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Mild clinical course of covid-19 in 3 patients receiving therapeutic monoclonal antibodies targeting c5 complement for hematologic disorders

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Mild Clinical Course of COVID-19 in 3 Patients Receiving Therapeutic Monoclonal Antibodies Targeting C5 Complement for Hematologic Disorders

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Case series
Patients: Female, 39-year-old • Female, 54-year-old • Female, 60-year-old
Final Diagnosis: COVID-19
Symptoms: Fever
Medication: —
Clinical Procedure: —
Specialty: Hematology • Nephrology • Rheumatology

Objective: Rare co-existance of disease or pathology

Background: Patients receiving immunosuppressive therapies might be more susceptible to COVID-19. Conversely, an exaggerated inflammatory response to the SARS-CoV-2 infection might be blunted by certain forms of immunosuppression, which could be protective. Indeed, there are data from animal models demonstrating that complement may be a part of the pathophysiology of coronavirus infections. There is also evidence from an autopsy series demonstrating complement deposition in the lungs of patients with COVID-19. This raises the question of whether patients on anti-complement therapy could be protected from COVID-19.

Case Reports: Case 1 is a 39-year-old woman with an approximately 20-year history of paroxysmal nocturnal hemoglobinuria (PNH), who had recently been switched from treatment with eculizumab to ravulizumab prior to SARS-CoV-2 infection. Case 2 is a 54-year-old woman with a cadaveric renal transplant for lupus nephritis, complicated by thrombotic microangiopathy, who was maintained on eculizumab, which she started several months before she developed the SARS-CoV-2 infection. Case 3 is a 60-year-old woman with a 14-year history of PNH, who had been treated with eculizumab since 2012, and was diagnosed with COVID-19 at the time of her scheduled infusion. All 3 patients had a relatively mild course of COVID-19.

Conclusions: We see no evidence of increased susceptibility to SARS-CoV-2 in these patients on anti-complement therapy, which might actually have accounted for the mild course of infection. The effect of anti-complement therapy on COVID-19 disease needs to be determined in clinical trials.

MeSH Keywords: Complement C5 • Coronavirus Infections • Hemoglobinuria, Paroxysmal • SARS Virus

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Background

Immunocompromised patients are naturally concerned that they may be more susceptible to the effects of SARS-CoV-2 infection. However, for patients on anti-complement therapy, there is evidence suggesting that they might actually be protected, since complement may play a role in the damage induced by the virus, as reported by Risitano et al. [1] and Noris et al. [2]. Preclinical studies also suggest that this could be the case. For example, in a mouse model of the earlier SARS-CoV infection, Gralinsky et al. [3] demonstrated that C3–/– knock out mice had no change in body weight, in comparison with infected wild-type mice, which had a statistically significant decrease in weight. The C3–/– mice also exhibited a decreased alteration in lung function parameters following SARS-CoV infection compared to the infected wild-type control mice. A mouse model of MERS-CoV infection also suggested that complement blockade at the C5 level is protective against lung damage [4]. We now have the opportunity to report on 3 patients who were on therapeutic anti-complement therapy at the time they became infected with the SARS-CoV-2 virus.

Case Reports

Case 1

This is a 39-year-old woman with a 19-year history of paroxysmal nocturnal hemoglobinuria (PNH), who originally presented with venous thromboses requiring thrombolytic therapy, and was found to be a carrier of the factor V Leiden allele. She had been on anticoagulation since diagnosis (most recently, fondaparinux) and had been on eculizumab since the age of 28. She also had mild pancytopenia (with a baseline absolute neutrophil count of approximately 1300/ul), and was being treated with cyclosporine, which had resulted in mild renal insufficiency with a creatinine level of 1.5 (range, 0.52–1.04 mg/dl). In early 2020, ravulizumab was substituted for eculizumab. Most recently, 100% of the granulocytes and 20% of the red cells exhibited the GPI-negative PNH phenotype. In the last week of March 2020, she developed fever lasting 4 days, which never reached above 37.9°C. She stated that she was fatigued but never experienced myalgia, cough, dyspnea, or gastrointestinal symptoms, and she self-quarantined at home. A nasopharyngeal specimen was sent to Quest Diagnostics, which used the FDA Emergency Use Authorization Cobas® SARS-CoV-2 test on the 6800/8800 system (Roche Diagnostics). The test result was positive. While waiting for the results, we treated her with ciprofloxacin for 5 days in the event that she could have had a meningococcal infection. After fever resolution, she remained asymptomatic and returned to work.

