies, including the 1) Mayo Clinic pseudovirus neutralization assay, 2) Ortho VITROS total IgG assay, and 3) Broad Institute SARS-CoV-2 neutralization assay.

Results

Demographic data showed that recipients were broadly representative of the US population in terms of race and ethnicity. Disease severity and concomitant medications changed over time with enrollment of less sick patients as the pandemic progressed over time and with reduced use of hydroxychloroquine/ azithromycin and increased use of remdesivir and steroids at later times.

Safety

Safety data are presented for a convenience sample of 20,000 recipients.

The incidence of all serious adverse events was low; these included transfusion reactions (n=89; <l%), thromboembolic or thrombotic events (n=87; <1 %), and cardiac events (n=680, - 3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were judged to be unrelated to the convalescent plasma transfusion per se. The seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).

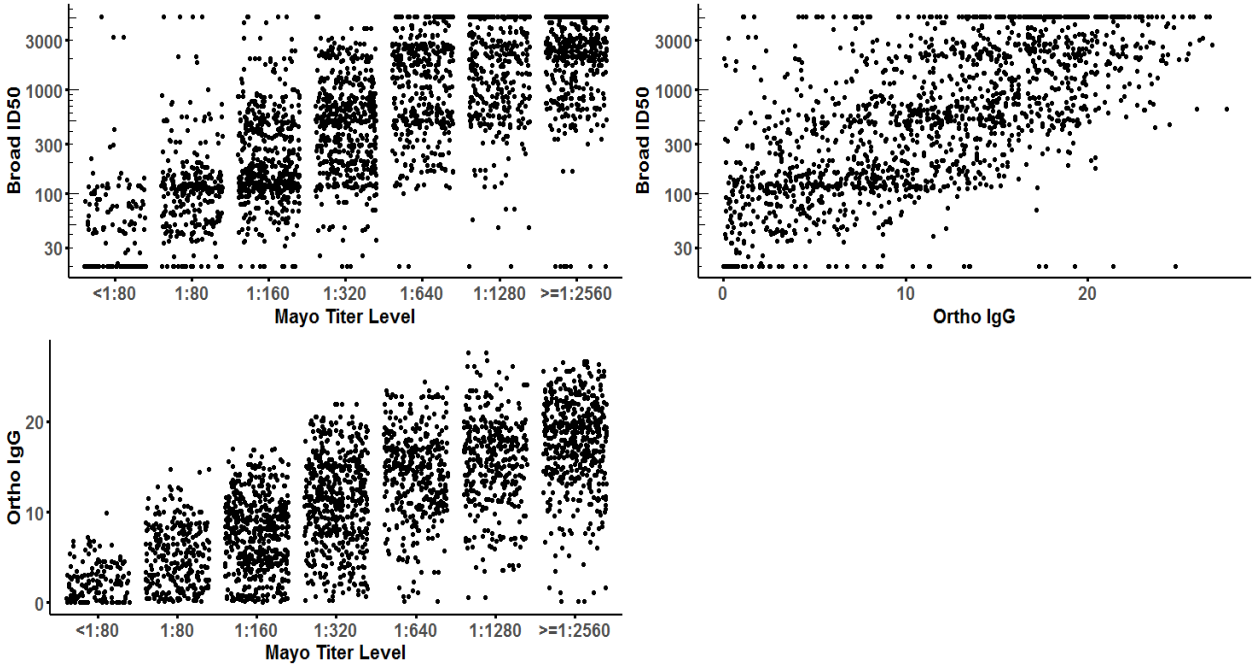
Overall mortality was higher in patients admitted to ICU (10.48%; 95% CI 9.99%, 11.06%) than in patients not admitted to ICU (6.02%; 95% CI, 5.53%, 6.55%), and in patients with mechanical ventilation (12.10%; 95% CI, 11.32%, 12.93%) than in those not on mechanical ventilation (6.17%; 95% CI, 5.75, 6.61%).

