COVID-IVIG Protocol Cover Page

Study Title: Randomized Open Label Study of Standard of Care Plus Intravenous Immunoglobulin(IVIG) Compared to Standard of Care Alone in the Treatment of COVID-19 Infection

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Primary Objective:

1. To identify whether or not IVIG can halt the progression to respiratory failure requiring mechanical ventilation in subjects admitted to the hospital with confirmed COVID-19.

Secondary Objectives:

1. To identify whether adding IVIG to the standard of care will reduce days requiring oxygen therapy.
2. To identify whether adding IVIG to the standard of care will reduce total hospital days.

Hypothesis: We hypothesize that the addition of IVIG will be beneficial in abating acute lung injury in subjects with SARSCoV-2 induced hypoxia that results in organ injury in such patients.

Background: Coronaviruses has been known zoonotic pathogens since the early 1970's. Bats have been identified as the main natural reservoir and domesticated animal intermediary species (e.g., camels, cats) have facilitated transmission to humans. In late 2019, a novel coronavirus (SARS-CoV-2) emerged in humans, originating in Wuhan, China and spreading across the globe as a pandemic, causing coronavirus disease of 2019 (COVID-19).

The current mortality rate (17MAR2020) is not well described because of the shortage of laboratory testing assays worldwide. Using WHO data on the cumulative number of deaths to March 1, 2020, mortality rates would be 5.6% (95% CI 5.4–5.8) for China and 15.2% (12.5–17.9) outside of China[8].

Grave concerns are raised about the ability of the US healthcare system to handle the demand of subjects affected by the COVID-19 pandemic. While 80-85% of identified COVID-19 patients are asymptomatic or have mild disease, the 15-20% of patients requiring medical support (of which 1/3-1/2 are estimated to require ICU care) would pose dire consequences of healthcare access with current resources. Therefore, while the spread of virus continues to escalate, the ability to abort subjects away from the path of acute lung injury requiring mechanical ventilation would render an extreme advantage to healthcare systems. The average time from hypoxia to mechanical ventilation is nine days, and once patients become ventilated, they frequently require support for 2 weeks.

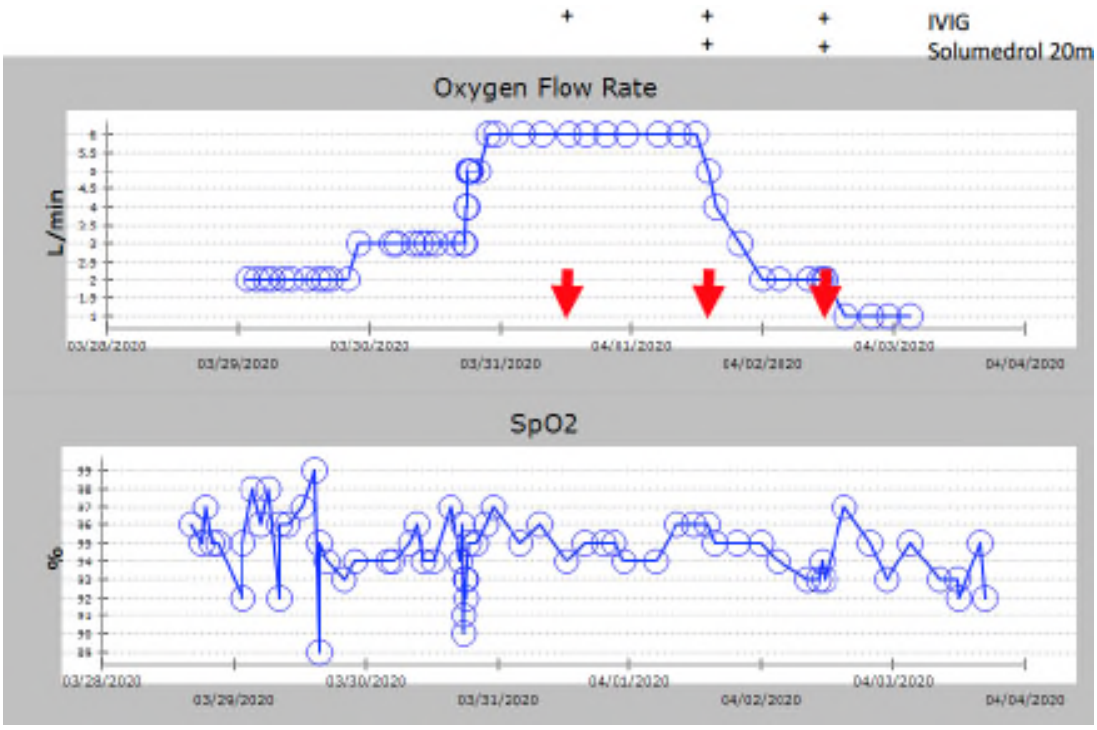
It is of interest that the natural history of COVID-19 frequently exhibits a biphasic illness seen with other acute viral and atypical infection. The first part of the illness is driven by direct viral

