Reduction in D-dimer Levels After Treatment with Auxora in Patients with Severe Covid-19 Pneumonia Reflects Endothelial Stabilization

Peter C. Hou, MD  
Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Joseph Miller, MD  
Henry Ford Hospital System, Detroit, MI

Charles Bruen, MD  
Regions Hospital, Health Partners, St. Paul, MN

Fady Youssef, MD  
Long Beach Medical Center, Long Beach, CA

Michael J. Schnaus, MD  
Methodist Hospital, St. Louis Park, MN

Kathy Brouillette, MD  
Maine Medical Center, Portland, ME

Raul Mendoza-Ayala, MD  
Aurora BayCare Medical Center, Green Bay, WI

Jeffrey Zhang, PhD  
Princeton Pharmatech, Princeton, NJ

Kenneth Stauderman, PhD  
CalciMedica, Inc, La Jolla, CA

Sudarshan Hebbar, MD  
CalciMedica, Inc, La Jolla, CA

Research Article

Keywords: Auxora, calcium release-activated channel (CRAC) inhibitor, severe COVID-19 pneumonia, D-Dimer

Posted Date: September 18th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3349602/v2

License: © This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Background

Auxora, a calcium release-activated channel (CRAC) inhibitor, was demonstrated to improve recovery and decrease mortality in patients with severe COVID-19 pneumonia initially in an open-label trial and then in CARDEA, a phase 2, randomized, double-blind, placebo-controlled trial. In the open-label trial, treatment with Auxora was noted to be associated with a decrease in D-Dimer levels. To confirm these findings, blood samples were collected in CARDEA and tested for D-dimer levels. In a subset of patients, additional biomarkers were assessed to elucidate a potential mechanism of action of Auxora in decreasing D-dimer levels.

Methods

In patients enrolled in CARDEA, blood samples were collected prior to randomization and again at 72 hours after the start of the first infusion of Auxora for testing of D-dimer levels. In patients who consented for additional biomarker testing, blood samples were collected prior to randomization and again at 96 hours for testing of Angiopoietin-1, Angiopoietin-2, renin, and sCD25 levels.

Results

The baseline mean D-dimer level in the Auxora group was 2.61 mg/L and in the placebo group 2.05 mg/L. Patients treated with Auxora had a significant decrease in D-dimer levels within the first 72 hours compared to those treated with placebo. The difference was -0.92 (95% CI: -1.82, -0.02; \( P < 0.0460 \)). The decrease in D-dimer levels correlated with an increase in imputed PaO\(_2\)/FiO\(_2\) (P/F) at 72 hours (\( r: -0.193; P<0.05 \)) which in turn correlated with improved clinical outcomes at 168 hours (\( r: 0.218, P<0.01 \)). Additional biomarker testing demonstrated that treatment with Auxora reduced levels of Angiopoietin-2 and sCD25 and increased Angiopoietin-1 levels at 96 hours.

Conclusion

In patients with severe COVID-19 pneumonia, Auxora reduced D-dimer levels which correlated with improved oxygenation and clinical outcomes. In addition, Auxora appears to have decreased endothelial activation through a reduction in systemic inflammation and likely had a direct effect on endothelium stabilization.

This trial is registered at ClinicalTrials.gov number, NCT04345614.

