Study Title: Dornase Alfa for ARDS in Patients with SARS-CoV-2

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Background and Significance

Health care systems across the world are being inundated with patients who are critically ill due to infection with Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) causing Coronavirus Disease 2019 (COVID-19). Around 10% of those infected will develop the most severe manifestation of the disease requiring admission to an intensive care unit[1]. Early reports suggested neutrophil extracellular traps (NETs) as being a potential contributor to the severity of disease in some patients with COVID-19[2]. The primary innate immune role for NETs is to trap and kill invading microbes, but in severe cases of COVID-19, NETs appear to cause significant morbidity in the lungs with associated microthrombi formation, endothelial damage, capillaritis, neutrophilic mucositis and mucus accumulation[3-6]. Plasma levels of NET activity are increased in patients who requiring intubation and are inversely correlated with arterial blood oxygen content to fraction of inspired oxygen ratio (PaO_2/FiO_2)[7]**.** Dornase alfa, currently is in use in patients with Cystic Fibrosis, works by degrading large extracellular DNA in the airways[8,9]. We proposed a trial of using inhaled dornase alfa as a therapeutic target to reduce excess NETs in patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19 pneumonia, with outcome aims including improved lung compliance and gas exchange[10].

Aims and Objectives

Aim #1: Determine if use of nebulized dornase alfa in ARDS secondary to COVID-19 will lead to improved pulmonary mechanics as measured by surrogate values of PaO2/FiO2 and static lung compliance.

Aim #2: Determine if use of nebulized dornase alfa in ARDS secondary to COVID-19 will lead to a reduction in alveolar and serum NET activity.

Research Design

A single center, non-randomized, controlled before-and-after clinical study was designed to examine the effects of inhaled dornase alfa in patients with acute respiratory distress syndrome secondary to COVID-19 pneumonia. A second standard of care patient population is to be collected as a case control group for comparison. After inclusion to the study and consent has been obtained, we will collect blood samples and perform diagnostic flexible bronchoscopy with bronchoalveolar lavage (BAL). Patients will then receive nebulized dornase alfa via vibrating mesh nebulizer through the ventilator circuit twice daily for 3 days. On day 4 after randomization, blood samples and BAL fluid samples will again be collected to determine change in serum and alveolar NET activity. Therapy will be discontinued in any patients who develop treatment failure defined as an increase in FiO2 by 20%, reduction in static lung compliance by more than 10 or need for rescue therapies such as extracorporeal membrane oxygenation (ECMO) or inhaled nitric oxide. Primary outcome measure will be change in arterial oxygen saturation to inhaled fraction of oxygen (PaO2/FiO2) before and after therapy. Secondary outcomes to be included will be change in static lung compliance, duration of mechanical ventilation, length of ICU stay, length of hospitalization, secondary bacterial infections, and mortality.

Study Population and Data Collection

Patients are to be recruited from the medical intensive care unit at the University of Missouri, a 250-bed academic tertiary care medical center, after confirmation of ARDS secondary to SARS-CoV-2 infection and progression of care to requiring mechanical ventilation. Inclusion criteria included age ≥ 18 years, hospitalized, and mechanically ventilated for illness related to SARS-CoV-2 infection, with individual or surrogate ability to sign informed consent, and negative urine-based pregnancy test in female patients. Exclusion criteria included contraindication or intolerance to dornase alfa, length of mechanical ventilation expected to be less than 48 hours, life expectancy less than 24 hours based upon judgment of treatment physician, pregnancy, or inability to obtain informed consent. For the first

5 days and at day 14 if applicable, daily measurements of PaO2/FiO2, static lung compliance, and positive end expiratory pressure (PEEP) will be collected. Demographic and clinical data of the patients to be obtained from electronic medical records at enrollment. Clinical study information will include age, sex, co-morbidities, therapies received, serological testing, ventilator data, bacterial and viral culture data, days of hospitalization, days in the intensive care unit, days of mechanical ventilation and mortality.

Primary Statistical Plan and Analysis

The primary hypothesis for this study is that by giving an inhaled medication targeting alveolar NET formation there will be an improvement in alveolar gas exchange. A control group for comparison is added who will have received standard of care. Improvement in alveolar gas exchange will be defined as a change in PF ratio from baseline for both the treatment and control groups with comparison of 95% CI between groups. Secondary endpoints of change in static lung compliance and change in PEEP will be analyzed in a similar fashion to change in PF ratio. The study is not powered to determine additional secondary endpoints such as mortality and length of hospitalization, but values will be collected and analyzed as unpaired t-test with significant p-value < 0.05. Bronchoalveolar fluid analysis for MPO-DNA will be compared before and after therapy with paired t-test analysis with significant p-value < 0.05.

Potential Impact

Resources

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