replication in permissive host tissues, which for COVID-19 is largely the respiratory tract. The host immune response to the primary infection results in a second phase, more catastrophic than the first, driven by immune system hyperactivity, often referred to as a 'cytokine storm.' Therefore, the successful treatment of more severe infection will likely rely more on immunomodulation rather than on antiviral therapy.[1] IVIG is an immunomodulatory agent used to treat the immunological complications of many infections, including immune-mediated encephalitis and Guillan-Barre.[2]

IVIG has successfully been used in the treatment of the influenza virus infection in both animals and humans.[3,4] van Gunten proposed that carbohydrate-binding antibodies may shield receptor binding sites of the virus, thus preventing cellular infection.[4] However neutralizing antibodies are thought to play only a minor role in attenuating severe viral sequelae, particularly those mediated by the immune-mediated second phase of illness. IVIG contains large amounts of sialylated antibiodies and recent studies have demonstrated that these are crucial for the anti-inflammatory effects of IVIG[5]. The main anti-inflammatory effect of IVIG is mediated through binding of the Fc-gamma region of the antibody molecule to Fc-gamma receptors on the surface of stimulated macrophages, essentially orchestrating a 'turn-off switch' to the cytokine response mediated by these important pro-inflammatory cells[1]. This mechanism is hypothesized to be crucial in aborting or attenuating the second more severe stage of COVID-19 infection.

To date, there have been very few human studies analyzing the effects of utilizing IVIG for COVID-19 infection. One small case series of only 3 patients from China demonstrated clinical improvement allowing hospital discharge in clinically deteriorating COVID-19 patients.[6] A more recently published larger trial also showed benefit of early IVIG.[7]

Motivated by this small study, we employed a similar algorithm in a 62 year old female with diabetes, hypertension, and a history of prior chemotherapy due to breast cancer who was clinically deteriorating from COVID-19 infection in the hospital, with ongoing fever and an oxygen requirement increasing from 2 L to 6L in the first 48 hours of hospitalization. After receiving IVIG, the patient demonstrated a remarkable clinical improvement, becoming afebrile and breathing room air in less than 72 hours, accompanied by improvement in inflammatory markers. She was discharged home uneventfully. We therefore believe that at least some COVID-19 patients may benefit from IVIG treatment. (SEE DETAILS BELOW)


