Early Treatment of Cytokine Storm Syndrome in Covid-19

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Protocol

Introduction

Macrophage Activation Syndrome (MAS) or Cytokine Storm Syndrome (CSS) is a disorder consisting of massive systemic inflammation, multi-organ system failure, disseminated intravascular coagulopathy, and often severe morbidity/mortality. Reports from areas initially impacted by Covid-19 confirm clinical and laboratory features present in patients with respiratory failure that are identical to those associated with Cytokine Storm Syndrome (CSS) occurring in the setting of other disorders and viral infections (1,2). The recombinant human IL-1 soluble receptor antagonist (rhIL-1ra) anakinra has a short half-life of 4-6 hours, is quick acting and in multiple case reports/series has been reported to be safe as well as effective in treating CSS occurring in the setting of herpes virus infections (EBV/CMV/HSV), ehrlichiosis, sepsis syndromes, adult Still disease/systemic JIA, and systemic lupus (3-6). In children with severe flares of sJIA, doses as high as 100 mg sc every 6 hours have been employed with success (7) and in the absence of significant noted toxicities. In previous trials of anakinra use for management of sepsis, doses up to 3500 mg/day were employed over 72 hours without any noted serious toxicities attributed to anakinra (8). In a recent study examining outcomes in the phase III sepsis trials, treatment with anakinra was associated with improved survival in a subgroup with MAS attributes including hepatic dysfunction and coagulopathy (4) Trials of anakinra to treat CSS in hospitalized patients with Covid-19 infection and features of CSS are therefore warranted.

Specific Aims

The specific aims of the trial are to determine whether treatment with anakinra added to standard of care treatment for hospitalized patients with Covid-19 pneumonia results in:

1. . Survival and discharge from the hospital without the need for intubation/mechanical ventilation. (Primary outcome)

1. No increase in oxygen requirement or oxygen delivery measures to maintain SaO2 > 90% at 48 hours compared to baseline at study entry/randomization. (Primary outcome)

22. No increase in oxygen requirement or oxygen delivery measures to maintain oxygen saturation >90% Day 2 (48 hours) through Day 105 (120 hours). (Secondary outcome)

33. At least 25% decrease in serum ferritin, LDH, CRP, and d-dimer at 48 hours. (Secondary outcome)

4. Normalization by Day 5 of laboratoy CSS attributes: ferritin, fibrinogen, AST, ALT, leucopenia, tryglycerides, sCD25 (Secondary outcome)

5. Normalization or ≥ 75% improvement by Day 10 (120 hours) in each of the following laboratory CSS attributes elevated beyond the normal range at randomization: ferritin, fibrinogen, AST, ALT, leucopenia, thrombocytopenia, d-dimer, CRP, triglycerides, sCD25. (Secondary outcome)

6. Decreased time to achievement of ≥93% oxygen saturation on room air. (Secondary outcome) 7. No increased prevalence of nosocomial bacterial or fungal or viral infection through the time of hospital discharge. (Secondary outcome)

8. No failure to develop neutralizing antibody to Covid-19 measured at Day 28. (Secondary outcome) 5. Discharge from hospital without the need for intubation/mechanical ventilation. (Secondary outcome)

Significance

If shown effective, early identification of CSS and repurposing anakinra for its treatment in severe Covid-19 illness will help reduce ICU admissions, improve patient outcomes and enhance survival. Confirmation of a genetic basis for susceptibility to Covid-19 associated CSS as we identified in H1N1 associated deaths (6) will also facilitate risk stratification and future targeted approaches to Covid-19 disease management.

Design
Recruitment and Enrollment: Thirty patients will be recruited for enrollment; potential subjects will be identified from the registry of Covid-19 patients admitted to the University of Alabama Hospital.

