Convalescent Plasma for Treatment of Patients Hospitalized with COVID-19 Respiratory Disease: A Randomized Controlled Trial

ClinicalTrials.gov Identifier: NCT04385199

Protocol May 4, 2020

Convalescent Plasma for Treatment of COVID-19 Study Protocol

Principal Investigators:

Geneva Tatem, MD
Fellowship Program Director, Pulmonary and Critical Care Medicine
Associate Division Head
Associate Clinical Professor of Medicine
Wayne State University School of Medicine
Detroit, MI

Ileana Lopez-Plaza, MD
Division Head, Transfusion Medicine
Department of Pathology, Henry Ford Hospital
Associate Clinical Professor of Medicine
Wayne State University School of Medicine

Jeffrey Jennings, MD
Associate Fellowship Program Director for Research
Pulmonary and Critical Care Medicine Fellowship Program
Henry Ford Hospital

Mayur Ramesh, MD
Division of Transplant Infectious Diseases and Immunotherapy
Henry Ford Hospital

1. STUDY AIM, BACKGROUND, AND DESIGN ABSTRACT

Background

The pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) is rapidly spreading, with few therapeutic options. There are currently 1.3 million confirmed cases worldwide as of April 6, 2020.

There are currently no vaccines or specific therapeutics against COVID-19. Novel antiviral therapies such as remdesivir are currently under investigation, and the efficacy has yet to be established.

The use of convalescent plasma has been previously recommended as empiric treatment for Ebola in 2014, and there has been suggestion that transfusion of convalescent plasma was effective in H1N1 influenza. (1) Single transfusion of convalescent plasma was associated with reduced cytokine levels, reduced respiratory tract viral load, and reduced mortality.

We hypothesize that use of convalescent plasma transfusion could be beneficial in patients infected with SARS-CoV-2.

This is a pilot study to assess tolerability and efficacy of transfusion of convalescent plasma in critically ill patients with respiratory failure due to SARS-CoV-2.

Specific Aims:

1. To evaluate the clinical improvement in patients with COVID-19 after receiving convalescent plasma

Rationale for the Project:

1. The current pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 has affected over 1.3 million people worldwide. Cases continue to rise due to the rapid transmission of the coronavirus responsible for disease. As this is a novel coronavirus, the population has no immunity to this virus. Currently there are no vaccines or drugs that are proven beneficial in prevention or treatment of COVID-19, but many are under development or investigation.
2. Human convalescent serum has been used as passive antibody therapy to provide immediate immunity for patients and has been used in previous outbreaks with other coronaviruses such as SARS-CoV-1, responsible for Middle Eastern Respiratory Syndrome (MERS) as well as Influenza A H1N1 2009 (1).
3. The anticipated mechanism for passive antibody therapy in COVID-19 is viral neutralization.
4. Viremia peaks in the first week of infection in most viral illnesses and patients develop primary immune response by days 10-14 followed by virus clearance. In COVID-19 disease, many patients become critically ill due to the vigorous immune response, resulting in the cytokine release syndrome, pneumonia, and renal failure.
5. Currently, the only individuals in the population with antibodies to SARS-CoV-2 are those who are previously confirmed to have COVID-19 and have clinically recovered.
6. Passive immunity for patients with COVID-19 could be achieved by transfusion of convalescent plasma obtained from those individuals previously confirmed to have COVID-19, have clinically recovered, and have sufficient neutralizing antibodies.

7. A case series of 5 critically ill patients in Wuhan, China treated with convalescent plaza demonstrated improvements in viral load, increased neutralizing antibody titers following plasma transfusion, and improvement in respiratory failure. (2)

Significance:

Establishing passive immunity for critically ill patients with COVID-19 could interrupt the exaggerated immune response from severe viremia responsible for precipitating the cytokine release syndrome that leads to pneumonia and severe hypoxia seen in COVID-19 disease.

2. SUBJECT POPULATION AND ELIGIBILITY

Methods

Study Subjects

Patients with laboratory confirmed COVID-19 diagnosed using qualitative reverse transcriptase-polymerase chain reaction (qRT-PCR) who are hospitalized with severe COVID-19 respiratory disease.