IVIG
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L/min
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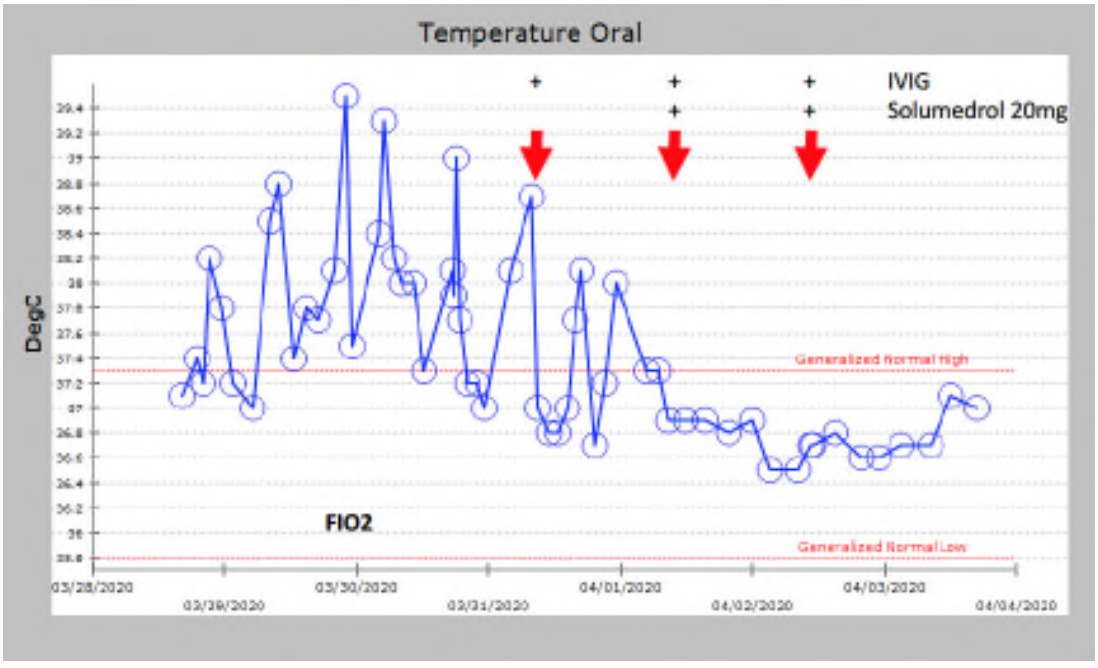
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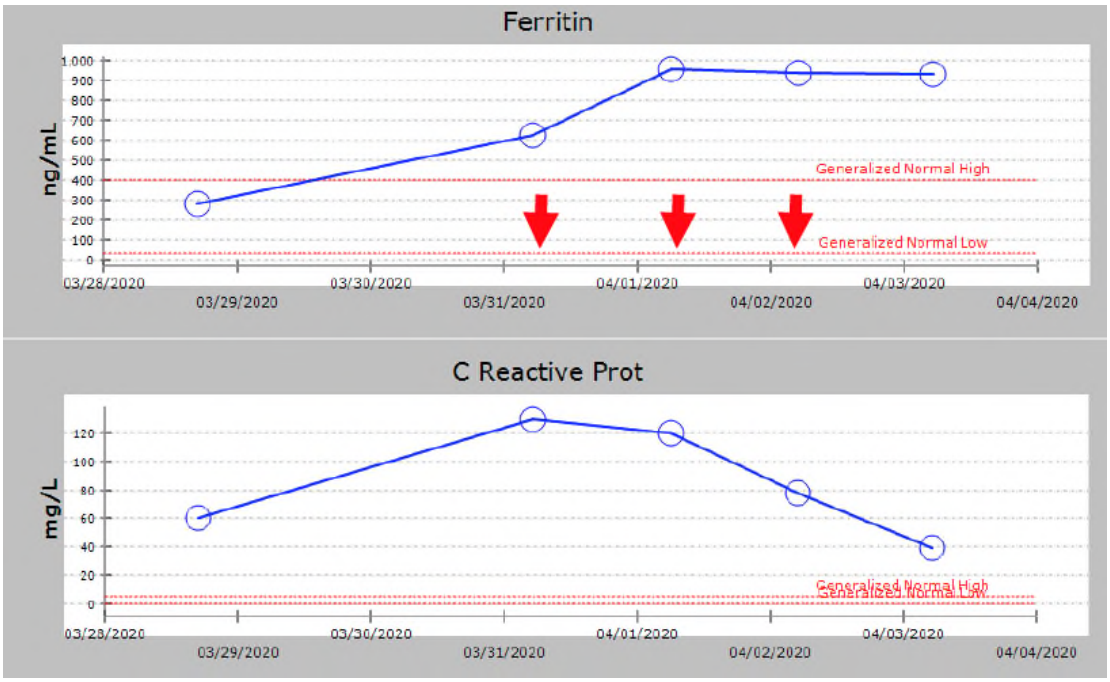

DISEASE STATE

It is currently believed that 80% of COVID-19 subjects will require no medical treatment, 15% will require non-ICU medical care, and 5% may require ICU admission. The goal of this study is to decrease the rate of subjects requiring mechanical ventilation, duration of days requiring oxygen therapy, and length of hospital stay.

