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COVID-19 the Use of Tocilizumab: A Case Report

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ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) is a modern and rapidly growing pandemic due to a novel coronavirus, SARS-CoV-2. The severity of this new virus strongly correlates with patients with advanced age or with underlying medical conditions. Those with advanced or severe symptoms from this virus are currently being treated with a trial of tocilizumab, an inhibitor of inflammatory responses including the cytokine Interleukin-6 (IL-6). As of current research there is no published clinical data supporting the use of this medication as treatment for this virus but have been discussed in anecdotal reports illustrating positive outcomes in COVID-19 infected patients.

Case Presentation: A 28-year-old obese and diabetic female presents to the emergency department with symptoms of shortness of breath, chills, and cough after being medically treated at a local urgent care facility one week prior. She endorsed worsening respiratory symptoms, fevers, and diaphoresis at the time and was eventually intubated and admitted to the ICU due to respiratory failure and having a strong clinical suspicion for COVID-19. Nasopharyngeal swab for SARS-CoV-2 was positive. The patient rapidly deteriorated despite treatment with hydroxychloroquine and underwent septic shock. Due to refractory treatment, the patient was administered a trial of tocilizumab and the patient had a remarkable clinical improvement over the next 12 hours, ultimately resulting in extubation. A combined regimen of tocilizumab, broad spectrum antibiotics, and a second course of hydroxychloroquine allowed the patient to make a full recovery.

Discussion: Given the novelty of SARS-CoV-2, evidence-based therapeutic strategies have not yet been developed. At this time, there are no medications approved by the US Food and Drug Administration (FDA) to treat COVID-19, per the Centers for Disease Control and Prevention (CDC). Supportive care measures include supplemental oxygen and mechanical ventilatory support when indicated. There are however several investigational COVID-19 treatment agents being evaluated and numerous clinical trials underway. Of the investigational agents being evaluated, hydroxychloroquine with or without azithromycin and IL-6 pathway inhibitors, such as tocilizumab, are being heavily studied due to positive anecdotal evidence. Currently, no guidelines outlining the use of these investigational agents exist. Individual institutions are encouraged to develop protocols for off-label use of these agents.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus, SARS-CoV-2, that first emerged in the Wuhan province of Hubei, China in December of 2019. It spread promptly, producing an epidemic in China defined by pneumonia and lower respiratory symptoms. Within a few short months, positive cases were identified in all continents, except for Antarctica. As new cases swiftly rise worldwide, and morbidity and mortality grow beyond expected measures, COVID-19 has become a global pandemic threatening the safety and wellbeing of individuals globally.

A prolonged incubation period, up to 14 days, allows for patients to be infected with COVID-19 without showing symptoms [1-3]. The disease severity ranges from asymptomatic to critical respiratory failure, shock, multiorgan dysfunction, and even death [4]. The majority of severe cases have occurred in elderly patients or those with underlying medical conditions such as: cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer, and chronic kidney disease [4-8]. The prolonged incubation period combined with the high asymptomatic presentation rate has allowed for rapid transmission.

Monoclonal antibodies that target and inhibit the interleukin-6 receptor (tocilizumab, sarilumab) have demonstrated positive outcomes in SARS-CoV-2 positive patients, particularly those with cytokine storm syndrome [9]. However, no large randomized control trials have been published, and of published reports the conclusions are anecdotal [9]. Tocilizumab has been associated with a number of adverse effects, most of which are non-life threatening. The most severe concerns are gastrointestinal perforation, neutropenia with potential for fatal infections with opportunistic.

pathogens, hepatic failure, and anaphylactic reactions. The presented case outlines a successful treatment of COVID-19 with tocilizumab.

Case Presentation

A 28-year-old female with a past medical history of obesity and uncontrolled diabetes mellitus presents to our facility's emergency department (ED) with symptoms including shortness of breath, chills, nonproductive cough, and a temperature of 102°F measured at home. Approximately one week prior to ED arrival, the patient reported that she had shortness of breath and a cough and sought care at a local urgent care on two separate occasions. There she was prescribed Tessalon Perles, azithromycin, and methylprednisolone which she was adherent to. However, the medications subsequently worsened her symptoms. Upon ED arrival the patient reported generalized weakness and presyncope during ambulation. She also endorsed diaphoresis, fatigue, chest pain, palpitations, and diffuse myalgias. She denies recent travel and has no known COVID- 19 contacts. However, the patient works in retail. She is a non-smoker, socially drinks alcohol, and denies any illicit drug use. Family history was noncontributory.

Initial workup in the ED revealed a temperature of 100.1°F, blood pressure of 101/66, heart rate of 123, respiratory rate of 20, and an oxygen saturation of 95%. Initial encounter revealed an obese, ill-appearing patient in acute distress. Physical exam revealed tachycardia with wheezing and rales bilaterally. The remainder of the physical exam was noncontributory. Arterial blood gas analysis showed a pH of 7.46, pCO2 of 26.5, and a pO2 of 67.2, reflecting an acute hypoxemia. A complete blood count revealed mild lymphopenia of 18.4 and a white blood cell count of 7.1. A comprehensive metabolic panel showed hyperglycemia of 306 and hyponatremia of 132. Additionally inflammatory markers were elevated with C-reactive protein (CRP) at 96.2, and ferritin at 1,200. Of note, the patient's procalcitonin was within normal limits. Rapid influenza testing for A/B antigens was negative. A pregnancy test was negative. Chest x-ray revealed confluent airspace opacities at the lung bases bilaterally (Figure 1). EKG showed sinus tachycardia. The patient was then tested for COVID-19 infection due to high clinical suspicion.