Introduction

The entry of the SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) into the host endothelial cell results in endothelial activation leading to inflammation, increased vascular permeability, and hypercoagulability [1]. Elevated levels of D-dimer, a biomarker of fibrinolysis, have been shown to be associated with serious adverse events, including mortality, in patients with SARS-CoV-2 infection (COVID-19). In a study of 2377 adults hospitalized with a positive polymerase chain reaction test for SARS-CoV-2 between March 1, 2020 and April 8, 2020, patients with a D-dimer level greater than 2 mg/L had the highest risk of critical illness, including respiratory failure, acute kidney injury, and death [2]. COVID-19, therefore, can be thought of as a disease involving endothelial injury in the setting of inflammation leading to a thrombotic microangiopathy and subsequent multiorgan failure [3].
Currently recommended therapeutics for patients hospitalized with severe COVID-19 pneumonia have mainly targeted inflammatory pathways rather than directly targeting the endothelium [4]. Dexamethasone remains the cornerstone of therapy for hospitalized patients with COVID-19 pneumonia needing oxygen therapy, while tocilizumab and baricitinib are recommended additions for those with a greater severity of illness [5]. Dexamethasone was noted in a pilot study of 31 patients with severe COVID-19 to reduce markers of endothelial activation [6] suggesting that the mechanism for the beneficial effect of dexamethasone may be multifactorial and potentially include endothelial stabilizing properties mediated via endothelial glucocorticoid receptors in addition to its anti-inflammatory effects [7]. This has not been evaluated in larger studies. Tocilizumab, a recombinant humanized monoclonal antibody against the interleukin-6 (IL-6) receptor, was noted in a trial of 80 patients with rheumatoid arthritis to improve endothelial function through a reduction in the inflammatory burden [8]. Baricitinib, a Janus kinase (JAK) inhibitor, has been shown to benefit patients with severe COVID-19 pneumonia but carries a warning for an increased risk of blood clots, especially in patients older than 50 years of age with at least one cardiovascular risk factor [9].

Anticoagulation has also become standard of care for patients hospitalized with COVID-19 pneumonia, but the intensity remains uncertain. Therapeutic anticoagulation is recommended for patients with severe COVID-19 pneumonia needing oxygen therapy if the D-dimer level is above the upper limit of normal and there is no increased risk of bleeding [5]. While this approach has reduced the incidence of venous thromboembolism, it has not decreased mortality, likely because anticoagulation does not sufficiently address the pathophysiology of upstream pathways such as endothelial damage and inflammation [10,11].

Auxora, a calcium release-activated calcium (CRAC) channel inhibitor that specifically blocks the Orai1 channel, was recently tested in patients with severe COVID-19 pneumonia. In an initial open-label trial of patients with severe COVID-19 pneumonia, it was observed that treatment with Auxora decreased D-dimer levels over the first 96 hours compared to standard of care [12]. Auxora was also noted to increase recovery and decrease the proportion of patients meeting a composite outcome of death or need for mechanical ventilation [13]. When designing a double-blinded, randomized controlled trial (CARDEA) to follow the initial open label trial, we hypothesized Auxora added to corticosteroids and prophylactic anticoagulation would improve outcomes and that the improved outcomes would correlate with a decrease in D-dimer levels. In addition, the potential mechanism of action of Auxora in decreasing D-dimer levels would be assessed by testing the endothelial biomarkers Angiopoietin-1, Angiopoietin-2, and renin, as well as the inflammatory biomarker soluble CD25 (sCD25). The improved clinical outcomes noted in CARDEA from the treatment of severe COVID-19 with Auxora, including reductions in mortality at Days 30 and 60, have been previously published [14]. We now report the results from the testing of samples for D-dimer and biomarker levels and analyzing the correlation of the changes to outcomes.

**Methods**

The present analysis is based on the results from the testing of serum samples from the predefined efficacy set of patients with a baseline imputed PaO2/FiO2 (P/F) >75 and ≤200 who enrolled in CARDEA (ClinicalTrials.gov identifier, NCT04345614). All patients were adults with ≥ 1 symptom consistent with COVID-19 infection, had a diagnosis of COVID-19 confirmed by laboratory testing using polymerase chain reaction or other assay, and pneumonia documented by chest imaging. At the time of enrollment, patients were receiving oxygen therapy via either a high flow (HFNC) or low flow nasal cannula but not non-invasive or invasive mechanical ventilation. All patients received dexamethasone or equivalent dose of another corticosteroid and 99% received pharmacological prophylaxis against development of venous thromboembolic disease. Remdesivir use was recommended for all patients, and convalescent plasma administration was allowed.
according to local standard of care. Other immunomodulators for the treatment of COVID-19 pneumonia, including tocilizumab and JAK inhibitors, were prohibited due to regulatory guidance. Auxora was administered by a 4-h IV infusion at 2.0 mg/kg (1.25 mL/kg) at 0-hour and 1.6 mg/kg (1 mL/kg) at 24 and 48 hours. Placebo was a matching formulation without the active pharmaceutical ingredient and was also dosed as a 4-h IV infusion at equivalent volumes of 1.25 mL/kg at 0-hour and 1 mL/kg at 24 and 48 hours.

