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Summary

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Abstract

COVID-19 has resulted in significant morbidity and mortality due to lack of effective therapies. Therapeutic strategies under investigation target the overactive cytokine response with anti-cytokine or immunomodulators therapies. We present a unique case of severe cytokine storm resistant to multiple anti-cytokine therapies, but eventually responsive to Etoposide. Thus, Etoposide may have a role as salvage therapy in treatment of cytokine storm in COVID-19. To our knowledge, this is the first reported case of use of Etoposide in COVID-19.

Introduction:

At the time of this writing, more than 7 million people worldwide have suffered significant morbidity and mortality due to infection with SARS-CoV-2.[1] Case fatality has been noted between 2-3% worldwide. The current literature suggests the severity of COVID-19 infection is due to high levels of inflammation related to cytokine storm syndrome that develops through activation of the innate immune system.[2 3] Viral entry into the cell occurs in two steps similar to MERS-CoV. First, the SARS-COV envelop spike glycoprotein binds to the cellular receptor ACE2.[4] The SARS-COV envelope spike glycoprotein then enters the cell, its viral RNA genome replicates and is translated into two glycoproteins and structural proteins. Lastly, the formed enveloped glycoproteins, genomic RNA, and nucleocapsid proteins are combined to form the virus, which is then released from the cell.

The second phase of COVID-19 presents as a heightened immune response. Similar to MERS and SARS, SARS-CoV-2 results in an enhanced innate immune response with elevated IL1B, IFNγ, IP10, MCP1, MIP1A, and TNFα, and suppression of the adaptive

immune response as indicated by a reduced lymphocyte count.[5 6] Secondary hemophagocytic lymphohistiocytosis (HLH) has a similar life-threatening cytokine profile and results in a fulminant hyperinflammatory syndrome characterized by cytopenias, markedly elevated ferritin, persistent fevers, and acute respiratory distress syndrome (ARDS).[7] The therapeutic target in COVID-19 is aimed at inhibiting viral replication and suppressing the severe inflammatory response.

Some widely used cytokine storm therapies include pulse-dose steroids, sarilumab, tocilizumab (monoclonal antibodies against the IL-6 receptor), anakinra (anti-IL-1 receptor antagonist) and various other biologic medications. Convalescent plasma offers some benefits at providing passive immunity and it may ameliorate the malignant inflammatory process, however a recent study from Wuhan China showed no difference in outcomes versus the standard of care.[8] Despite receiving these medications, some patients progress to multisystem organ failure and death.

Etoposide, a topoisomerase II inhibitor, has successfully been used to treat hyperinflammatory syndromes like HLH, both secondary(due to viral syndromes) and familial types .[9, 10] It has been proposed that SARS-CoV-2 directly activates Cytotoxic T-lymphocytes(CTLs) which leads to cytokine release thus augmenting the activity of macrophages. In addition, augmented macrophage function leads to prolonged antigen presentation, thus not allowing CTLs to eliminate activated macrophages. Etoposide can control the fevers, splenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia as seen in murine HLH models, by

selectively acting to eliminate activated CTLs and cause suppression of inflammatory cytokine production.[10,11] In addition to improving hyercytokinemia, low-dose etoposide has also shown in murine models to renew Cytotoxic T-Lymphocytes, thus allowing elimination of activated macrophages, SARS-CoV-2-infected cells and associated immunomodulatory abnormalities of SARS-CoV-2 infection.[11]

Etoposide has not been reported yet as treatment for the COVID-19 induced hyperinflammatory response that is encountered in some patients with some similar features observed in HLH. Herein, we present a patient with cytokine storm due to COVID-19 who received etoposide for a progressive hyperinflammatory response despite immunomodulatory therapy.