Inclusion criteria:

- Age >= 18

With one or more of the following:

- Dyspnea
- RR >30
- O2 saturation <= 93%
- PaO2/FiO2 < 300 mmHg
- Bilateral airspace opacities on CXR >50% within 24 to 48 hours

Exclusion criteria:

- Participation in any other clinical trial for COVID-19
- Patients who are incarcerated
- Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug infusion; excluding steroids and/or hydroxychloroquine or other standard treatment
- Negative rRT-PCR from nasopharyngeal swab or respiratory secretions within 48 hours prior to eligibility assessment
- History of allergic reaction to blood or plasma products

- Known IgA deficiency
- Acute myocardial infarction within past 30 days
- Acute stroke within past 30 days
- VV-ECMO or VA-ECMO

Donor Subjects

- Must have confirmed prior diagnosis of COVID-19 confirmed via laboratory testing
- Must have complete resolution of symptoms at least 14 days prior to donation
- Confirmed negative testing for COVID-19 from one or more nasopharyngeal swab specimens or molecular diagnostic test from blood prior to donation
- Female donors must be HLA antibody negative
- Have blood collected at designated blood center

Informed Consent:
Study Subjects

Informed consent will be obtained by the research coordinator after explanation of the study procedure, as well as potential risks and benefits.

Donor Subjects

Informed consent will be obtained by the research coordinator after explanation of study procedure, as well as potential risks and benefits. Included will be consent for serologic testing and rT-PCR for SARS-CoV-2.

3. STUDY PROCEDURES

Project Design and Protocol:

Open label randomized controlled study with 2:1 enrollment of patients with hypoxemic respiratory failure receiving transfusion of convalescent plasma from donors recovered from COVID-19.

Subjects meeting inclusion criteria will be screened for eligibility and upon consent randomized to either the treatment arm or control arm in 2:1 (treatment : control) allocation.

Those randomized to the treatment arm will receive transfusion of one 200mL unit of ABO matched convalescent plasma in addition to standard therapy for COVID-19 according to current treatment guidelines per our health system standard of care.

Those randomized to the control arm will receive standard therapy for COVID-19 according to current treatment guidelines per our health system standard of care.

Data for all enrolled patients will be recorded and will include baseline characteristics, laboratory and clinical data,

Study Subjects

1. Patients admitted to HFHS with confirmed COVID-19 will be reviewed daily
2. Critically ill patients meeting the inclusion criteria for study subjects will be approached for informed consent.
3. The treating physician will be notified of potential for study enrollment
4. Potential study subjects will have consent form given to them in the room by bedside nurse. Research personnel will have a discussion with the patient through ICU phone explaining the benefits and risks of participation, as well as inform them that participation will not affect their standard care.
5. Upon agreement to participate, consent form will be signed with a copy provided to the patient or their representative.
6. Once enrolled the patient history and laboratory data will be reviewed and collected. Baseline data review will include:
    a. CBC
    b. Electrolyte panel
    c. Crp
    d. IL-6 (if available)
    e. D-dimer
    f. LDH
    g. ABG
    h. PaO2/FiO2 ratio or
    i. SaO2/FiO2 ratio if ABG unavailable
    j. Ventilator settings (if mechanically ventilated)
7. HLA antibody testing and blood typing will occur.
8. Study consent form and hospital transfusion consent will be sent to the HFHS blood bank along with a request form for a single 200 mL unit of ABO matched convalescent plasma. All blood will be screened, tested, and plasma banked according to current blood bank standards per FDA regulations.
9. The HFHS blood bank will allocate the unit of ABO matched convalescent plasma from the blood collection center (Versiti) or HFHS blood bank.
10. In the event that the HFHS blood bank cannot allocate an ABO matched convalescent plasma unit, they will be provided plasma through the expanded access program.
11. The blood bank will inform the study subject's care team when convalescent plasma is available and ready for transfusion.
12. Provider will place an order for plasma transfusion in the EMR.