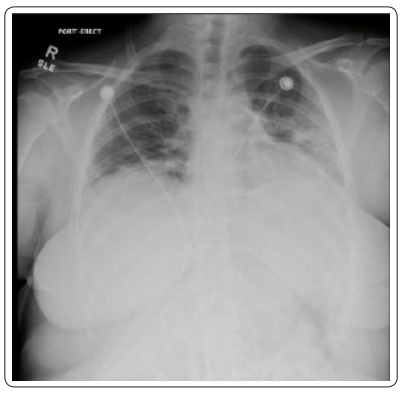

Figure 1: Chest radiograph on admission

The patient was subsequently diagnosed with bilateral pneumonia and was admitted to the medicine floor on telemetry. The patient was placed on supplemental oxygen, aggressive pulmonary hygiene, and special airborne isolation precautions. Infectious disease was consulted for treatment of pneumonia and initially recommended azithromycin and aztreonam. On hospital day 1 the patient developed worsening hypoxemia on 6L nasal cannula and was subsequently increased to 30L high flow nasal cannula which reduced the patients symptoms. Critical care was consulted for expectant management due to impending respiratory failure. On hospital day 2 the patient desaturated to 79% with minimal ambulation, which prompted the patient to be transferred to the ICU due to acute hypoxemic respiratory failure. The patient was subsequently intubated and a central venous catheter was placed. In the ICU the patient was started on hydroxychloroquine 200 mg twice daily, oseltamivir, cefepime, vancomycin, and azithromycin. On ICU day 1 the patient went into septic shock which necessitated vasopressor support. Blood cultures were negative after 72 hours. The patient continued to require ventilatory and vasopressor support. On ICU day 3 the patient's antimicrobial regimen was changed from vancomycin and cefepime, to ceftaroline and levofloxacin due to difficulty controlling vancomycin at therapeutic range. On day 4 the patient remained intubated and was able to be weaned off of vasopressors due to resolution of septic shock. On day 5 the patient's temperature increased to 100.6°F and chest x-ray revealed worsening bilateral patchy airspace opacities. Additionally, COVID-19 testing returned with a positive result. On day 6 the patient was able to pass a spontaneous breathing trial on the ventilator. However, the patient continued to spike fevers overnight reaching 100.9°F. Repeat urine, blood, and respiratory cultures remained negative for growth. On ICU day 7 the patient remained febrile with a temperature of 101.1°F. The patient's ferritin was drawn for the last time on day 7 and returned with a value of 1134.2. Prior to this, the patient's ferritin trend was as follows: 1200.7, 1711.9, and 1322.8. Due to her persistent symptoms, the patient was started on tocilizumab 400 mg once daily, and a second course of hydroxychloroquine. Also, the antibiotic regimen was changed from ceftaroline and levofloxacin to meropenem and doxycycline. Chest x-ray on ICU day 7 revealed stable multifocal bilateral pulmonary infiltrates (Figure 2). On ICU day 8 the patient was apyrexial and she successfully completed another spontaneous breathing trial and was extubated after meeting all criteria. The patient was subsequently transferred to the step down unit for observation. In the step down unit the patient was saturating at 100% on room air, and per infectious disease her antibiotics were discontinued due to significant clinical improvement. After 1 day without antibiotic therapy, the patient was discharged and was prescribed to complete her second course of hydroxychloroquine. She was also advised to practice self-imposed isolation, and to follow up with infectious disease in two weeks.

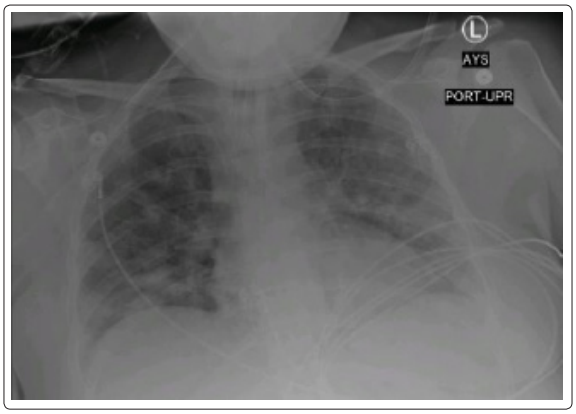

Figure 2: Chest radiograph prior to discharge

Discussion

Given the novelty of SARS-CoV-2, evidence-based therapeutic strategies have not yet been developed. At this time, there are no medications approved by the US Food and Drug Administration (FDA) to treat COVID-19, per the Centers for Disease Control and Prevention (CDC). Rather, clinical management involves infection prevention and control measures and supportive care. Supportive care measures include supplemental oxygen and mechanical ventilatory support when indicated. There are, however, several investigational COVID-19 agents being evaluated and numerous

clinical trials underway. Of the investigational agents being evaluated, hydroxychloroquine with or without azithromycin and IL-6 pathway inhibitors, such as tocilizumab, are being heavily studied due to positive anecdotal evidence. Currently, no guidelines outlining the use of these investigational agents exist. Individual institutions are encouraged to develop protocols for off-label use of these agents.