Case Presentation:

The patient is a 66 year-old-female with a past medical history of type 2 diabetes (T2DM, last glycosylated Hemoglobin of 6.7), hypertension (HTN), hyperlipidemia (HLD) who was admitted with a chief complaint of insomnia, shortness of breath, and malaise of five-day duration. Review of systems was otherwise negative, and she denied any recent travel or sick contacts. Initial vital signs revealed a temperature of 98.2 degrees Fahrenheit, heart rate of 68 beats per minute, blood pressure of 119/45 mmHg, respiratory rate of 20, and oxygen saturation of 100% on room air. Her physical exam was significant for bibasilar crackles.

Initial laboratory findings were significant for urinary tract infection and acute kidney injury. She was initially admitted to the general medical service, and then developed progressive acute hypoxic respiratory failure unresponsive to progressive increase in doses of supplemental oxygen. The patient was then transferred to the intensive care unit (ICU) where she failed non-invasive ventilation and required intubation. Nasopharyngeal swab for SARS-CoV-2 was sent and resulted as positive. She was subsequently enrolled in a randomized placebo controlled double blind clinical trial for sarilumab, an anti-IL6 drug, used to treat cytokine storm syndrome due to COVID-19. Despite treatment with study drug, the patient did not show any improvement with continued elevation of inflammatory markers consistent with worsening cytokine storm. Rheumatology was consulted, who recommended a 7-day course of anakinra (anti-IL1 receptor antagonist) and a 3-day course of intravenous immunoglobulin (IVIG). She initially responded well to this therapy, however had a prolonged and complicated ICU course. The patient underwent tracheostomy for prolonged intubation, and developed a ventilator associated pneumonia. Then on hospital day 18, the patient had worsening hypoxia along with significant thrombocytopenia. Heparin-induced thrombocytopenia (HIT) was suspected, HIT antibodies and serotonin assay were sent, heparin was discontinued and bivalirudin was initiated. Computed tomography angiography (CTA) of the thorax was performed which confirmed our clinical suspicion of pulmonary embolism (PE), found in the right lower lobe (figure 1). HIT antibody was indeterminate and serotonin release assay resulted as negative, but since the patient's platelets improved with cessation of heparin, the patient was treated for presumed HIT as she also had clinical evidence of digital necrosis. It was also felt that the administration of IVIG had

affected the HIT Ab testing. On hospital day 20, she again developed worsening hypoxia, persistent fevers, and an increase in inflammatory markers as noted in figure 2. Bronchoscopy was performed which showed normal airways without purulence. Bronchial washings were negative for any acute infection, however SARS-CoV2 PCR from the BAL fluid was positive.

Given her deteriorating clinical status despite multiple immunomodulator therapies, a multidisciplinary meeting was arranged between pulmonary, rheumatology, and hematology to discuss further treatment options. Etoposide had previously been discussed as an agent that may be effective at treating a COVID-19 related hyperinflammatory state similar to HLH if refractory to other available treatments. Alternative therapies were not available given the novelty of disease and limited options of largely theoretical or experimental treatments. The readministration of anakinra and IVIG was not considered because the effects were only temporary, and her prognosis continued to worsen. The decision was made to give etoposide as the patient met four of the eight criteria for HLH (hyperferritinemia, cytopenia as noted by the anemia and thrombocytopenia, hypertriglyceridemia, and fevers). The target treatment endpoints at initiation of therapy were a decline in biomarkers, liberation from the ventilator, and improvement in overall clinical condition to allow for hospital discharge. She was started on trimethoprim-sulfamethoxazole and acyclovir for pneumocystis pneumonia and herpes simlex prophylaxis respectively, along with dexamethasone followed by intravenous etoposide once a week at 50 mg/m2. There was a robust clinical response to treatment with etoposide and steroids, with marked improvement in inflammatory markers and oxygenation. Per protocol, the second dose was given after 7 days. The

patient was noted to have a mild transaminitis that subsequently resolved. Trends in laboratory inflammatory markers along with her clinical course is shown in Figure 2. The clinical radiographic changes in response to therapy are highlighted in Figure 3.