After obtaining informed consent and before randomization, the clinical status of each patient was assessed using an 8-point ordinal scale (Table S1) in a standardized manner as described in the electronic case report form. The patient’s medical record was also reviewed to document the lowest SpO₂/FiO₂ (S/F) recorded during the previous 24 hours. The SpO₂ was obtained using pulse oximetry. The FiO₂ was read from the controlled oxygen source in patients requiring HFNC. For patients on an uncontrolled oxygen source, a conversion table was provided to all sites to estimate the FiO₂ based on the method of oxygen delivery and oxygen flow rate. After randomization and the infusion of the first dose of study drug, an assessment of the clinical status of the patient using the ordinal scale and review of the lowest S/F were again performed before each subsequent infusion, then every 24 h until 240 h, and then continued every 48 h until Day 30 or discharge. A blood sample to check a D-dimer level was obtained prior to randomization and then every 72 hours while the patient remained hospitalized. The blood sample for D-dimer was processed, and results obtained, at each individual institution using their standard operating procedures and laboratory equipment.

Patients were also asked to consent separately for additional blood draws to obtain samples for Angiopoietin-1, Angiopoietin-2, renin and sCD25. These samples were collected prior to randomization and again at 96 hours in those patients who provided the additional consent. Blood for biomarker testing was placed in a red top serum separator tube, gently mixed by inverting the tube five times, and then allowed to clot undisturbed for 30 minutes with the tube standing upright. This was followed by centrifugation at 1800g until the clot and serum separated. The serum was then transferred by pipette to a collection kit and stored at -80°C. The samples were batched at each site and shipped frozen to Cincinnati Children's Hospital Medical Center for testing. The levels of Angiopoietin-1, Angiopoietin-2, renin and soluble CD25 were determined by the enzyme-linked immunosorbent method utilizing kits from R&D Systems (Minneapolis, MN, USA) on the Dynex Elisa Processor.

Objectives

The objective of the analyses was to confirm the decrease in D-dimer levels that had been noted after treatment with Auxora in the initial open-label trial and to correlate a decrease, if observed, to changes in the daily imputed P/F and clinical outcomes as categorized by the 8-point ordinal scale. In addition, a secondary objective was to determine if Auxora decreased levels of Angiopoietin-2, soluble CD25, and renin, as well as increased Angiopoietin-1 levels, and whether those changes correlated with the changes in D-dimer levels, oxygenation, and clinical outcomes.

Statistical Analysis

We used descriptive statistics with 95% confidence intervals (CIs) to summarize data according to treatment group. We analyzed differences between treatment groups using MMRM modeling for the daily imputed P/F, ANCOVA modeling for other continuous variables, proportional odds testing for ordinal variables, and Cochran-Mantel-Haenszel testing for discrete variables. The ANCOVA model included the baseline value of the endpoint as a covariate and the treatment as
fixed effect. The Cochran-Mantel-Haenszel test was stratified by the baseline imputed PaO2/FiO2 of ≤100 vs. >100. The PaO2 was imputed from the SpO2 using a published table based on Ellis's inversion of the Severinghaus equation [15]. A two-sided alpha amount of 0.05 was used to test for differences in treatment outcomes without adjustments for multiplicity. The pairwise Pearson correlations between change from baseline of the clinical endpoints and the change from baseline of lab parameters were conducted by treatment groups.

**Results**

Patient enrollment occurred from September 8, 2020, to May 24, 2021. The efficacy set consisted of 261 patients with a baseline imputed PaO2/FiO2 ≤ 200 with 130 in Auxora and 131 in placebo groups. In total, 191 patients in the efficacy set consented to additional blood draws for biomarker collection (biomarker set). The baseline demographics of the biomarker set were similar to that of the efficacy set (Table 1).

