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Etoposide as Salvage Therapy for Cytokine Storm Due to Coronavirus Disease 2019



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Coronavirus disease 2019 (COVID-19) has resulted in significant morbidity and mortality because of a 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.

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KEY WORDS: COVID-19; etoposide

At the time of this writing, more than 7 million people worldwide have suffered significant morbidity and mortality due to infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).¹ Case fatality has been noted between 2% and 3% worldwide. The current literature suggests the severity of COVID-19 infection is due to high levels of inflammation related to cytokine storm syndrome, which develops through activation of the innate immune system.^{2,3} Viral entry into the cell occurs in two steps, similar to Middle East respiratory syndrome coronavirus. First, the SARS-CoV envelope spike glycoprotein binds to the cellular receptor angiotensin-converting enzyme 2.⁴ The SARS-CoV envelope spike glycoprotein then enters the cell, its viral RNA genome replicates, and it is translated into two glycoproteins and structural proteins. Finally, 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 Middle East respiratory syndrome and SARS, SARS-CoV-2 results in an enhanced innate immune response with elevated IL-1B, interferon- γ , interferon γ -induced protein 10 (IP10), monocyte chemoattractant protein-1 (MCP1), macrophage inflammatory proteins 1 alpha (MIP1A), and tumor necrosis factor alpha, 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 ARDS.⁷ The therapeutic target in COVID-19 is

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; CTL = cytotoxic T-lymphocyte; HIT = heparin-induced thrombocytopenia; HLH = hemophagocytic lymphohistiocytosis; IVIG = IV immunoglobulin; SARS-CoV-2 = severe acute respiratory syndrome coronavirus-2

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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 vs the standard of care.⁸ Despite receiving these medications, some patients progress to multisystem organ failure and death.

Etoposide, a topoisomerase II inhibitor, has been used successfully to treat hyperinflammatory syndromes such as 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 hypercytokinemia, low-dose etoposide has also been shown in murine models to renew CTLs, 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 woman with a medical history of type 2 diabetes (last glycosylated hemoglobin of 6.7), hypertension, and hyperlipidemia, who was admitted with a chief complaint of insomnia, shortness of breath, and malaise of 5 days' duration. Review of systems was otherwise negative, and she denied any recent travel or sick contacts. Initial vital signs showed a

temperature of 36.8 °C, heart rate of 68 beats/min, BP of 119/45 mm Hg, respiratory rate of 20 breaths/min, and oxygen saturation of 100% on room air. Her physical examination 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 ICU, where noninvasive ventilation failed 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-IL-6 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-IL-1 receptor antagonist) and a 3-day course of IV immunoglobulin (IVIG). She initially responded well to this therapy; however, she had a prolonged and complicated ICU course. The patient underwent tracheostomy for prolonged intubation and developed a ventilator-associated pneumonia. 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. CT angiography of the thorax was performed, which confirmed our clinical suspicion of pulmonary embolism, found in the right lower lobe (Fig 1). HIT antibody was indeterminate, and serotonin release assay resulted as negative, but because the patient's platelets improved with cessation of heparin, the patient was treated for presumed HIT, because she also had clinical evidence of digital necrosis. It was also believed that the administration of IVIG had affected the HIT antibody 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-CoV-2 polymerase chain reaction 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

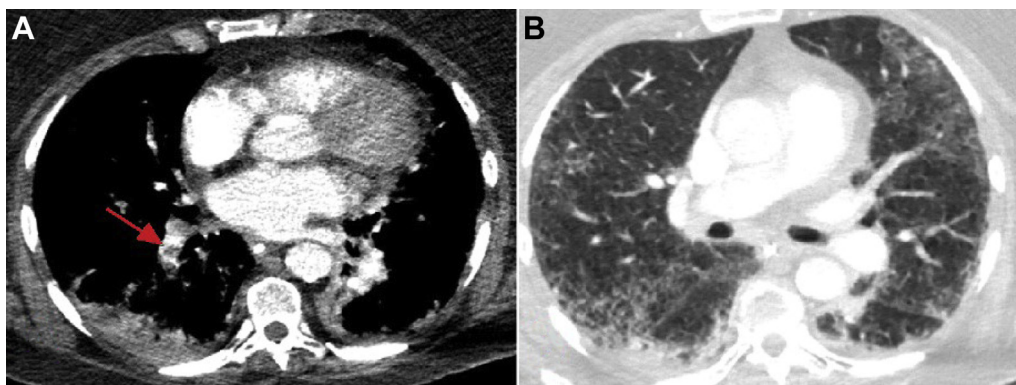


Figure 1 – CT angiography of the thorax. A, Arrow shows right lower lobe pulmonary embolism. B, Multifocal peripheral ground-glass opacities.