Efficacy

Survival and 7-day mortality were evaluated according to neutralizing antibody titers assessed by various methodologies, including a pseudovirus neutralization assay developed at the Mayo Clinic, a commercial assay from Ortho Diagnostics (Ortho VITROS total IgG) and a SARS-CoV-2 BSL-3 neutralization assay developed at the Broad Institute. Data demonstrating the correlation between these assays are provided in Figure 1. Based on the available evidence, it was determined that the Broad Institute titers would serve as the reference standard for diagnostic accuracy to which the others would be compared. Note that while these assays generally correlated with each other, precise performance characteristics based on a reference panel or gold-standard methodology (plaque reduction neutralization titer) were not available at the time of this determination.

Using the Broad neutralization titers with a cutoff value of an ID_{50} of 250, which corresponds to an Ortho VITROS IgG S/C level of 12 as determined by a cross-laboratory titer comparison study, there was no difference in 7-day survival noted in the overall population of treated patients, nor was there any difference in this parameter for the pre-specified subset of patients who were intubated at the time of treatment. However, in the prespecified subset of patients who were not intubated at the time of treatment (approximately 2/3 of those analyzed), comparing patients treated with plasma with a neutralizing antibody titer greater than an ID_{50} of 250 to those patients treated with lower titers there was a 21% reduction in 7-day mortality from 14% to 11% (p=.03).

Figure 1: Comparison of Assay Performance



The Broad ID50 was determined using a BSL-3 neutralization assay, the Mayo Titer level was obtained using a pseudo-neutralization assay, and the Ortho IgG was determined using the Ortho Vitros IgG antibody assay.

Additionally, in a subset analysis that was not included in the original analysis plan, those patients not intubated at the time of treatment, less than 80 years of age, who were treated within 72 hours of diagnosis, comparing those treated with plasma with a neutralizing antibody titer greater than an ID50 of 250 to those patients treated with lower titers there was a 45% reduction in 7-day mortality from 11.3% to 6.3% (p=0.008)

In additional analyses of survival using a Kaplan-Meier approach, the survival trends observed at 7 days persisted over a longer time period, with significantly improved survival in non-intubated patients (Figure 2, p=0.032) and a larger benefit in the subset of patients not intubated at the time of treatment, less than 80 years of age, who were treated within 72 hours of diagnosis (Figure 3, p=0.0081)

Figure 2: Kaplan-Meier plot of survival following the administration of convalescent plasma in patients not on ventilators.