13. Subjects will be given oral medication to prevent fever and allergic reactions. Acetaminophen 325mg orally, Diphenhydramine 25mg orally, and Famotidine 20mg orally will be given to subjects to take 30 minutes prior to transfusion.
14. The unit of ABO matched convalescent plasma will be delivered to the patient bedside.
15. The 200mL unit of plasma will be verified for ABO compatibility by bedside nurse according to standard practice and will be transfused by bedside nurse over 3 hours. Transfusion of donor plasma will be performed according to current Tier 1 Nursing Protocol for Blood and Blood Product Transfusion (found at https://henryford.policystat.com/policy/6696852/latest/).
16. The recipient will be monitored for transfusion reactions, and infusion immediately discontinued if any signs or symptoms of transfusion reaction. Any transfusion reaction will be reported to transfusion medicine.
17. Clinical and laboratory data will be collected at baseline, 30 minutes after convalescent plasma transfusion, and study days 1,3,5,7,14 and 28. This data will include:
    a. CBC
    b. Electrolyte panel
    c. Crp
    d. D-dimer
    e. LDH
    f. Ventilator settings (if mechanically ventilated)
    g. Chest x-ray and ABG will be performed on day 3 after plasma transfusion.
    h. Chest x-ray will also be performed on day 28.

<u>Donor Subjects</u>

1. Eligible candidates for convalescent plasma donation will be approached for testing.
2. Upon agreement to participate, informed consent form will be signed with a copy provided to the donor or their representative.
3. Confirmation of negative testing for COVID-19 from a nasopharyngeal swab specimen via RT-PCR or molecular diagnostic blood test will be performed.
4. Donor subjects meeting plasma donation criteria will have plasma collected by apheresis at a designated blood collection center for this study.
5. Collected plasma will be frozen and stored in the blood bank after being tested and screened according to current blood bank standards per FDA regulations.

Co-Interventions

The primary clinical team will have independent control of all treatment management, and outside of plasma transfusion will not be influenced nor impacted by the investigational team.

Data regarding co-interventions will be collected on the data forms.

Outcome Measures:

Primary Outcomes:

Improvement in oxygenation as documented by PaO2/FiO2 or Sa/FiO2 (if ABG was unavailable at enrollment) 72 hours after infusion

Secondary Outcomes:

I. Clinical recovery
   i. Improvement in SOFA/mSOFA score at days 1,3,5,7,14, and 28 after plasma transfusion
   ii. Avoidance of intubation (within 7 days of plasma infusion for those not intubated at time of enrollment)
   iii. Ventilation days
   iv. ICU length of stay
   v. Hospital length of stay
   vi. Mortality at 28 days

II. Laboratory recovery
   i. Crp measured on days 1,3,5,7,14, and 28
   ii. IL6 measured 72 hours after plasma transfusion
   iii. Improvement of airspace opacities on chest radiograph done 72 hours after plasma transfusion
   iv. Improvement of airspace opacities on chest radiograph done on day 28

Data Collection:

1. Baseline characteristics:
   a. Demographics: Age (years), Gender, Height, Weight, Race/Ethnicity
   b. Comorbidities
   c. Preadmission Medications

2. Laboratory evaluation:
   a. CBC, electrolytes, creatinine clearance, LDH, ferritin, CPK, manually calculated SOFA or mSOFA score

3. Clinical evaluation (daily measurements at 9pm)
   1. COVID-19 therapy (hydroxychloroquine, solumedrol, etc.)
   2. FiO_2

3. SaO_2
4. P/F Ratio
5. S/F Ratio (if ABG unavailable)
6. Notation of prone positioning
7. Volume status
8. SOFA or mSOFA score (manually calculated)

4. Radiographic imaging
    a. CT or chest radiograph reports will be collected and temporally related to point of admission to study. Subsequent chest x ray imaging will be done 3 days after plasma transfusion and on day 28.

Necessary laboratory work and/or imaging needed for study completion will be performed during hospitalization. If patient is discharged prior to study completion, it will be performed at the enrolling HFHS site.

Data Analysis:

This is a pilot study to assess safety, tolerability and efficacy of transfusion of convalescent plasma to gain information on safety and possible effect sizes for efficacy.

Thirty patients will be enrolled using a 2:1 (treatment:control) randomization strategy, for 20 patients in the treatment arm and 10 patients in the control arm.

Descriptive statistics will be presented.

Randomization:

Study subjects will be randomized into the treatment or the control arm using a 2:1 overall ratio.