Patient Compensation: Not applicable

Eligibility/Inclusion Criteria:
Inclusion criteria:
1. 18 years old or older
2. Molecular diagnosis of SARS-CoV-2 infection and Covid-19 pneumonia
3. Radiographic imaging consistent with Covid-19 pneumonia
4. Room air oxygen saturation <93%
5. Hyperferritinemia (>700 ng/ml)
6. Any three of the following:
a. elevated d-dimer (> 500 ng/ml)
b. thrombocytopenia (< 130,000/mm3)
c. leucopenia (WBC < 3500/mm3) or lymphopenia (<1000/mm3)
d. elevated AST or ALT (> 2X ULN)
e. elevated LDH (> 2X ULN)
f. CRP > 100 mg/L

Exclusion criteria:
1. Participation in other investigational treatment protocols for Covid-19 infection
2. Culture confirmed active bacterial infection requiring antibiotic therapy
3. On mechanical ventilation
4. Previous known hypersensitivity reaction to anakinra
5. Previous known hypersensitivity reaction to E Coli derived proteins
6. Pregnant or breast-feeding females

Subjects in the SoC only arm with deterioration of respiratory parameters and CSS markers at 48-96 hours will be transitioned to treatment with anakinra. Patients will stay on anakinra until all CSS markers no longer exceed the thresholds required for enrollment or through Day 5 of anakinra treatment, whichever comes first. Anakinra may be continued after Day 5 of treatment at the discretion of the treating physicians.

Informed Consent:
Identified patients who may be eligible for enrollment will be asked to consider participation in the protocol in the context of the informed consent process whereby the risks and benefits of their participation are discussed with a study investigator. As subjects with CSS/MAS are often severely ill,

those with any suspected altered sensorium will not be enrolled without the assent of a family member who is the designated representative of the patient to assist with their decision whether or not to participate.

Randomization:
Randomization will be assigned by the study coordinator using a computer-based randomization algorithm. The respective PIs will remain blinded to treatment group assignment for all subjects until study completion.

Visit Schedule and Study Procedures
Following obtaining informed consent and 1:1 randomization by computer, study assessments will be as follows:
Day 0:
- Record vital signs, ventilation and oxygen support, heart function, and kidney function/support.
- Blood drawn for these tests:
- ferritin, CBC with diff, CMP, ESR, CRP, fibrinogen, D-dimer, INR/PT, LDH
triglyceride level
- Cytokine-12 panel, IL-18, CXCL9, sCD25, sCD163, IL-1β, NK/B/T-cell lymphocytes
- NK cell function assay
- Blood sample for genetic testing for perforin pathway (genetic traits associated with CSS)

Every effort will be made to procure remdesiver as available under existing PUA for all enrolled subjects.

Following completion of the baseline assessments, dosing of study agent (100 mg anakinra or equal volume saline placebo) will commence every 6 hours by subcutaneous administration.

Day 1-Day 9:
- Record vital signs, ventilation and oxygen support, heart function, and kidney function/support.
- Blood drawn for these tests: ferritin, CBC with diff, CMP, ESR, CRP,CRP fibrinogen, D-dimer, INR/PT, LDH

Day 10:
- Record vital signs, ventilation and oxygen support, heart function, and kidney function/support.
- Blood drawn for these tests:

ferritin, CBC with diff, CMP, ESR, CRP, fibrinogen, D-dimer, INR/PT, LDH,
triglyceride level
Cytokine-12 panel, IL-18, CXCL9, sCD25, sCD163, and subsets of NK/B/T-cell lymphocytes

If after Day 5 but before Day 10, lab studies show that the levels of ferritin, d-dimer, CRP, LDH, AST, ALT have all returned to normal or improved ≥ 75% from noted Day 0 elevations in these laboratory tests AND the subject has ≥ 93% saturation on room air oxygen, the dose of IP will be decreased to twice daily until Day 10.

All study participants will continue to receive current standard of care treatment for Covid-19 infection. It is understood the standard is evolving and that some treatments that are newly considered standard of care (such as remdesivir) may not be available to enrolled subjects.