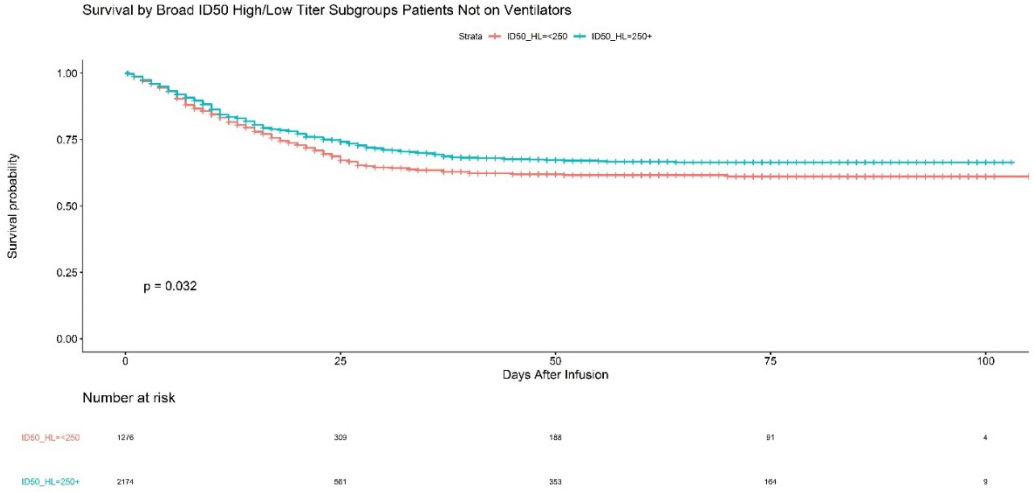
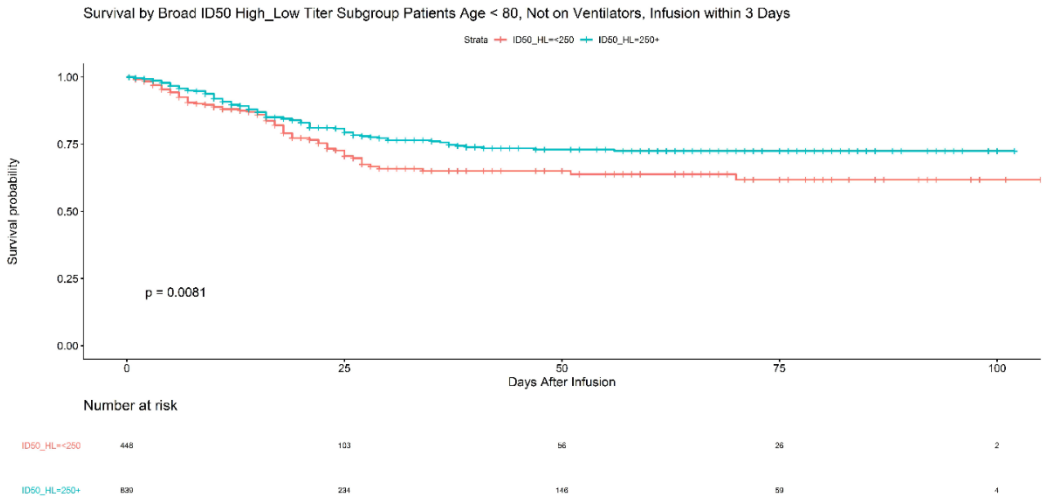


Figure 3: Kaplan-Meier plot of survival following the administration of convalescent plasma in patients in the subset of patients not on ventilators, less than 80 years of age who received plasma within 3 days of diagnosis.



Additional analyses of data from the EAP were posted publicly by Mayo Clinic investigators and collaborators. In their analyses, the investigators observed an association between reductions in adjusted 7-day and 30-day mortality and earlier transfusion (<=3 days) of COVID-19 Convalescent Plasma and high antibody levels. Antibodies were measured using the Ortho VITROS IgG assay. Low, medium, and high antibody levels were defined as <4.62, 4.62-18.45, and >18.45 (S/C ratio), respectively[27].

Conclusion

These data provide evidence to support the conclusion that that transfusion of convalescent plasma to treat hospitalized patients with COVID-19 meets the "may be effective" criterion for issuance of an EUA. The data are consistent with earlier findings suggesting that administration of convalescent plasma to hospitalized patients, particularly with units containing higher titers of SARS-CoV-2 antibodies, and early on during the disease course, may be effective in reducing mortality in hospitalized patients with COVID-19.

7. POTENTIAL RISKS AND BENEFITS

7.1. Risk-Benefit Assessment

7.1.1. Risks

Known risks associated with plasma transfusion include transfusion-transmitted infections (e.g. HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura have also been described.

FDA guidance issued April 2020 and updated on May 1, 2020 indicate that the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.[25]

A theoretical risk of administration of convalescent plasma is the phenomenon of antibody-dependent enhancement of infection (ADE). ADE has been described in other viral infections, such as dengue, and involves an enhancement of disease in the presence of certain antibodies. For coronaviruses, several mechanisms of ADE have been proposed, including the theoretical concern that antibodies to one type of coronavirus could enhance infection to another strain. Preparations with high titers of antibody against the same virus strain are thought to be less likely to cause ADE.

Another theoretical risk is that antibody administration may attenuate the immune response and make patients more susceptible to re-infection. There are no such reports in the literature at this time.