Number of Subjects: 40

Inclusion Criteria:

1. Confirmed COVID-19 positive test result (including presumptive positive).
2. Hospitalization
3. Requiring ≥4 liters/min O_2 nasal cannula to maintain oxygen saturation ≥ 92%, but not mechanically ventilated
4. Age ≥18 years old.
5. Access to a phone in the hospital room or an electronic device that is capable of receiving phone calls and/or video calls and/or e-mail.
6. Able to read/write/speak English or Spanish fluently.
7. Subjects must have the capacity to provide consent or an appropriate Legally Authorized Representative (LAR) to provide informed consent.
8. Negative pregnancy test for women of childbearing potential.

Exclusion Criteria:

1. Severe allergy to any IVIG product formulation
2. History of DVT, PE, thromboembolic stroke or other thrombotic events

3. Hypersensitivity to corn. Octagam® contains maltose which is a sugar derived from corn.
4. Uncontrolled hypertension (SBP>180 mm Hg or DBP>120mmHg)
5. Active participant in another research treatment study
6. Mechanically ventilated patient
7. Code status is Do Not Resuscitate or Do Not Intubate

Age of Subjects: ≥18 years of age

Gender of Subjects: Either male or female

Racial and Ethnic Origin: Non-specific

Vulnerable Subjects: Hospitalized subjects

Study Design: Investigator initiated, open label, multicenter, two arm, randomized study to compare the impact of adding IVIG to the Standard of Care (SOC) to the SOC without IVIG. Randomization ratio will be 1:1.

Procedures and Study Visits:

1. The PI will be notified of a COVID-19 tested positive patient via hospital generated alert.
2. The PI or designee will prescreen the patient using the inclusion and exclusion criteria.
3. PI or Sub-I will contact the study team, if the patient passes prescreening.
4. The CRC will obtain an informed consent from the subject or LAR either electronically utilizing DocuSign® or with a paper copy utilizing an impartial witness:
    a. The research team will utilize DocuSign® for the signing of the consents in order to be compliant with the infection control measures taken place for Highly Infectious Diseases. Below are the steps of the DocuSign® procedure:
        i. Upon receiving confirmation of the subject passing prescreening, the CRC will call the subject/LAR to assure the consent process is being conducted in a private place and manner and obtain a valid email address. If the subject does not have a valid email address, instructions will be provided to help them set up an email address account. The CRC will also ask the subject/LAR if he or she would prefer to have the consenting process conducted via video call if this technology is available to all persons involved in the consent discussion).
        ii. If the subject/LAR agrees to participate the CRC will send the DocuSign® instructions via email to the subject.
        iii. The CRC will send out Consent via DocuSign® to the subject/LAR (it will appear in their email inbox).
        iv. Subject/LAR will use any electronic device that is able to access DocuSign® email and open consent. Subjects/LAR may be instructed to

place their phone on speaker mode (while maintaining privacy) to ensure that they can see the consent during the process.

v. The CRC will consent subjects/LAR via phone. CRC will ask the subject/LAR to verbally confirm that he or she is alone in the room to ensure privacy and confidentiality. If the subject/LAR wishes to include additional participants (e.g., next of kin) in the informed consent discussion, the subject/LAR may add the additional participant(s) to the call.

vi. Subject/LAR will sign consent using any electronic device that is compatible with DocuSign®. Once they are finished, the consent will be sent to the CRC's email inbox and the CRC will sign the consent electronically.