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, because

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 simplex prophylaxis respectively, along with dexamethasone

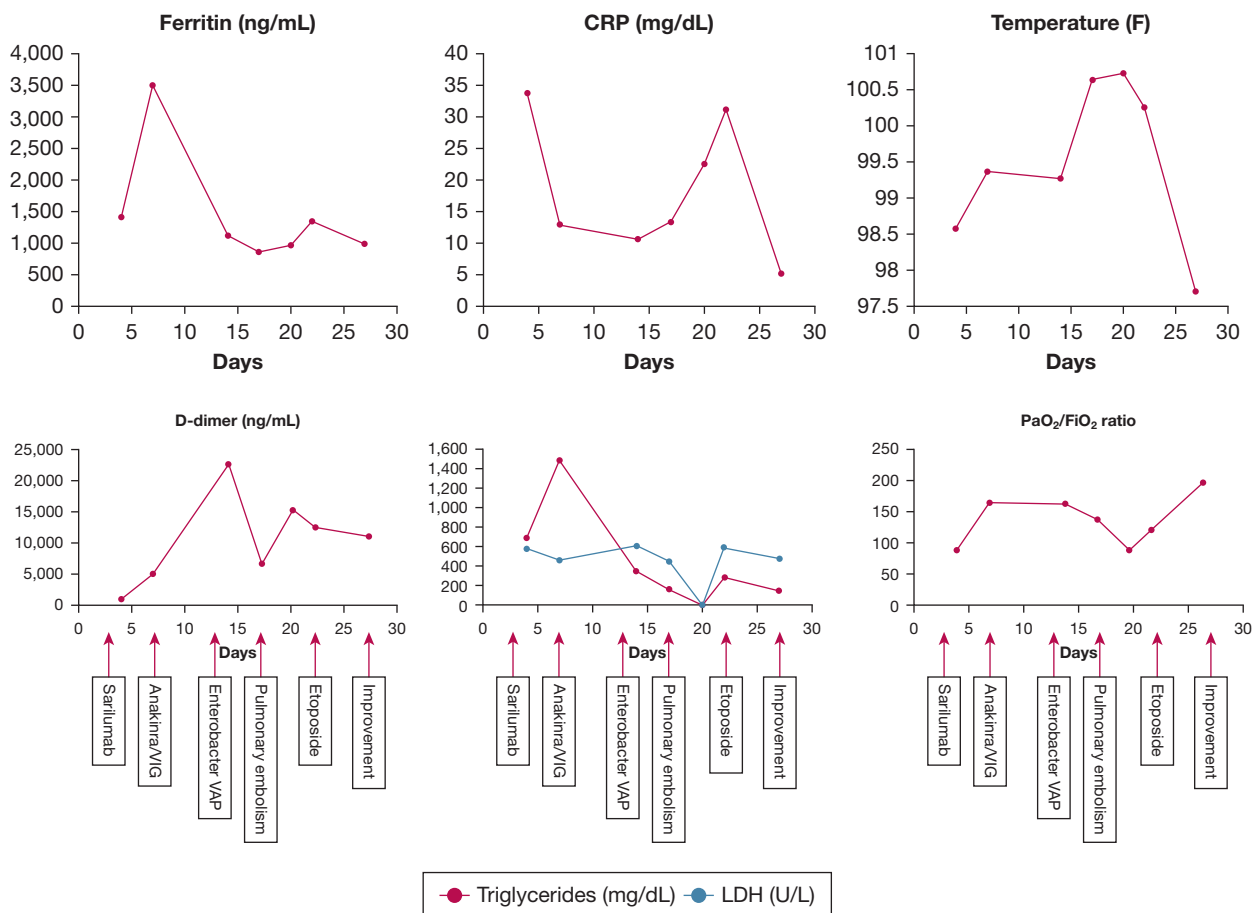


Figure 2 – Trends of laboratory and clinical markers.

followed by IV etoposide once per 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 are shown in [Figure 2](#). The clinical radiographic changes in response to therapy are highlighted in [Figure 3](#).

After 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. The patient has not had any readmissions or additional infections since being discharged from the hospital.

