Convalescent plasma in the Treatment of COVID 19

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1.0 Background

The epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)/COVID-19 originated in Wuhan, China in Dec 2019 and has rapidly spread worldwide. On March 11th 2020, WHO declared this a pandemic, and as of March 30th, 737,929 people in 177 countries have been affected with a total of 34,800 deaths. As of March 30th 2020, the United States has reported 143,055 positive cases and 2513 deaths.

At Trinity Health of New England we have 234 patients who are positive for COVID-19 with 56 patients who are hospitalized and in critical condition. Currently there are no approved treatment options for COVID-19 and there are trials underway for antiviral medications such as Remdesivir.

In 2014, the use of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks. The use of convalescent plasma for the treatment viral infections such as SARS, H5N1 avian influenza and H1N1 influenza have suggested that transfusion of convalescent plasma was effective. Shen C et al published a case series of 5 critically ill patients with COVID-19 and Acute Respiratory Distress Syndrome (ARDS) who were treated with convalescent plasma containing neutralizing antibody and detected an improvement in the patients' clinical status. Research has shown that IgM and IgG antiviral antibodies can be detected in the serum samples of infected patients. After infection with COVID-19, the virus antigen stimulates the immune system to produce antibodies that can be detected in the blood. Among these antibodies, IgM antibodies appears early and are mostly positive after 3-5 days of onset. IgM titers then decrease while the IgG antibody potency starts to rise rapidly. During the recovery phase, the titer of the IgG antibody may increase four times or more compared to the acute phase.

The purpose of this prospective interventional study is to gain clinical experience using convalescent plasma transfusion administered to critically ill patients with COVID-19.

2.0 Rationale and Specific Aims

- To study the efficacy of plasma from patients recovered from COVID-19 infection with a high neutralizing antibody titer (NAT) as treatment for individuals who are critically ill with COVID-19.
- Determine if the antibodies from convalescent plasma will suppress virus load in critically ill patients with COVID-19.

Primary Outcomes:

- Mortality within 28 days
- Viral load on days 0, 3, 5 and 7

- Serum antibody titers on days 0, 3, 5 and 7

Secondary Outcomes:

- Changes of body temperature
- Days on Ventilator post transfusion
- Length of stay
- PAO2/FIO2

Safety end-points include but not limited to

- Transfusion related acute lung injury
- Transfusion associated circulatory overload
- Allergic/anaphylactic reactions

Other less common risks include:

- Transmission of infections
- Febrile non-hemolytic transfusion reactions
- RBC allo-immunization
- Hemolytic transfusion reactions.

3.0 Inclusion/Exclusion Criteria

INCLUSION CRITERIA FOR OBTAINING CONVALESCENT PLASMA

- Male donors
- Female donors negative for HLA antibodies
- Age > 18 yrs and < 90 yrs
- Prior diagnosis of COVID-19 documented by a confirmed laboratory test within the last 45 days.
- Currently negative for COVID-19 by test
- Complete resolution of symptoms at least 14 days prior to donation
- Defined SARS-CoV-2 neutralizing antibody titers (optimally greater than 1:40)
- Defined SARS –CoV IgG antibody titer > 1: 320

EXCLUSION CRITERIA FOR OBTAINING CONVALESCENT PLASMA

- No gender exclusion
- Age < 18 yrs and > 90 yrs
- No positive diagnosis of COVID-19 within the last 45 days. Symptomatic with COVID-19
- H/o HIV
- H/o Hepatitis B or C

- Temp > 99.5
- Pregnancy or 6 weeks post-partum
- Female Hb/HCT: < 12.5 gm/dL /38%
- Male Hb/HCT: < 13 gm/dL /39%
- H/o prior blood donation within the last 6 months
- Weight < 50 Kg

INCLUSION CRITERIA FOR RECEIVING CONVALESCENT PLASMA

- All genders
- Age > 18 yrs and < 90 yrs
- Must have laboratory confirmed COVID-19
- Must provide informed consent
- Must have severe or immediately life-threatening COVID-19,
  Severe disease is defined as:
    - dyspnea,
    - respiratory frequency ≥ 30/min,
    - blood oxygen saturation ≤ 93%,
    - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300
    - lung infiltrates > 50% within 24 to 48 hours