Case 2

This patient is a 54-year-old woman who received a deceased donor kidney transplant in September 2019 because of end-stage renal disease from lupus nephritis. Her immediate post-transplant course was notable for delayed graft function and clinical findings suspicious for systemic thrombotic microangiopathy (TMA): anemia, thrombocytopenia, elevated LDH, low haptoglobin, and schistocytes on peripheral smear. Tacrolimus was therefore held starting on postoperative day 1. A kidney biopsy performed on postoperative day 4 confirmed acute TMA and exhibited strong staining for the C5b-9 complex in the glomerular capillary walls, small arteries, and arterioles, without evidence of rejection. An inhibitor to CFH was not detected and she was found to have a missense mutation of the *CFD* gene, of unknown significance. She was started on eculizumab on postoperative day 13 after a repeat biopsy demonstrated ongoing acute TMA, despite several sessions of plasmapheresis. The repeat biopsy also showed rejection, which was treated with antithymocyte globulin. She continued eculizumab as an outpatient and was eventually able to discontinue dialysis. A repeat biopsy performed in December 2019 showed resolution of both acute cellular rejection and acute TMA. In addition to eculizumab, she had been maintained on tacrolimus, mycophenolate, low doses of prednisone, and hydroxychloroquine.

In early April 2020, she presented with 2 weeks of cough, a maximum fever at home of 38.7°C, shortness of breath, and bibasilar pulmonary infiltrates. She was admitted for observation for 4 days and was found to be positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) using the Cepheid Xpert Xpress assay. During the course of hospitalization, her oxygen saturation ranged from 94–99% on room air, and she had a maximum temperature of 37.5 °C. Laboratory results showed the total hemolytic complement (CH50) level was 4 (range, 60–144 units), suggesting that the eculizumab was at therapeutic levels at the time of hospitalization. The ferritin level peaked at 4700 (range, 5-204 ng/ml), d-dimer at 1051 (range, <230 ng/ml), CRP at 29.9 (range, <0.5 mg/L), and ESR at 120 (range, 0–20 mm/h). The interleukin (IL)-6 level was 13 pg/ml (range, <5 pg/ml), and the soluble IL-2 receptor alpha (CD25) level was 1259 (range, <1033 pg/ml). The levels of IL-2, IL-4, IL-5, IL-8, IL-10, IL-12, IL-13, IL-1β, and TNF-α were normal. The creatinine level was 4.8 mg/dl, which was the same as the recent baseline measurement. The patient was subsequently discharged in good condition. Despite a delay in the administration of her outpatient dose of eculizumab, she remained without evidence of recurrent microangiopathy and has since received additional doses of therapy. However, 2 months after her discharge for COVID-19, she was admitted for a small bowel obstruction and has required dialysis ever since. Although the Abbott chemiluminescent microparticle

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immunoassay for anti-SARS-CoV-2 IgG antibodies remained negative on 2 occasions, at 7 weeks and 9 weeks after the infection, there was no evidence of viral persistence, based on negative viral swab results from testing with the Cobas® SARS-CoV-2 real-time RT-PCR system.