A higher baseline D-dimer level predicted both a greater all-cause mortality rate at Day 60 and also a greater reduction in all-cause mortality after treatment with Auxora versus placebo (Table 2). The baseline mean D-dimer level in the efficacy set was 2.61 mg/L in the Auxora group and 2.05 mg/L in the placebo group. The mean D-dimer level significantly decreased in patients treated with Auxora over the first 72 hours but not in patients treated with placebo. Additionally, the decrease in the Auxora group was significantly different compared to placebo (Table 3). We also noted a more rapid rise in the imputed P/F compared to baseline in the patients receiving Auxora than placebo, and that the difference in the changes from baseline reached a statistically significant difference at 168 hours (Day 7) of 36.65 (95% CI: 10.38, 62.91; P<0.01). (Figure 1). A correlation analysis of D-dimer, imputed P/F, and status on the ordinal scale at 168 hours showed that the decrease in D-dimer levels noted in the first 72 hours after treatment with Auxora correlated with an increase in the imputed P/F over the same time period (r: -0.193, P<0.05) which in turn correlated with improvement on the ordinal scale at 168 hours (r: 0.218, P<0.01). As reported previously, the median time to recovery for patients in the efficacy group treated with Auxora was 7 days (168 hours) [14].

In patients consenting for additional biomarker testing, Angiopoietin-2 and sCD25 levels significantly decreased over the first 96 hours in patients treated with Auxora and not in patients treated with placebo. Angiopoietin-1 levels significantly increased in those treated with Auxora over the same time period, whereas renin levels significantly increased in those treated with placebo but not Auxora (Table 4). The correlation analysis after the addition of these biomarker results revealed a complex relationship among endothelial dysfunction, inflammation, hypercoagulability, and oxygenation. A decrease in Angiopoietin-2 level at 96 hours correlated with both a decrease in D-dimer level at 72 hours (r: 0.314, P<0.01) and a decrease in sCD25 at 96 hours (r: 0.834, P<0.001). An increase in the imputed P/F ratio at 72 hours correlated with a decrease in sCD25 at 96 hours (r: -0.223, P<0.05), a decrease D-dimer at 72 hours (r: -0.193, P<0.05), and improvement on the ordinal scale at 168 hours (r: 0.210; P<0.05). Finally, increases in Angiopoietin-1 at 96 hours correlated directly with improvements on the ordinal scale at 168 hours (r: 0.233, p-value: <0.05) (Figure 2).

**Discussion**

Severe COVID-19 pneumonia is characterized by pulmonary endothelial cell activation with elevated levels of Angiopoietin-2, an endogenous antagonist of the Angiopoietin-1/Tie2 signaling pathway that is released by the endothelium in response to noxious stimuli such as inflammation and hypoxia. Levels of Angiopoietin-2 have been shown to be higher in severe COVID-19 pneumonia than in other causes of acute respiratory distress syndrome (ARDS) [16]. The deactivation of Tie2 signaling by Angiopoietin-2 results in destabilization of the vessel wall, increased endothelial cell permeability, and inhibition of the anti-inflammatory and anticoagulant responses promoted by Angiopoietin-1 [17]. The endothelial damage...
noted in severe COVID-19 pneumonia is also associated with increased serum renin levels, which rise as a compensatory response to the reduced concentration of endothelial angiotensin converting enzyme (ACE) and decreased angiotensin II generation [18].

Marked alveolar and systemic inflammation are also characteristics of severe COVID-19 pneumonia. High levels of sCD25 reflect this inflammation and signal shifts towards a proinflammatory T-cell response that has been correlated with increased mortality in patients with COVID-19 pneumonia [19]. It had been noted in murine models that sCD25 enhances the release of IL-17 [20], a proinflammatory cytokine signaling pathway strongly activated by SARS-CoV-2 infection compared to other respiratory viruses [21]. Blockade of CRAC channels with zegocractin, the active compound in Auxora, abrogates the release of multiple proinflammatory cytokines from human lymphocytes, including IL-6, IL-17, and IFNγ that have been implicated in COVID-19 alveolitis [22, 23, 34]. In addition, the initial results of a pharmacodynamic study embedded in a Phase II placebo-controlled clinical trial of Auxora in critical COVID 19 pneumonia (NCT04661540) show a reduction in inflammatory gene expression in both T cells and monocytes in the lungs of patients with COVID-19 pneumonia who were treated with Auxora compared to placebo [25].