4. ANTICIPATED RISKS

Patients will be followed for 28 days during which time all adverse events (AE) and significant adverse events (SAE) will be recorded and reported.

Likely
• **Not applicable**
Less Likely – Blood transfusion reactions
• **Fever (1%)**

• **Mild allergic reaction (1%)** • **Transfusion related volume overload / excess fluid in lungs (1%)**
Rare but Serious – Blood transfusion reactions
• **Transfusion related acute lung injury also known as "TRALI" (< 0.8%)** • **Hemolysis or low blood count due to red blood cell destruction (0.1%)** • **HIV (1 in 2 million)** • **Hepatitis B (1 in 800,000)**

In the event of an acute transfusion reaction the transfusion will be stopped immediately and must be reported to the blood bank and the investigator team. Study subjects will be monitored for 24 hours post-transfusion related for the development of signs/symptoms after the transfusion of the convalescent plasma. The standard of practice described in the Tier 1 Nursing Protocol for Blood and Blood Product Transfusion will be followed.

A safety monitoring board will review all events and will have authority to stop the trial if deemed necessary.

5. ANTICIPATED BENEFITS

Clinical improvement with reduced oxygen requirements, radiographic improvement, and decreased ICU LOS.

6. RENUMERATION/COMPENSATION

No compensation is available for participation in this study.

7. COSTS

There is no cost for participation in this study.

8. ALTERNATIVES

Subjects do not have to participate in this study. If they choose not to participate, they will continue to receive current standard therapy for COVID-19.

9. CONSENT PROCESS AND DOCUMENTATION

1. Potential study subjects will have consent form given to them in the room by bedside nurse. Research personnel will have a discussion with the patient through ICU phone explaining the benefits and risks of participation, as well as inform them that participation will not affect their standard care.
2. Upon agreement to participate, consent form will be signed with a copy provided to the patient or their representative.

10. WITHDRAWAL OF SUBJECTS

Subjects will be withdrawn from the study if a suitable ABO matched plasma unit cannot be obtained.

11. PRIVACY AND CONFIDENTIALITY

Name and MRN of subjects will be collected to ensure that all laboratory specimens and results are attained and recorded properly. Once all of the data is collected, all patient identifiers will be removed/de-identified and each subject assigned a numeric identifier. An electronic data base with de-identified data will be kept by the PI, in a password protected database on an HFHS computer. The data will only be accessible behind the HFHS firewall. The data will be kept at least 1 year post study completion to allow for adequate data review and publication.

12. DATA AND SAFETY MONITORING PLAN

Assuring patient safety is an essential component of this protocol. Each participating investigator has primary responsibility for the safety of the individual participants under his or her care. After 5 patients have been enrolled in the study, and for each 5 patients thereafter, safety data will be reviewed by the data safety monitoring committee (committee consisting of panel of at least 2 physicians unrelated to the study but with expertise in the field of this research) to evaluate the study related data and look at any adverse events that have been reported and assess the severity of the events on case by case bases. Study data will be monitored every week for accuracy and patient safety stand point. Any issues found during the safety data monitoring will be conveyed to the IRB by the study coordinator after that report has been reviewed by the study lead investigator. Risk to the patient is removed by stopping study intervention (plasma infusion) and providing necessary supportive care according to existing clinical guidelines.

The Investigators will determine daily if any adverse events occur during the period from enrollment through study day 28 or hospital discharge, whichever occurs first and will determine if such adverse events are reportable.

The following adverse events will be considered reportable and thus collected in the adverse event case report forms:

- Serious adverse events
- Non-serious adverse events that are considered by the investigator to be related to study procedures or of uncertain relationship (Appendix A)
- Study-specific clinical outcomes (Primary and Secondary Outcomes and Assessments During the Study), including serious adverse events such as organ failures and death, are systematically recorded in the case report forms and are exempt from adverse event reporting unless the investigator deems the event to be related to the administration of study drug (plasma infusion) or the conduct of study procedures (or of uncertain relationship) as outlined in Appendix A.

