COVID19 Infection in A Patient Undergoing Treatment for Paroxysmal Nocturnal Hemoglobinuria (PNH) with Ravulizumab

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Case report

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Abstract

Background: In the recent COVID19 pandemic, patients with hematological malignancies were considered high risk for severe disease. Limited data is available regarding course of COVID19 infection in this subgroup.

Case Presentation: We describe a case of 32-year-old man with paroxysmal nocturnal hemoglobinuria (PNH) undergoing treatment with ravulizumab (Ultomiris) who presented with COVID19 infection. He experienced only mild symptoms and had a rapid recovery from COVID19 infection.

Conclusion: This case may demonstrate the beneficial effects of ravulizumab on complement mediated inflammatory damage linked with COVID19 infection especially in PNH patients.

Background

Coronavirus disease 2019 (COVID-19) has become a global pandemic with at least 21.5 million confirmed cases accounted for a total of 772,000 death worldwide as of August 2020 [1]. In December 2019, an outbreak of COVID19 disease was detected in China caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The clinical manifestation of COVID-19 is characterized by respiratory distress, and in more severe cases can progress towards acute respiratory distress syndrome (ARDS) and death [2]. COVID19 infection carries a potentially fatal risk especially with an immunocompromised state and multiple comorbidities [3]. Currently, there is no approved drug or vaccine available and treatment is entirely symptomatic.

COVID19 infection causes hyperactivation of the complement system and excessive inflammatory response leading to worsening lung injury and poor clinical outcomes [2, 4]. The interaction between the complement system and COVID-19 infection raises the possibility that immunosuppression could be a promising approach to inhibit the consequences of complement mediated inflammatory destruction in COVID19 infection. Moreover, patients with PNH may be vulnerable to COVID-19 complications due to impaired immune status [5]. Based on this immunological rationale, it was speculated that the therapeutic use of complement inhibitors might be an effective strategy to control the systemic inflammation in COVID19 infection.

Although complement blockade strategies are being prospectively studied in clinical trials and reported in the case reports, no cases of PNH with COVID-19 infection managed with complement blocker agents have been reported [6, 7]. Herein, we report the first case of COVID-19 pneumonia in a patient with PNH on treatment with intravenous ravulizumab, a complement component C5 inhibitor. He had a favorable clinical course linked to COVID19 infection and was discharged without any complication.

Case Presentation

Our patient was a 32-year-old Nigerian immigrant male who presented around September 2018 with a clinical picture of severe aplastic anemia and initially treated with Antithymocyte globulin (ATG), cyclosporin A and eltrombobag. The diagnosis of PNH was made and the patient was started with eculizumab for 5 cycles then switched to ravulizumab around March 2019 with the last dose in February 2020. He remained profoundly pancytoepnic and he was waiting for an allogenic transplant.

He presented in March 2020 with fever, runny nose, dry cough and altered taste (dysgeusia) for 4 days. Physical examination revealed a normal blood pressure, fever (38.3 °C), tachypnea (30 breaths per min) with baseline oxygen saturation of 95% on room air. COVID19 test using targeted rich mutliplex polymerase chain reaction of nasopharyngeal swab came back positive for SARS-CoV-2 infection. A chest radiography did not show infiltrates (Fig. 1). Infectious work up including blood and urine cultures were negative. Respiratory viral panel was negative for influenza A and B. Laboratory tests revealed WBC 1.93 cells/mm3, absolute neutrophil count (ANC) 950 cells/mm3, Hb 8 gm/l, Platelet 37,000/mm3; increased levels of acute phase reactants, including CRP (108 mg/l; normal range < 5 mg/l), ferritin (3355 ng/ml; normal range 10–322 ng/ml), serum lactate dehydrogenase (364 U/l; normal range 112–236 U/l), and fibrinogen (615 mg/dl; normal value 150–450 mg/dl). The patient was treated with azithromycin, hydroxychloroquine and prophylactic enoxaparin. He had no respiratory symptoms, remained afebrile and oxygen saturation was maintained around 95% on room air. He demonstrated a rapid and progressive improvement of the cough and altered taste in the next few days of his hospital stay. He was discharged from the hospital 4 days after diagnosis with no immediate complications and no evidence of breakthrough hemolysis.