The decrease in systemic inflammation noted with CRAC channel inhibition has been previously reported in preclinical studies as preventing endothelial activation. In a murine model, the systemic administration of LPS resulted in endothelial cell activation, with subsequent increases in vascular permeability and lung edema. These increases were abrogated by the administration of a CRAC channel inhibitor; the proposed mechanism for the protective effect was the inhibition of calcium-mediated NFAT signaling in the endothelium and decreased production of inflammatory cytokines [26]. The strong correlation of the decrease in Angiopoietin 2 with the decrease in sCD-25 in our study supports the beneficial effect of Auxora on the endothelium through a reduction in systemic inflammation. Clinically, this beneficial effect of Auxora on endothelial stabilization may be noted within 72 hours by a reduction in the D-dimer level.

Finally, the demonstrated increase in Angiopoietin-1, which did not correlate with the decrease in systemic inflammation, suggests that CRAC channel inhibition with Auxora directly promoted endothelial stabilization as predicted by the murine LPS model. Supporting this suggestion of a direct effect on the endothelium are the results of a recently published study in in-vivo ACE2 humanized inbred mice and in-vitro cultured human and mice pulmonary vascular endothelial cells that demonstrated that the receptor binding domain of the SARS-CoV-2 virus caused pulmonary vascular endothelial damage in part by upregulating Orai1 and triggering calcium influx [27]. Treatment with Auxora would block this calcium influx and consequently prevent endothelial damage independently of a decrease in systemic inflammation.

There may be an additional mechanism by which Auxora decreased D-dimer levels that was not evaluated in CARDEA. Orai-1 deficient mice have been noted to have reduced store operated calcium entry in platelets resulting in impaired activation and resistance to arterial thrombus formation without adversely affecting primary hemostasis [28]. It is possible, therefore, that treatment with Auxora also directly reduced platelet activation and thrombus formation. This potential mechanism of action may be especially germane to patients with severe COVID-19 pneumonia given that a study of hospitalized patients with COVID-19 revealed the presence of excessive platelet aggregation in 90% of patients and that there was a strong correlation between the concentration of platelet aggregation and the severity of the infection.29
The major limitations to this analysis are the 70 patients who did not consent to the additional blood draw for biomarker testing and the missing biomarker samples in those that did consent. Of the 191 patients who did consent, however, 95 and 96 patients were in the placebo and Auxora groups, respectively, and there were no significant differences in the baseline characteristics between the efficacy and biomarker cohorts. Hence, randomization was also balanced in the biomarker cohort and the results from the biomarker analysis are suggestive evidence to the biological mechanism of Auxora.

**Conclusions**

This study of biomarkers collected from patients enrolled in CARDEA confirms the observation from the initial open-label trial that D-dimer levels decreased in patients treated with Auxora and demonstrates that the decrease in D-dimer levels correlated with improved oxygenation and outcomes. The study also suggests that Auxora reduced endothelial activation which correlated with both a reduction in inflammation and hypercoagulability. Finally, Auxora appears to have directly promoted endothelial stabilization in patients with severe COVID-19 pneumonia likely by reducing the calcium influx in pulmonary vascular endothelial cells caused by the receptor binding domain of the SARS-CoV-2 virus. The beneficial effects of Auxora on the endothelium that were noted in this study should be investigated in other critical illnesses associated with inflammation and endothelial damage, such as sepsis, acute kidney injury and ARDS.

**Declarations**

**Ethics approval and consent to participate**

The trial protocol was approved by an institutional review board at each site and was overseen by an IDMC. The trial was conducted in accordance with Good Clinical Practice guidelines and guiding principles of the Declaration of Helsinki and was approved by the local institutional review boards. Informed consent was obtained from either the patient or from the patient’s legally authorized representative if the patient was unable to provide consent. This trial is registered at ClinicalTrials.gov number, NCT04345614.