  Life-threatening disease is defined as:
    - respiratory failure,
    - septic shock
    - multiple organ dysfunction or failure

EXCLUSION CRITERIA FOR RECEIVING CONVALESCENT PLASMA

- No gender exclusion
- Age < 18 yrs and > 90 yrs
- COVID-19 negative

4.0 Enrollment/Randomization

We propose to conduct a prospective study on patients admitted with COVID-19 to Trinity Health Of New England Hospitals (Saint Francis Hospital and Medical Center, Mount Sinai Rehab Hospital, Saint Mary's, Mercy Medical Center, Johnson Memorial. There will no randomization. Subjects will be enrolled if the satisfy the inclusion and exclusion criteria

5.0 Study Procedures

Obtaining convalescent plasma

COVID-19 convalescent plasma will only be collected from recovered individuals if they are eligible to donate blood. Subjects are eligible to participate if they are over the age of 18 years and below the age of 90 years and were diagnosed with COVID-19 and confirmed by lab tests within the last 45 days. Eligible subjects who meet inclusion criteria will be contacted by the Study Team by telephone. See telephone script. Once informed consent is obtained, subjects will be screened with a medical history screening and will be tested to make sure they are currently COVID-19 NEGATIVE. This will be done with a nasal swab and in some subjects with both the nasal swab and salivary sample. The salivary sample will be compared with results of the nasal swab in order to have it validated at Boston Heart Diagnostics. They will then have have blood drawn to measure serum SARS-CoV-2 specific antibody titers,neutralizing antibody titers (when kit is available) and viral load. Blood will be collected and stored so we can measure SARS-CoV-2– specific antibody(IgM and IgG) binding titers and a neutralization titers. We will be patnering with Boston Heart Diagnostics for these tests.
We hope to screen and collect plasma from 300 subjects.

The subject will then be sent to the New York Blood Center (NYBC) where plasma is obtained according to NYBC Standard Operating Procedures (SOP) for plasma collection by apheresis methods. Plasma is frozen within 24 hours of collection per NYBC SOPs. Plasma will be labeled: **Caution: New Drug--Limited by Federal (or United States) law to investigational use along with the IND number.** It is then stored for up to one year, and thawed when needed. Plasma will be stored at Saint Francis Hospital local lab. The subject's plasma samples will be assigned an unique number and de-identified. Duty of Privacy and Confidentiality has been outlined in the Master Blood Services Agreement and the Affiliate Participation Agreement.

Risks to subjects may include side effects from intravenous needle insertion site. This includes skin irritation, pain, swelling, bleeding, bruising and infection. Other symptoms include light-headedness, dizziness, nausea after drinking.

Treating patients with convalescent plasma

Once we have availability of the convalescent plasma from the NYBC patients are eligible to participate if they are over the age of 18 years and below the age of 90 years and are critically ill with COVID-19, meet inclusion criteria and are not responding to supportive care. We will study the use of Convalescent Plasma on 45 eligible recipients. Eligible subjects or legally authorized representative (LAR) will be asked for consent by the treating physician. Once informed consent is obtained, subjects will have ABO blood types determined for compatibility with the convalescent plasma donor and will receive two consecutive convalescent plasma infusions of 200 -250 ml each. Total transfusion time can last 2-4 hours.

Viral load after convalescent plasma treatment will be measured on day 0 prior to administering the convalescent plasma and then on days 3, 5, and 7. In addition antibody titers will be measured on day 0 prior to administering the convalescent plasma and thereafter on days 3, 5 and 7.