7.1.2. Benefits

COVID-19 is a serious and potentially fatal or life-threatening human disease. The potential benefits of COVID-19 convalescent plasma therapy could include improvement in symptoms, reduced need for supplemental oxygen and mechanical ventilation, and possibly reduced mortality. Data suggest that use of COVID-19 convalescent plasma with high antibody titers is more likely to be effective in reducing mortality in hospitalized patients with COVID-19, the use of low titer units also may be effective. Current evidence suggests benefit is most likely in patients treated early in the course of the disease. Units containing anti-SARS-CoV-2 IgG

antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by a test found acceptable for this purpose as part of the manufacture of COVID-19 Convalescent Plasma by FDA (see section 8.1), are considered Low Titer COVID-19 Convalescent Plasma units and are authorized for use and will be labeled as "Low Titer." Health care providers can decide whether to use such units based on an individualized assessment of patient benefit:risk.

7.1.3. Risk-Benefit Assessment

Based on the totality of scientific evidence available at this time, it is reasonable to conclude that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks.

Information derived from ongoing clinical trials of COVID-19 convalescent plasma, particularly randomized, controlled trials, as well as clinical trial results from studies of other investigational medical products to treat COVID-19, will continue to inform this risk benefit assessment.[26]

7.2. Contraindications

COVID-19 convalescent plasma may be contraindicated in patients with a history of severe allergic reactions or anaphylaxis to plasma transfusion.

7.3. Use in Specific Populations

Pediatric

The safety and effectiveness of COVID-19 Convalescent Plasma has not been evaluated in pediatric patients. The decision to treat patients <18 years of age with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

Geriatric

In the ongoing National Expanded Access Treatment Protocol sponsored by the Mayo Clinic, 56,472 patients were treated as of August 5, 2020. Preliminary analyses of the first 20,000 patients indicated that 5,423 (27.1%) were 60-69 years of age, 4,114 (20.6%) were 70-79 years of age, and 2,568 (12.8%) were 80 year of age or older. Although adverse event rates in the geriatric subgroup have not yet been provided, the rates in the overall population for the individual events of mortality within 4 hours, transfusion-associated circulatory overload (TACO), Transfusion related acute lung injury (TRALI), severe allergic transfusion reaction, thrombotic/ thromboembolic complication, sustained hypotension, and cardiac events were ≤ 0.37%.

Pregnancy

The safety and effectiveness of COVID-19 convalescent plasma in pregnancy has not been evaluated. It should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. The decision to treat pregnant women with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit

Nursing Mothers

It is not known whether or not transfused anti-SARS-CoV-2 antibodies are excreted in human milk. The safety and effectiveness of COVID-19 convalescent plasma in nursing mothers has not

been evaluated. The decision to treat nursing mothers with COVID-19 convalescent plasma should be based on an individualized assessment of risk and benefit.

8. CHEMISTRY, MANUFACTURING, AND CONTROLS

The manufacture of COVID-19 Convalescent Plasma requires qualification of the donor and assessment of the donated plasma for appropriate antibody titers.

8.1. Donor Eligibility and Donation Suitability

a. COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10 and 21 CFR 630.15). Note the additional donor eligibility requirements for the collection of plasma by plasmapheresis in 21 CFR 630.15(b). Donation testing for relevant transfusion-transmitted infections must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

b. COVID-19 convalescent plasma must be collected from individuals who meet the following qualifications:

- Evidence of COVID-19 documented by an FDA-authorized diagnostic test (e.g., nasopharyngeal swab) at the time of illness, or

  Individuals who did not have a prior diagnostic test and/or never had symptoms of COVID-19 may be qualified to donate if they have reactive (positive) results in two different tests authorized by FDA to detect SARS-CoV-2 IgG antibodies

- Complete resolution of symptoms (if present) at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

- Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

8.2. SARS-CoV-2 Antibody Testing

a. Plasma donations should be tested for SARS-CoV-2 IgG antibodies as a manufacturing step to determine suitability before release. Units tested by the Ortho VITROS SARS-CoV-2 IgG test and found to have a signal-to-cutoff (S/C) ratio of 12 or greater qualify as High Titer COVID-19 Convalescent Plasma. If a blood establishment is considering using an alternative testing assay in manufacturing in order to qualify High Titer COVID-19 Convalescent Plasma, it should contact CBER to determine acceptability of the proposed test, which if accepted, would require an amendment to the EUA.