vii. Subject/LAR will have a digital copy of the signed consent accessible through DocuSign®. The subject/LAR may also request a printed copy of the signed consent to be mailed to their home address.

viii. After the consenting process, the CRC will download an electronic copy of the consent from DocuSign®. The CRC will email the subject/LAR an electronic copy of the consent and print out a copy for the site's research binder. After this, the CRC will delete the stored copy in DocuSign®. The CRC will also delete the subject contact information stored in DocuSign®.

b. If the subject/LAR is unable or unwilling to use DocuSign®, the informed consent process may be conducted via phone, or via video conference (if this technology is available to all persons involved in the consent discussion). An impartial witness will be present during the consenting process.

i. Upon receiving confirmation of the subject passing prescreening, a nurse or investigator will provide a paper copy of the consent to the subject/LAR when they enter the room for the provision of routine care. The CRC will call the subject to assure the consent process is being conducted in a private place and manner. The CRC will also ask the subject/LAR if he or she would prefer to have the consenting process conducted via video conference. An impartial witness will be added to the phone or video call. If the subject/LAR wishes to include additional participants (e.g., next of kin) in the informed consent discussion, the subject/LAR may add the additional participant(s) to the call.

1. The CRC will review the informed consent with the subject/LAR and respond to any questions the subject may have.
2. The impartial witness will confirm that the subject's/LAR's questions have been answered.
3. The CRC will confirm that the subject/LAR is willing to participate in the trial and sign the informed consent document while the witness is listening on the phone.

4. The subject/LAR will verbally confirm that they would like to participate in the trial and that they have signed and dated the informed consent document that is in their possession.

ii. If feasible, the subject/LAR or hospital staff will take a picture of the informed consent document signature pages to be saved with the study records. If this is not feasible, a signed and dated attestation will be obtained from the impartial witness who participated in the call and from the person obtaining informed consent, confirming that the subject/LAR agreed to participate in the study and that they signed the informed consent. The CRC will save the signed/dated attestation with the study record.

5. A urine or blood pregnancy test will be ordered using urine or blood previously collected for routine care for subjects of childbearing potential who have passed all the other screening criteria and signed consent. If no leftover urine or blood is available, the patient will be asked to take a urine pregnancy test. If the patient already had a pregnancy test during their hospitalization, the results will be extracted from the EMR and used to determine eligibility.
6. The designated research team member will randomize the subject. The randomization will be computer generated using this website in a block of 10. (https://www.sealedenvelope.com/simple-randomiser/v1/lists).
7. If the subject is randomized to the "study arm", then the Research Pharmacy will enter in the order for the IVIG and will not charge the subject. If the subject is randomized to the SOC arm, there is no additional work to be completed by the Research Pharmacy.
8. There are 3 endpoints for this study: discharge to home, receipt of mechanical ventilation, or death. Once one of these endpoints is reached, the subject's participation in the study will end. As such, the subject may be a candidate for enrollment in another research protocol where appropriate.

Dose: IVIG (Octagam) 0.5g/kg IVPB actual body weight daily x 3 days, with premedication methylprednisolone 40 mg IV push x 1 30-50 minutes before each IVIG infusion.

- Initial infusion rate of IVIG (Octagam) will be of **0.6 mL/kg/hour**, increasing to a maximum rate of 100ml/hr, if tolerated. This is consistent with the standard of care for IVIG at Sharp HealthCare.

Procedure Classification: Aside from a urine or blood pregnancy test for subjects of childbearing potential, there are no other extra tests, imaging scans or procedures that will be performed as part of the study.

Potential Hazards and Precautions: Potential hazards to subjects are described in the "Potential Risks" section, and precautions for subjects are described in the "Protection Against Risks" section.

Research team members will take precautions to minimize exposure to COVID-19 infection by obtaining informed consent electronically, and by collecting data from routine clinical tests as opposed to conducting protocol-specific tests.