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Withdrawal of Participant Consent and Discontinuation of Study Drug:
Study participation may be discontinued for any of the following reasons:
a. Subject decision to withdraw consent for study
b. Evidence of allergy to administered anakinra
c. Intolerable adverse event as judged by study investigator and participant
d. Decision to terminate the study by the investigator and the DSMB due to one or more of the following:
• Death in any subject in which the cause of death is judged to be probably or definitely related to the study drug by the treating investigator.
• The occurrence in any subject of a life-threatening SAE whose causal relationship to study drug s judged to be probable or definite by the treating investigator.
• Two occurrences of Grade 3 or higher toxicities (per NCI CTCAE) that are assessed to be related to the study drug by the investigator.
• Two occurrences of a clinically significant Grade 3 or higher laboratory abnormality (per NCI CTCAE) assessed to be related to the study drug by the investigator.

If the study drug is discontinued, unless the subject withdraws consent, the subject will be followed for the full treatment/observation period (through Day 60) and all data will be collected as scheduled.
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Data Collection:
Clinical and laboratory data as described in 6.1.4.1. as well as concomitant meds, duration of ICU stay, duration of hospitalization and any noted adverse events, will be collected and stored on a secure UAB server. The data will be de-identified, referenced to the assigned study subject number only.

Safety Data and Adverse Events:
An adverse event (AE) will be defined as any untoward medical occurrence in a patient or clinical investigation subject administered anakinra or placebo during the study, and which does not necessarily have to have a causal relationship with this treatment. An AE will therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of anakinra/placebo, whether or not considered related to the medicinal product. All treatment emergent AEs will be recorded on source documents (i.e. original documents, data, and records). AEs include those reported spontaneously by the subject and those noted incidentally or as observed by the investigator or study personnel. To avoid vague, ambiguous, or colloquial expressions, the AE will be recorded using standard medical terminology that is as specific as possible, rather than the subject's own words. Whenever the investigator is confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results will be grouped together and recorded as a single AE.

All clinically significant abnormalities noted upon physical examination, or other diagnostic test results will be reported as an AE, except for baseline measurements that may be considered part of the medical history. In addition, all clinically significant AEs that continue at Study Termination will be followed up by the investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolved, or is determined to have resolved with sequelae. All AEs will be evaluated for intensity and causal relationship with use of the study medication (or study procedures if applicable) by the investigator.

AEs that occur following completion of study termination/early termination procedures will be recorded on a designated AE page of the source documents only if the investigator considers the event as clinically significant and as related to study medication or study procedures.
All adverse events that are deemed to be serious and meet the definitions provided in section 6.1.5.2, for serious adverse events will be reported as SAEs.

SAEs
Any AE that results in any of the following outcomes will be considered an SAE, as per outcomes as defined according to Code of Federal Regulations (CFR) Title 21 part 312.32.

- Death
- Life-threatening situation (subject was at risk of death at the time of the event. This does not refer to an event that might have caused death if it was of greater intensity.)
- Prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes (based upon appropriate medical judgment)

A data safety monitoring board (DSB) comprised of three UAB Rheumatologist, a UAB pulmonary and critical care specialist, a UAB specialist in infectious disease, UAB specialist in hematology, and a UAB specialist in nephrology will meet following enrollment of the first 15 subjects or quarterly to review inter-current study outcomes and safety data. The DSB for this study will also review any and all deaths that occur during the study within two weeks of the time of death. If it is the assessment of the DSB that deaths or other SAEs during the course of the study are significantly more prevalent in the anakinra treatment arm or the placebo arm, the study will be prematurely terminated.

Statistical Analysis Plan

The primary efficacy analysis will be conducted on a modified intention-to-treat basis and defined as all patients who underwent randomization and received either anakinra or placebo before intubation/mechanical ventilation or death. Descriptive statistics will be used to characterize participants. Continuous data will be summarized by means and standard deviation (SD) and analyzed by student t tests. Categorical data will be described with frequencies and percentages and compared using Fisher's exact or chi square tests. Cox proportional hazards models will be used to calculate hazard ratio for the association between treatment group and death from any cause or need for mechanical ventilation; due to small sample size control for demographic characteristics, clinical variables and comorbidities will likely not be possible. Calculated 95% confidence interval (CI) and $p<0.05$ will be considered significant. All analysis will be conducted with SAS v 9.4 (Cary, NC, USA).