Discussion

Because of 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. Although 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 al¹² explain that convalescent plasma provides passive immunity and antiinflammatory cytokines, among other proteins from donors.¹² Unfortunately, convalescent plasma 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 Second, it has been shown to suppress RNA virus replication in in vitro studies.¹⁵ The combination of etoposide and dexamethasone also has

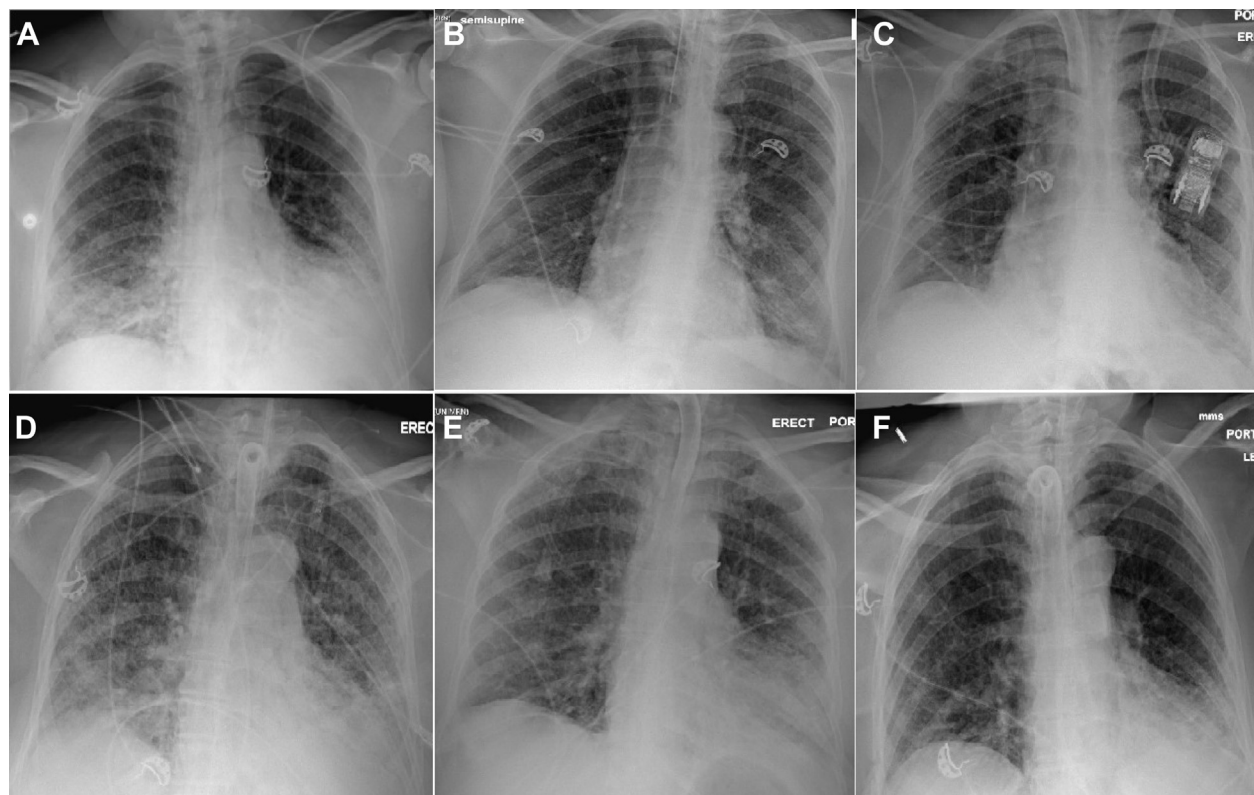


Figure 3 – Chest radiograph progression for patient 1. A, Day 1, showing diffuse bilateral interstitial and airspace opacities throughout both lungs with a basilar predominance. B, Day 8, with improved interstitial/airspace opacities. C, Day 14, increased infiltrate on right lung base. D, Day 20, worsening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

been 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 The patient demonstrated significant improvement in inflammatory markers and oxygen requirements after administration of etoposide and dexamethasone.

Although etoposide was effective in the 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 the patient. The dose used in the patient is typically not associated with cytopenia.¹¹ Hepatotoxicity is another potential adverse reaction with etoposide, and a mild transaminitis was noted in the 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 health care system to date, we have cared for more than 1,500 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 reach 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 the patients, and we invite others to share their experiences with etoposide as well. In closing, randomized controlled trials¹⁸ 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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Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

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