Blood will be sent off to Boston Heart Research labs for antibody titers using **DIAZYME DZ-LITE SARS-CoV-2 IgM CLIA KIT.** They will also measure the viral load

Risks to subjects may include side effects from intravenous injection like skin irritation, pain, swelling, bleeding or bruising. Serious risks include:

- Transfusion related acute lung injury
- Transfusion associated circulatory overload
- Allergic/anaphylactic reactions

Other less common risks include:

- Transmission of infections
- Febrile non-hemolytic transfusion reactions
- RBC allo-immunization
- Hemolytic transfusion reactions.

6.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

- Using the Full unanticipated problem and Adverse event report all AE, unanticipated AE and SAE will be reported to the IRB and the FDA. . The PI and study team will follow regulatory requirements related to the reporting of unexpected serious adverse drug reactions to the regulatory authority and the IRB.
- In each safety report, the study team will identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and will analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.
- *In the case of Unexpected fatal or life-threatening suspected adverse reaction t*he PI and study team will notify FDA of any unexpected fatal or life-threatening

suspected adverse reaction as soon as possible but in no case later than 5 calendar days after the PI's initial receipt of the information.

As defined in 21 CFR 312.32(a):

Adverse event - means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction - An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction - An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction - means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction - An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by

virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

	STUDY PERIOD FOR DONOR			
Eligibility				
Day	-14 to 0	Visit 1	Visit 2	Re-test Visit (as needed)
Informed Consent	X			
Demographics and History		X		
COVID-19 Symptom screen		X		
COVID-19 test for eligibility		X		X
Antibody titer		X		X
Viral load		x		X
Blood stored for future testing		X		
Adverse Event Monitoring		X	X	
NYBCvisit to donate plasma			X	

STUDY PERIOD FOR RECIPIENT							
Eligibility							
Day	-14 to 0	0	3	5	7	14	28
Informed Consent	X						
Convalescent Plasma Infusion		X					
Vital Signs	X	X	X	X	X	X	X
Physical Examination		X	X	X	X	X	X
Medications	X	X	X	X	X	X	X
Co-morbid illnesses	X						
Adverse Event Monitoring		X	X	X	X	X	X
Laboratory Testing							
CBC and CMP		X	X	X	X	X	X
COVID-19 test	X						
Viral Load		X	X	X	X		
Antibody titers		X	X	X	X		
Cytokine Panel		X	X	X	X		
CxR*	X						
EKG *							
ECHO *							
• *Only if clinically indicated							

7.0 Statistical Considerations

The analysis will focus on two primary comparison groups. Within the intervention group, viral load and antibody titers overall and at 0, 3, 5, and 7 will be compared by patient survival, patient demographics, and clinical profile. Viral load and antibody response at each time point will be graphed. A secondary analysis will compare in-patient mortality between the intervention group and a matched control group of COVID-19 inpatients cared for prior to the intervention. Descriptive statistics and

comparisons will include patient demographics, comorbidities, medications, laboratory values, APACHE score, and other clinical variables. Variables pertaining to hospital stay will include admission dates, date of onset of COVID-19 symptoms, length of stay and days in the ICU. Continuous variables will be compared using the Wilcoxon rank-sum test or t-test; categorical variables will be compared using χ^2 tests or Fisher's exact test. Outcomes will be considered statistically significant at a p-value < 0.05.

8.0 Privacy/Confidentiality Issues

Discuss the methods for ensuring participant privacy, and the methods for protecting All data collected will be stored in the hard drive of a password-protected and encrypted computer at Saint Francis Hospital and Medical Center. The subjects' research folder and medical records for both the donor and the recipient of the plasma will be kept in a locked file cabinet in the co-investigators' office at the Research Department at Saint Francis Hospital and Medical Center and will only be accessible by study staff. The study database will contain only de- identified data points. A study identifier, linked to the database through a key code, will be kept separate from the data set, stored in a password protected and encrypted database accessible only to the Primary Investigator. The study identifier will be used only to verify and confirm the accuracy of the data collected from the medical record. This study identifier will be kept separate and hidden from the database, and also maintained on a password protected and encrypted database in files accessible only to the Primary Investigator.

9.0 Follow-up and Record Retention

All records will be maintained for 3 years after study completion.

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