Discussion And Conclusions

PNH is a clonal disorder of hematopoietic progenitor cells caused by an acquired mutation of the X-linked phosphatidylinositol glycans class A (PIG-A) gene [8]. The absence of glycosylphosphatidylinositol (GPI) anchored complement regulatory proteins CD55 and CD59 from the membrane of circulatory cells is responsible for activation of the complement system on the surface of the red cell membrane. This leads to complement mediated intravascular hemolysis, activation of platelets, and the coagulation cascade resulting in a hypercoagulable state [8]. PNH, although rare, can be fatal and includes an increased risk of thromboembolism and severe end-organ damage. Approximately, 35% of patients die within five years if untreated due to thrombosis and related complications [9].

Ravulizumab (ALXN1210; Alexion Pharmaceuticals, Inc) is a second generation humanized monoclonal antibody that prevents complement protein 5 (C5) cleavage and activation, ultimately blocking membrane attack complex (MAC) formation in the complement pathway [10]. Ravulizumab is now approved by the FDA to treat PNH. It has an extended 8 weeks maintenance dosing interval and reduces the need for frequent drug administration with subsequent improvement in symptom control and better quality of life.

The complement system activation is a critical component in the sequalae of COVID19 infection. Evidence suggests that severe outcomes in COVID19 infection are attributed to the excessive activation of the complement cascade leading to acute lung injury and associated is with an increased prothrombotic state [2, 4, 11, 12]. Notably, C5a concentration was noted to be higher in patients with COVID19 infection [2, 12]. Based on these observations, complement component blockers can be used as potential therapeutic targets in COVID-19 patients.

Several clinical trials have been ongoing to target the complement mediated inflammatory response in the emerging COVID19 outbreak. An anti C3 agent, compstatin analog Cp40/AMY-101 has shown efficacy in complement mediated severe ARDS in COVID19 patients, and a phase II clinical trial is ongoing [6]. In addition, a multicenter phase II/III trial using monoclonal neutralizing anti-C5a antibody (IFX-1) is recruiting patients with severe COVID19 pneumonia [7]. Following these studies, a phase III trial is underway investigating the effect of ravulizumab (Ultomiris®, Alexion Pharmaceuticals, Boston, MA, USA) in COVID-19 patients on survival, duration of mechanical ventilation, and hospital stay with severe pneumonia/ARDS (NCT04369469, first posted 4/30/2020)[13]. Alexion also initiated a clinical trial in critical COVID19 patients on a related drug, eculizumab (Soliris®, Alexion Pharmaceuticals, Boston, MA, USA)[14]. However, thus far, therapeutic use of complement inhibitors has not been approved in immunocompromised patients.

Immunocompromised patients are at higher risk for severe COVID19 infections and may experience prolonged hospitalization due to COVID19-related morbidity, and mortality. Additionally, administration of most scheduled anti-cancer treatments may be delayed or interrupted. In our case, the continuation of Raviluzumab during COVID19 infection may have assisted a prompt recovery by attenuating complement activation.

The CDC recommends adopting strategies to minimize the risk of COVID19 exposure, such as limiting contacts between patients and health-care providers. Ravulizumab has a longer therapeutic window and therefore less frequent dosing schedule than eculizumab. We recommend against interrupting or holding the dose of ravulizumab even during systemic inflammation to combat complement mediated tissue damage and multiorgan failure. We also recommend switching the PNH patients who are on eculizumab to every 8 weeks schedule with ravulizumab to minimize exposure to COVID19 and other infections and reduce economic burden on hospital systems due to less frequent dosing.

Given the worldwide COVID19 pandemic, specific clinical and economic cost effective therapeutic options should be explored and prioritized. Treatment with ravulizumab during COVID19 pneumonia was safe, cost-effective, and found to have a favorable clinical course in a patient with PNH. A systemic prospective trial is warranted to demonstrate the utility and usefulness of ravulizumab in patients with PNH in the COVID-19 outbreak.

Declarations

Ethics approval and consent to participate: Not applicable as no patient identifiable data was included

Consent for publication: Informed consent for publication of their clinical details and Imaging was obtained from the patient.

Availability of data and materials: Not applicable

Competing interests: The authors declare that they have no competing interests

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Authors' contributions:

SS made substantial contributions to the conception and design, drafting of the manuscript, analysis, and interpretation of data, and revising the manuscript and gave final approval for publication. AB, and EM, provided clinical care for the patient and critically revised the manuscript for important intellectual content. MK served as primary consultant in the management of the patient and made substantial contributions to the conception and design; analysis and interpretation of data; drafting of the manuscript; and revising the manuscript critically for important intellectual content; and gave final approval of the version to be published. All authors read and approved the final manuscript.

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