Study Timeframe: The study time frame would be from IRB approval date to the end of the pandemic or until our sites reach 40 subjects, whatever comes first. We anticipate that at the current COVID-19 rate, it should take about 6 weeks to enroll all patients from the time of study initiation.

The end of study for each individual subject will be the date of discharge from the Sharp HealthCare hospital. The subject will not be followed if there is a transfer to a non-Sharp hospital or any sub-acute care setting (i.e., SNF, LTAC, rehabilitation center). A subject's participation will also end if the subject's goals of care have transitioned to palliation, including changing the code status to Do Not Resuscitate or Do Not Intubate of which would render the patient no longer a candidate for intubation.

Method of Subject Identification and Recruitment: The PI or Sub-I will be notified of a COVID-19 confirmed positive patient via hospital generated alert as part of the Infectious Disease Team at each hospital.

Subject Capacity: Subjects who are cognitively impaired or lack the capacity to provide informed consent (as described in HRP-013 section 5.2) may be enrolled in the study if they have an appropriate LAR to provide written informed consent on their behalf. The researchers will follow the guidance outlined in HRP-013 "Legally Authorized Representatives (Surrogate Consent)" when obtaining surrogate consent.

Subject/Representative Comprehension: Subjects/LARs must have the ability to understand the requirements of the study, provide informed consent, and provide authorization of use and disclosure of personal health information. Subjects with impaired cognitive or decision-making capacity (determined by the PI or designee's assessment of the subject's ability to understand and express a reasoned choice, according to HRP-013 section 5.2.1) must have an appropriate LAR to provide consent on their behalf. If the research subject lacks capacity to consent, the investigator will describe the research to the subject in a manner consistent with the standard consent process and indicate the intent to obtain surrogate consent. This communication will be documented in the research record. If the research subject is non-responsive, the investigator will document this observation in the research record and a note in the subject's medical record that references the research record. If the research subject expresses resistance or dissent to being in the research or to the use of the surrogate consent by word or gesture, she/he will be excluded from the research study.

Documentation of Consent/Assent: Consenting will be conducted as described above in the Procedures and Study Visits section. Consents will be printed and stored in the subject's research binder in a secure location.

Reimbursements or Payments: None

Costs to the Subject: None

Data Sources: Sharp HealthCare electronic medical records (EMR) for hospital in-patients who meet inclusion criteria at acute care facilities.

Data Collection/ Assessment Instruments: The Case Report Form will include the following data elements: Demographics (age, gender, race/ethnicity, insurance), medical status (pre-existing comorbid conditions (based on the Charlson Comorbidity Index), ferritin level (results will only be collected if lab is ordered as part of the subject's standard of care), CRP level. The tool used to calculate the Charlson Comorbidity Index can be found here https://www.mdcalc.com/charlson-comorbidity-index-cci#next-steps). Other data to be collected from standard of care procedures includes vital signs, result of blood or urine pregnancy test, serum creatinine, calculated creatinine clearance (Cockroft and Gault equation), white blood cell count, platelet count, maximum body temperature in the past 24 hours and oxygen demand rate, whether or not there is an admission to the ICU, any concomitant antimicrobials including azithromycin, doxycycline, hydroxychloroquine, chloroquine, and remdesivir. Receipt of interventions will include standard of care in those who have tested positive for COVID-19. Measures of healthcare service utilization will include length of stay, number of days in ICU, number of days requiring oxygenation, discharge disposition and mortality.

Data Collection Resources: The Study Coordinator will complete the Case Report Forms, with assistance from Sharp's Clinical Analytics team to extract information from the EMR.

Data Analysis: Descriptive statistics will be conducted to describe frequencies of demographics and clinical characteristics including the following: age at discharge, gender, race/ethnicity, payer, comorbid conditions based on the Charlson Comorbidity Index, receipt of medical interventions (mechanical ventilation, medications) and healthcare service utilization (ICU admission and Length of Stay in the hospital). Frequencies and descriptive statistics will be conducted using chi-square or 2-tailed Fisher exact statistics depending on the final sample size for categorical data and t-tests for continuous data. Kaplan-Meir analysis will be performed with assistance from a biostatistician regarding the endpoints of mechanical ventilation and discharge to home endpoints. We do not anticipate number of patient deaths for be sufficient for a meaningful analysis.