**Consent for publication**

Not applicable

**Availability of data and materials**

The datasets generated and/or analyzed during the current study are not publicly available due to the Clinical Study Report being finalized but will be available from the corresponding author upon request.

**Competing interests**

KS and SH are full time employees of CalciMedica and hold stock options. JM, PCH, and MS report research grants made to their institutions from CalciMedica. PCH reports payment for expert testimony from Ross Feller Casey and stock options from Doc Telehealth solutions. FY reports honoraria for grand rounds. JZ reports payment and consultant fees to Princeton Pharmatech from CalciMedica. CB, RM, and KB report no conflicts of interest.
Author Contributions

PCH, JM, CB, KS, SH contributed to the trial concept and design, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the trial or data collection. JZ, KS, SH verified the data and reviewed the statistical analysis. All authors interpreted the data, drafted the manuscript, and decided to submit for publication. All authors reviewed, commented on, and approved this manuscript for publication.

Data Availability Statement for this Work

The datasets generated and/or analyzed during the current study are not publicly available due to the Clinical Study Report being finalized but will be available from the corresponding author upon request.

References


Non-standard Abbreviations

ARDS, acute respiratory distress syndrome
CRAC, calcium release-activated calcium
HFNC, high flow nasal canula
IL-6, interleukin-6
JAK, Janus kinase
P/F, PaO2/FiO2
Severe acute respiratory syndrome coronavirus 2, SARS-CoV-2
sCD25, soluble CD25
S/F, SpO2/FiO2

Tables

Table 1. Baseline Demographics.

<table>
<thead>
<tr>
<th></th>
<th>Efficacy Set</th>
<th>Biomarker Set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=131)</td>
<td>Auxora (N=130)</td>
</tr>
<tr>
<td>Mean Age (SD)</td>
<td>60.4 (12.3)</td>
<td>59.4 (12.1)</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>92 (70.2%)</td>
<td>84 (64.6%)</td>
</tr>
<tr>
<td>White n (%)</td>
<td>98 (74.8%)</td>
<td>85 (65.4%)</td>
</tr>
<tr>
<td>Black n (%)</td>
<td>12 (9.2%)</td>
<td>19 (14.6%)</td>
</tr>
<tr>
<td>Hispanic n (%)</td>
<td>58 (44.3%)</td>
<td>45 (34.6%)</td>
</tr>
<tr>
<td>Mean BMI kg/m² (SD)</td>
<td>32.0 (7.0)</td>
<td>32.8 (8.8)</td>
</tr>
<tr>
<td>HFNC n (%)</td>
<td>82 (62.6%)</td>
<td>81 (62.3%)</td>
</tr>
<tr>
<td>Mean baseline imputed P/F (SD)</td>
<td>105.1 (32.8)</td>
<td>109.7 (36.8)</td>
</tr>
</tbody>
</table>

Table 2. All-Cause Mortality at Day 60 Based on Baseline D-Dimer Levels.
### Table 3. Change in D-Dimer from Baseline to 72 hours (ANCOVA model).

<table>
<thead>
<tr>
<th>Baseline D-dimer Levels</th>
<th>Placebo (N=131)</th>
<th>Auxora (n=130)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>27 (20.6%) (n=131)</td>
<td>18 (13.8%) (n=130)</td>
<td>-6.75 (-15.75, 2.24)</td>
</tr>
<tr>
<td>&gt;0.5 mg/L</td>
<td>25 (24.3%) (n=103)</td>
<td>15 (15.3%) (n=98)</td>
<td>-8.48 (-19.27, 2.31)</td>
</tr>
<tr>
<td>&gt;0.75 mg/L</td>
<td>20 (25.6%) (n=78)</td>
<td>14 (17.3%) (n=81)</td>
<td>-8.34 (-20.88, 4.19)</td>
</tr>
<tr>
<td>&gt;1.0 mg/L</td>
<td>17 (29.3%) (n=58)</td>
<td>12 (19.0%) (n=63)</td>
<td>-10.65 (-25.39, 4.10)</td>
</tr>
</tbody>
</table>

Cochran-Mantel-Haenszel test stratified by the baseline imputed PaO2/FiO2 of <=100 vs. >100.