Case 3

A 60-year-old woman with a history of PNH since 2006 presented with severe intra-abdominal venous thromboses, and was found to have 25% PNH III red cells and 65% PNH II red cells. She was treated with thrombolytics and had been anticoagulated. Eculizumab treatment was added in 2012, when this became available for her. Anticoagulation treatment was discontinued in 2013 because of bleeding complications. Her renal function and neutrophil count had been normal and she had had mild thrombocytopenia. She returned to our clinic as scheduled in the first week of April 2020, 2 weeks after the previous infusion of eculizumab. She reported that she had been experiencing 1 to 2 weeks of mild, non-productive cough, fatigue, malaise, mild dyspnea, and a severe headache which she described as being worse than her usual migraines. She tested positive for SARS-CoV-2 using a Cepheid GenXpert real-time RT-PCR system, and based on this, went into home isolation and missed a scheduled infusion. However, she did well during this time and was later able to return to make up her missed dose. At that point, there was no evidence of recurrent hemolysis based on the LDH and reticulocyte count.

Discussion

Here, we show that in 3 patients who were maintained on chronic C5 blockade, it was possible to have a relatively mild course of COVID-19. This interpretation needs to be considered while taking into account other factors that may have helped ameliorate the clinical outcome; for example, anticoagulation in 1 patient and additional immunosuppressing drugs in 2 of the patients. Conversely, each of these patients might have been expected to have done poorly based on the following: (1) the thrombotic histories in 2 patients along with a genotype known to contribute to hypercoagulability in 1 of those 2 patients, (2) a genotype possibly affecting complement activation in 1 patient, and (3) at least some degree of renal insufficiency in 2 of the patients.

There is now reason to believe that complement activation is part of the pathophysiology of severe COVID-19 lung injury, and therefore there is reason to suspect that these 3 patients could have been protected by their anti-complement therapies. Magro et al. [5] recently demonstrated C5b-9 deposition in the skin and lungs of patients with severe COVID-19, which may be triggered by the deposition of MASP-2, a key protein in the lectin pathway of complement activation. Indeed, there is recent evidence that the N protein of the SARS-CoV-2 virus binds to and activates MASP-2 [6,7]. It was shown that C5a was elevated, particularly in patients with a severe form of COVID-19, and the BDB-001 monoclonal antibody directed at C5a was used with some success to treat 2 patients [6,7]. Since then, 5 patients with COVID-19 have been treated with eculizumab to target C5, also with apparent success [8]. A recent case report describes improvement in a patient receiving the novel C3 inhibitor AMY-101 [9]. If anti-complement therapy is useful for COVID-19, it could be because (1) the release of C3a and C5a contributes to the inflammatory reaction in the lungs and elsewhere, (2) because the C5b-9 membrane attack complex is resulting in the death of alveolar pneumocytes, or (3) because complement may be activating the coagulation cascade, and vice versa [10].

While it is reasonable to expect that C5 blockade could be helpful in the treatment of COVID-19 disease, the blockade of C3 or, specifically, the inhibition of the lectin pathway, might also decrease the production of C3a and C3b, which could be a further advantage. While it is possible that complement inhibition would predispose patients to bacterial superinfection, in patients on long-term C5 complement blockade, an increase in infections other than meningococcemia are not typically seen, and bacterial superinfections were not observed in the 3 patients described in the present case report. Currently, there are ongoing randomized trials of C5 inhibitors (eculizumab/NCT04346797, Ravulizumab/NCT04390464/NCT04369469, and zilucoplan/NCT04382755), a C5a inhibitor (BDB-001/NCT04449588), a C5a receptor inhibitor (avdoralimab/NCT04371367), C3 inhibitors (AMY-101/NCT04395456 and APL-9/NCT04402060), and a recombinant C1 esterase inhibitor (conestat alfa/NCT04414631) for the treatment of patients with COVID-19. Therefore, the safety and efficacy of complement blockage in treating patients with COVID-19 will hopefully be elucidated in the near future.

Conclusions

The mild cases of SARS-CoV-2 infection in these 3 patients may have been related to anti-complement therapy, as suggested by preclinical models and reports of other patients who have received anti-complement therapy for COVID-19. Larger series and randomized trials are needed to determine the benefit and confirm the safety of anti-complement therapy as a treatment for COVID-19.

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