After randomization**,** adverse events must be evaluated by the investigator. If the adverse event is judged to be reportable, as outlined above, then the investigator will report to the IRB their assessment of the potential relatedness of each adverse event to the study drug or protocol procedure IRB specified process. Investigators will assess if there is a reasonable possibility that the study procedure caused the event, based on the criteria outlined in Appendix A. Investigators will also consider if the event is unexpected. Unexpected adverse events are events not listed in the anticipated risk of the study intervention. Investigators will also determine if adverse events are unanticipated given the patient's clinical course, previous medical conditions, and concomitant medications.

If a patient's treatment is discontinued as a result of an adverse event, study site personnel must report the circumstances and data leading to discontinuation of treatment in the adverse event case report forms.

APPENDIX A: Adverse Event Reporting and Unanticipated Events

Investigators will report all rare but serious adverse events immediately to transfusion medicine. The transfusion-related adverse event will be investigated and treated according to transfusion medicine protocols, including investigation for blood product ABO incompatibility.

As noted before, investigators will report all adverse events that are serious and study drug/intervention or study procedure related (or of uncertain relatedness) to the IRB within 24 hours.

The study Medical Monitor will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study drug or study procedure, as outlined below. The Medical Monitor will also determine if the event is unexpected for the study treatment. An adverse event is considered “unexpected” if it is not listed in the study protocol anticipated risks (section 4). If a determination is made that a serious adverse event has a reasonable possibility of having been caused by a study procedure or the study drug, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

The investigator/ coordinator will report all unexpected deaths, serious and treatment related adverse events, and SUSARs to the DSMB and IRB within 7 days after receipt of the report from the study group. A written report will be sent to the DSMB and the IRB within 15 calendar days. The DSMB will also review all adverse events and clinical outcomes during scheduled interim analyses. The investigator will distribute the written summary of the DSMB’s periodic review of adverse events to the IRB in accordance guidelines for safety review and guidance for study continuance.

The DSMB will inform the Investigator regarding study termination in the event of clear harm (worsening of clinical status, need for increased interventions beyond standard of care for minimal transfusion reaction) to multiple study subjects.

a. Unanticipated problems (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

• Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved

research protocol and informed consent document; and the characteristics of the subject population being studied;

• Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;

• Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

b.Determining relationship of adverse events to procedures

Investigators will be asked to grade the strength of the relationship of an adverse event to study procedures as follows:

• Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) Evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.

• Probably or Possibly Related: The event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "probably" or "possibly" associated should be selected.

• Probably Not Related: The event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.

• Definitely Not Related: The event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.

• Uncertain Relationship: The event does not meet any of the criteria previously outlined.

c. Clinical outcomes that may be exempt from adverse event reporting:

Study-specific clinical outcomes of patient's condition, as outlined as primary and secondary outcomes and assessments during the study are exempt from adverse event reporting unless the investigator deems the event to be related to the study procedures

(or of uncertain relationship) or if the event leads to discontinuation of study procedures. The following are examples of events that will be considered study specific clinical outcomes:

• Death not related to the study procedures

• Cardiovascular events: need for vasoactive drugs or fluids for hypotension or hypotension not temporally related to study drug infusion as outlined in section

• Respiratory events: decreased PaO2/FiO2, hypoxia, worsening acute respiratory distress syndrome, or respiratory failure not related to the study procedures

• Hepatic events: hepatic injury or liver dysfunction that leads to an increase from baseline in the serum level of bilirubin.

• Renal events: renal failure, renal insufficiency, or renal injury that leads to an increase from baseline in serum creatinine

13. QUALIFICATIONS OF THE INVESTIGATOR(S)

Dr. Tatem is board certified in Pulmonary and Critical Care Medicine and has been a senior staff physician at HFH for the past 12 years. She has been involved in educational research as well as retrospective data review for quality improvement projects within the critical care setting. She has been actively involved in care of patients with COVID-19 and collaborating with intensivists regarding research protocols in the PETAL network for this population.

14. REFERENCES

1. Hung IF, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis.* 2011;52(4):447-456.
2. Shen C, et al. *JAMA* 2020;E1-E8.
3. Arabi YM et al. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *Emerging Infect Dis.* 2016;22(9):1154-1561.
4. Zhang W, Du RH, Li B, et al. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microb Infect. 2020; 9:386–389. doi: 10.1080/22221751.2020.1729071
5. Chen WL, Lan Y, Yuan XZ, et al. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. Emerg Microb Infect. 2020; 9:469–473.