In this case, the decision to start hydroxychloroquine and azithromycin occurred on hospital day 2. Hydroxychloroquine, a commonly used antimalarial drug, has demonstrated inhibition of SARS-CoV-2 in vitro [10]. However, clinical data assessing the efficacy is sparse and conflicting. One such study describes an association with a higher rate of undetectable SARS-CoV-2 RNA compared to no specific treatment. This study also describes an association with a more rapid decline in viral RNA with hydroxychloroquine when combined with azithromycin. However, there were concerns regarding methodologies of this study as well as data suggesting findings to the contrary in another study. Additional evidence against hydroxychloroquine use has been cited by a pilot study showing no difference in the proportion of patients with viral clearance using hydroxychloroquine compared with standard of care [11]. In contrast, a recent randomized trial has revealed a quicker clinical improvement with the addition of hydroxychloroquine to standard care in patients with mild COVID-19 [12]. In summation, while several studies have demonstrated more rapid viral clearance with the use of hydroxychloroquine versus standard of care, other studies have demonstrated no difference [11-14]. Despite the sparse and conflicting clinical data, hydroxychloroquine is being utilized at numerous institutions across the nation. For example, both hydroxychloroquine and azithromycin were initiated in this case upon the patient's clinical deterioration prompting transfer to the ICU. The decision to utilize these investigational agents can be attributed to the compounding effect of in vitro and extrapolated evidence supporting hydroxychloroquine use and, more importantly, lack of definitively effective alternatives.

Seven days after initiating the hydroxychloroquine and azithromycin regimen, the patient failed to improve. Thus, the decision to start tocilizumab was made on ICU day 7. Tocilizumab, an immunosuppressive agent typically used in the management of autoimmune disorders, is another agent under investigation. The postulated mechanism of immunosuppressant use relates to the increased concentration of proinflammatory cytokines seen in COVID-19 patients [15]. The cytokines released in COVID-19 infected patients resemble those that are released in a hyperinflammatory syndrome known as secondary hemophagocytic lymphohistiocytosis (sHLH) [16]. sHLH involves sudden and potentially fatal onset of hypercytokinemia with multiorgan failure, often secondary to viral infection [9,16]. Unremitting fever, cytopenias, and hyperferritinemia are classic features of sHLH with pulmonary involvement such as acute respiratory distress syndrome (ARDS), occurring in about half of patients [17]. It has been suggested that hyperinflammation might be associated with mortality, as elevated ferritin and IL-6 have both been demonstrated in COVID- 19 patients [18,19]. Upon reviewing the expanding literature, a recent study suggests cytokine release syndrome (CRS) as an important component of severe COVID-19 cases [20]. Thus, it was hypothesized that neutralizing inflammatory factors involved in CRS, such as IL-6, could result in mortality benefit [20].

This case supports this hypothesis and current literature, as the patient eventually improved following initiation of tocilizumab. Furthermore, hyperinflammation evidenced by elevated ferritin levels was demonstrated in this patient, which supports the hyperinflammatory process occuring in COVD-19 patients cited in the literature. However, several components of this case need to be considered, such as patient comorbidities (eg, obesity, diabetes), outpatient treatment with azithromycin and corticosteroids prior to hospitalization, and initiation of hydroxychloroquine with azithromycin prior to tocilizumab. In order to assess the effectiveness of any investigational agent, obtaining controlled data via ongoing clinical trials is imperative. Health care professionals should be cognizant of current clinical trials and enrollment should be discussed with patients and their surrogates.

In conclusion, much more investigation is needed regarding the use of tocilizumab. Nonetheless, the success demonstrated in the current case provides anecdotal evidence supporting tocilizumab initiation. Furthermore, this case and review of current literature elicits several clinical questions to be explored. For example, laboratory findings associated with hyperinflammation (eg, increasing ferritin, decreasing platelet counts, and erythrocyte sedimentation rate) could serve as a screening measure to identify patients that would gain mortality benefit with immunosuppression initiation [9]. This screening process could be standardized with HScore, a scoring system that generates a probability for the presence of sHLH, given the similarities between sHLH and COVID-19 [15,21]. Laboratory findings associated with hyperinflammation could also serve as a method to stratify patient risk, as current literature suggests an association between inflammatory markers and mortality [18,19]. Perhaps, tocilizumab should be initiated sooner in patients with higher inflammatory markers. It is apparent that much remains unknown about this novel virus. However, it is important to consider the knowledge to be gained from the growing number of cases and subsequent clinical trials, as this will eventually lead to the development of evidence-based therapeutic strategies.

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