Privacy of Subjects: There will be limited access to the subject due to standard of care isolation protocols. The Informed Consent process will emphasize the personal nature and privacy

concerns related to communications regarding the subject's condition and infectious disease test results.

Confidentiality of Data and Storage: Subjects information will be recorded on a master list accessible to the investigator and research staff. It will be stored electronically on a secure server. Information included on master list: subject ID, hospital, date screened, patient name/room#, FIN, group, age, gender, enrollment status, telephone number, email address, and address. All binders will be stored and secured at Sharp's Center for Research office in accordance with all regulatory and organizational requirements, and will be accessed only by authorized personnel. No subject-specific data will be reported. Sharp FIN will be used to link subject records across data systems and hospital visits. Protected Health Information (PHI) will be safeguarded as specified by Sharp HealthCare policy. There is a risk of disclosure of PHI from inappropriate access to the study database. All efforts will be made to protect PHI, including password protecting the database with access only allowed to study members who are Sharp HealthCare employees. All datasets will be de-identified prior to any statistical analyses conducted by the Statistician. Identifiers will be destroyed two years after study end date, once data has been aggregated for reporting.

Data Monitoring: A designated person (or group of designees) who is not part of the Research Team will review and will report the outcomes to the SHC IRB after a total of 10, 20, and 40 patients (5, 10, and 20 in each arm, respectively) have completed/met the endpoint of the study. Additionally, if unexpected adverse outcomes are identified at any point in the enrollment the designated person will review the case on an individual basis.

Benefits to Individual Subjects: Potential reduction in ICU hospitalization, potential avoidance of mechanical ventilation and potential decrease in length of stay in the hospital.

Potential Benefits (Value) to Society: Any data collected will be a benefit to society whether we prove or disprove the hypothesis. However, if it is determined that the studied intervention indeed does reduce demand for mechanical ventilation and ICU care, it may provide significant relief to a medical care system that is anticipated to be overwhelmed at pandemic peak. The benefits will most likely be realized in the next SARS-CoV-2 epidemic. There are potential benefits to each institution that participates in this study to reduce the demand of mechanical ventilation and reduce the demand for isolated negative pressure ICU rooms.

Risk Category: Greater than minimal risk

Potential Risks: All of the adverse reaction and hypersensitivities are detailed in the package insert. These risks are also explained in layman's terms in the Informed Consent Form. The most common adverse reactions include the following: Headaches, allergic reaction and anaphylaxis, aseptic meningitis, venous thrombosis.

Protection Against Risks:

1. Pre-medicate with methylprednisolone IV to reduce/avoid infusion related reactions, including headache, aseptic meningitis.
2. The subject will be in the in-patient acute care setting with the Standard of Care monitoring as would be done if the drug were to be administered outside of the study setting.
3. If the subject experiences side effects that are suspected to be due to the IVIG for subjects in the study group, it will be up to the discretion of the treating clinician/PI whether to continue the IVIG or not.
4. There are no adequate and well-controlled studies of methylprednisolone in pregnant women, and it is not known whether Octagam 10% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Therefore, pregnant women are excluded from participation, and women of childbearing potential will undergo a blood or urine pregnancy test prior to randomization.

Termination of the Study:

1. If the subject prematurely stops study treatment, the study team will continue to collect data until discharge.
2. If the subject progresses into mechanical ventilation, those who are actively receiving IVIG will be stopped.
3. If there are additional doses schedule per protocol and the subject has progressed into the intensive care unit, the additional doses will not be administered.
4. The patient retain the right to terminate the study drug for any reason.
5. Discharge to home
6. Patient's goals of care have transitioned to palliation, including changing the code status to Do Not Resuscitate or Do Not Intubate of which would render the patient no longer a candidate for intubation.
7. Death

References:

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