Following clinical improvement after therapy with etoposide, she was able to be transferred out of the ICU to a long-term ventilator unit within 5 days. Here the patient was liberated from the ventilator. The patient was then transferred to an acute rehab unit where she is currently undergoing rigorous physical therapy. Patient has not had any readmissions, additional infections since being discharged from the hospital.

Discussion

Due to its novelty and lack of known effective therapies, the emergence of COVID-19 has introduced an unprecedented treatment challenge. One of the most challenging aspects of COVID-19 management is controlling the damage related to cytokine storm while also trying to mitigate viral replication. While the use of monoclonal antibodies directed against IL-6 receptor and IL receptor antagonistic therapy have been under investigation for the treatment of COVID-19 related cytokine storm, not much is known about the use of etoposide. Rojas et al explain that convalescent plasma (CP) provides passive immunity and anti-inflammatory cytokines, among other proteins from donors.[12] Unfortunately, CP was not available at our center at the time. Moreover, a recent study showed no improvement in time to clinical improvement within 28 days.[13]

The rationale for using etoposide is twofold. First, etoposide has already been shown to

be effective in regulating HLH, a hyperinflammatory syndrome. It results in a potent selective deletion of activated T-cells along with an efficient suppression of inflammatory cytokine production.[14] Secondly, it has been shown to suppress RNA virus replication in in-vitro studies.[15] The combination of etoposide and dexamethasone has been also shown to be successful in the treatment of hyperinflammatory syndromes associated with other viral illnesses such as severe swine flu A/H1N1, and avian influenza A/H5N1 infections.[16, 17] In addition, our modified dose of 50 mg/m2 was based on aforementioned Swine influenza A/H1N1 related hyperinflammatory syndromes in the elderly.[16] Our patient demonstrated significant improvement in inflammatory markers and oxygen requirements following administration of etoposide and dexamethasone.

Although etoposide was effective in our patient, it should be noted that it is a chemotherapeutic drug with a dose-dependent side effect profile. Reactive cytopenias are a commonly observed side effect, which did not occur in our patient. The dose used in our patient is typically not associated with cytopenia.[11] Hepatotoxicity is another potential adverse reaction with etoposide, and a mild transaminitis was noted in our patient after receiving the second dose. The susceptibility for developing further hematologic malignancies after etoposide administration should also be considered.[9]

To our knowledge, this is the first case report about the use of etoposide as treatment for COVID-19. We want to highlight that this is a salvage therapy and should not be used first line. In our healthcare system to date we have cared for more than 1500

patients with COVID-19, yet etoposide has only been used successfully in one patient. At our institution, the use of etoposide is approved only after a multidisciplinary team of hematologists, rheumatologists, and pulmonologists reaches a consensus agreement. The decision to administer etoposide should be made on a case by case basis and should be considered for a subset of patients who are severely ill but with potential for recovery. In this emerging and rapidly changing clinical environment, we will continue to follow the progress of our patients, and we invite others to share their experiences with etoposide as well. In closing, randomized controlled trials (currently ongoing: NCT04356690)[18] are needed to evaluate the overall usage and efficacy of etoposide for the treatment of cytokine storm due to COVID-19.

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Figure 1: Computed Tomography Angiography of the thorax. Image A: arrow shows right lower lobe pulmonary embolism. Image B: Multifocal peripheral ground glass opacities.

Figure 2: Trend of Laboratory and clinical markers.

Figure 3: Chest X-ray progression for patient 1. Image A: Day 1 showing diffuse bilateral interstitial and airspace opacities throughout both lungs with a basilar predominance. Image B: Day 8 with improved interstitial/airspace opacities. Image C: Day 14, increased infiltrate on right lung base. Image D: Day 20, worsening patchy opacities with basilar predominance. Image E: Day 26 improvement in opacities 5 days after receiving etoposide. Image F: Day 29, continued improvement in opacities following etoposide.