### Table 4. Change in Additional Biomarkers from Baseline to 96 hours (ANCOVA model).

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=131)</th>
<th>Auxora (n=130)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean value, mg/L (SD)</td>
<td>2.05 (3.9) (n=122)</td>
<td>2.61 (7.4) (n=119)</td>
<td></td>
</tr>
<tr>
<td>Mean 72-hour Value, mg/L (SD)</td>
<td>2.15 (3.8) (n=82)</td>
<td>1.35 (1.2) (n=78)</td>
<td></td>
</tr>
<tr>
<td>Change LS Mean, mg/L (95% CI)</td>
<td>0.04 (-0.59, 0.67)</td>
<td>-0.88 (-1.52, -0.23)</td>
<td>-0.92 (-1.82, -0.02)</td>
</tr>
<tr>
<td>P value</td>
<td>0.8990</td>
<td>0.0082</td>
<td>0.0460</td>
</tr>
</tbody>
</table>

The ANCOVA model includes Baseline value of the endpoint as a covariate and treatment as fixed effect.
<table>
<thead>
<tr>
<th>Baseline mean value, pg/mL (SD)</th>
<th>Placebo (N=95)</th>
<th>Auxora (N=96)</th>
<th>Placebo (N=95)</th>
<th>Auxora (N=96)</th>
<th>Placebo (N=95)</th>
<th>Auxora (N=96)</th>
<th>Placebo (N=95)</th>
<th>Auxora (N=96)</th>
<th>Placebo (N=95)</th>
<th>Auxora (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean value, pg/mL (SD)</td>
<td>38455.63 (16572.74)</td>
<td>38395.45 (16408.26)</td>
<td>3045.34 (1766.576)</td>
<td>2963.65 (1713.513)</td>
<td>18.02 (26.901)</td>
<td>25.03 (39.070)</td>
<td>2913.53 (1619.133)</td>
<td>2553.95 (1773.301)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 96-hour Value, pg/mL (SD)</td>
<td>40106.31 (18821.75)</td>
<td>41651.42 (15876.91)</td>
<td>2891.39 (2570.137)</td>
<td>2423.96 (1342.434)</td>
<td>33.60 (43.143)</td>
<td>29.82 (46.414)</td>
<td>2653.27 (2079.435)</td>
<td>2515.29 (2545.708)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change LS Mean, pg/mL (95% CI)</td>
<td>1678.32 (-1941.61, 5298.24)</td>
<td>4832.61 (1212.69, 8452.54)</td>
<td>-203.92 (-689.95, 282.11)</td>
<td>-636.49 (-1122.52, -150.46)</td>
<td>13.38 (2.96, 23.81)</td>
<td>3.97 (-6.45, 14.39)</td>
<td>-59.41 (-340.45, 221.63)</td>
<td>-291.26 (-567.02, -15.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.3607</td>
<td>0.0093</td>
<td>0.4077</td>
<td>0.0107</td>
<td>0.0125</td>
<td>0.4509</td>
<td>0.6759</td>
<td>0.0386</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ANCOVA model includes Baseline value of the endpoint as a covariate and treatment as fixed effect.

Figures
Figure 1

LS Mean Change in P/F from Baseline to Day 28.

Change from Baseline Over Time of the Imputed P/F using the MMRM Model. Patients receiving Auxora experienced a more rapid rise in the imputed P/F from baseline when compared with placebo. The difference in the changes from baseline reached a statistically significant difference at Day 7 (95% CI: 10.38, 62.91; P<0.01).

Figure 2

Endothelial Dysfunction

- Decrease Angiopoietin 2 at 96 hours
- Decrease sCD 25 at 96 hours

Hypercoagulability

- Decrease D-Dimer at 72 hours
- Increase P/F at 72 hours

Endothelial Integrity

- Increase Angiopoietin 1 at 96 hours
- Improved Status by Ordinal Scale at 168 hours
Correlation between Changes in Biomarkers and Severe COVID-19 Pneumonia Outcomes.

This correlation analysis revealed a complex relationship among endothelial dysfunction, inflammation, hypercoagulability, and oxygenation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalMaterials11Aug2023.docx