b. Units containing anti-SARS-CoV-2 antibodies but not qualified as High Titer COVID-19 Convalescent Plasma by the test described above, are considered Low Titer COVID-19 Convalescent Plasma units and must be labeled accordingly. These units are authorized for use. Healthcare providers can decide whether to use such units based on an individualized assessment of benefit:risk. FDA will continue to evaluate this authorized use based on additional data that become available.

8.3. Other Considerations

Blood establishments should be aware of the following considerations:

a. Registered-only or licensed blood establishments that collect plasma intended for transfusion do not need to request a supplement to their license to collect and manufacture COVID-19 convalescent plasma for the authorized use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulations, and 2) collect plasma from individuals that meet the donor qualifications specified above.

b. Once manufactured, COVID-19 convalescent plasma may be distributed for use under the EUA.

c. Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect COVID-19 convalescent plasma.

8.4. Labeling

The requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.

a. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.
b. FDA recommends the use of a uniform container label for COVID-19 convalescent plasma. In particular, FDA recommends the use of the International Society of Blood Transfusion (ISBT) format specified in the United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.
c. The manufacturing process used and the expiration date on the label for COVID-19 convalescent plasma should be the same as for other plasma products that are of the same type. For example, COVID-19 Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection, stored at -18C or colder and have an expiration date one year from the date of collection.
d. Convalescent plasma units should be clearly labeled, based on the test results that are used as part of manufacturing, as being High Titer COVID-19 Convalescent Plasma or Low Titer Convalescent Plasma based on the level of SARS-CoV-2 antibodies.

e. Convalescent plasma container label must not indicate a license number.

9. FACT SHEET FOR HEALTHCARE PROVIDERS

Refer to Attachment 1.

10. FACT SHEET FOR RECIPIENTS

Refer to Attachment 2

11. PROGRAM SCHEMA

COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies and procedures. Testing for relevant transfusion-transmitted infections (21 CFR 610.40) must be performed and the donation must be found suitable (21 CFR 630.30). Units of COVID-19 convalescent plasma under this EUA will be documented to contain antibodies to SARS-CoV-2 and labeled according to Section 8.4.

12. INSTRUCTIONS FOR USE

12.1. Dosage of COVID-19 Convalescent Plasma

Health care providers will administer COVID-19 convalescent plasma with neutralizing SARS-CoV-2 according to standard hospital procedures and institutional medical and nursing practices.

Clinical dosing may first consider starting with one convalescent plasma unit (about 200 mL), with administration of additional convalescent plasma units based on the prescribing physician's medical judgement and patient's clinical response.

Patients with impaired cardiac function and heart failure may require a smaller volume or more prolonged transfusion times.

12.2. Administration of COVID-19 Convalescent Plasma

Health care providers will administer COVID-19 convalescent plasma infusion through a peripheral or central venous catheter according to standard institutional medical and nursing practices for the administration of plasma. (http://www.aabb.org/tm/coi/Documents/coi1017.pdf)

12.3. Storage and Packaging

COVID-19 Convalescent Plasma, may be stored frozen at -18C or colder, and has an expiration date one year from the date of collection. Once thawed, it can be refrigerated for up to 5 days prior to patient transfusion.

13. ADVERSE EVENT MONITORING

Healthcare Providers must maintain records and conduct a thorough investigation of adverse reactions after transfusion of convalescent plasma, and must report fatalities related to transfusion, as required blood or blood components under 21 CFR 606.170.

14. LABELING

Please refer to Attachment 2 for additional patient information that will be provided to recipients.

15. RECORD KEEPING, REPORTING, AND RECORD ACCESS BY FDA

Record keeping, reporting and record access must be maintained per 21 CFR 606.100.

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