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LETTER TO THE EDITORS

COVID-19 in a patient treated with eculizumab for aquaporin-4 neuromyelitis optica

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Dear Sirs,

Eculizumab is an anti-C5 humanized monoclonal antibody that is approved for the treatment of aquaporin-4 (AQP-4) seropositive neuromyelitis optica (NMO). There are limited data on best treatment practices for patients with NMO, treated with eculizumab in the setting of COVID-19. We report a woman with NMO and multiple comorbidities who presented with SARS-CoV-2 infection, days after infusion with eculizumab, experiencing a favorable outcome while continuing eculizumab.

A 56-year-old woman with AQP-4 seropositive NMO, diagnosed 8 years earlier, was seen in December 2020. Concomitant diagnoses included systemic lupus erythematous (SLE) with pericarditis, positive lupus anticoagulant with deep venous thrombosis, Sjögren's disease, and myositis. Her neurologic examination was remarkable for no light perception OD, right relative afferent pupillary defect, diffuse hyporeflexia, and lower extremity monoplegia. Findings were stable compared to her prior visit (2019). Her most recent MRI brain and spinal cord had chronic white matter demyelinating changes.

She began eculizumab in February 2020 to treat her NMO and possibly NMO-related myositis. She received 900 mg IV infusions which were interrupted due to the COVID-19 pandemic in March, after just two doses. She was managed with prednisone 7.5 mg by mouth daily.

Eculizumab 900 mg IV was resumed in December 2020 (Fig. 1). A few days after her first dose, a young household family member was exposed to COVID-19. Within 3 days, she presented with shortness of breath, headache, fever, and cough. These symptoms resolved after 3 days. She had a positive nasopharyngeal swab test for SARS-CoV-2 infection by reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay, 10 days after her eculizumab infusion. She did not receive any specific therapy or oxygen for COVID-19 but she self-dosed her steroids, taking 20 mg daily once then 10 mg daily afterwards. 3 weeks later, she emergently presented for chest pain and palpitations. On physical examination, she had normal vital signs and her laboratory tests were reassuring: serum D-dimer was negative and her troponin levels were normal. Follow-up has been uneventful at 8 weeks. She continued steroids (7.5 mg daily), and received eculizumab 900 mg IV 3 and 7 weeks after her COVID-19 diagnosis. Serum COVID-19 nucleocapsid antibody was positive 49 days after her first COVID-19 symptoms.

We present a patient with PCR-confirmed, symptomatic COVID-19 while treated with eculizumab for NMO, highlighting her overall favorable outcome. There are reports of patients with other autoimmune diseases on chronic treatment with eculizumab presenting with confirmed confirmed SARS-CoV-2 infection [1–6] (Table 1); most had a mild disease course without recognized sequelae. It is possible that eculizumab renders people susceptible to SARS-CoV-2 infection; however, a protective effect against the development of severe COVID-19 disease may also occur [7–9]. Although eculizumab has been given safely during COVID-19, a survey of 192 neurologists from the United States and Canada in April 2020 found that many felt eculizumab could put their patients at risk for COVID-19 [10].

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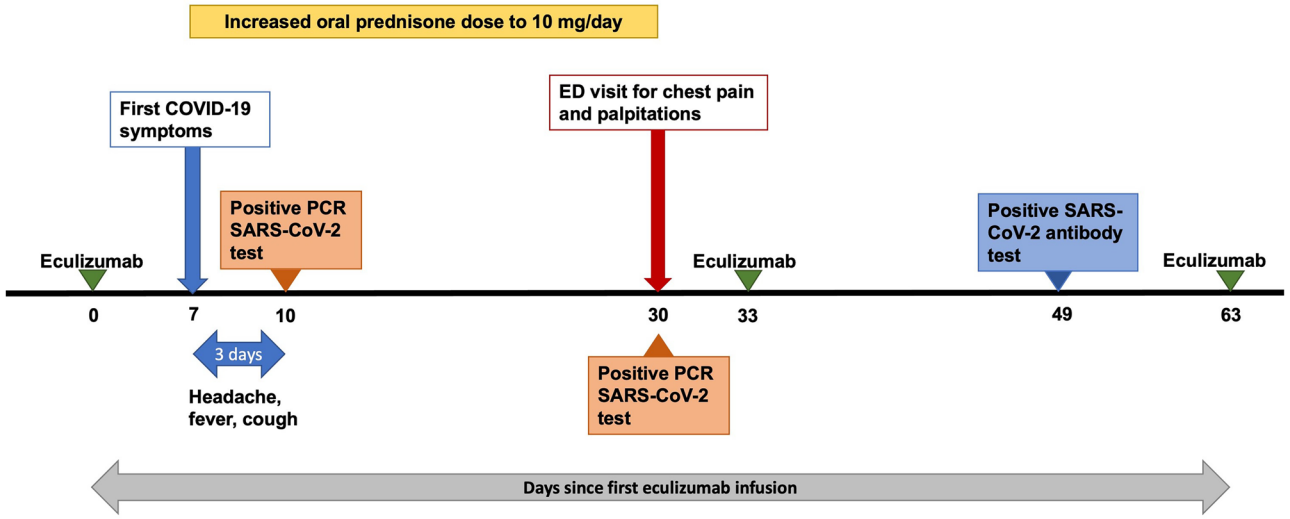

Fig. 1 Clinical course. Symptoms started 7 days after the eculizumab infusion, were mild and lasted for 3 days. The patient visited the emergency department for chest pain and palpitations, and a follow-up PCR test for SARS-CoV-2 was positive. The next scheduled eculizumab infusions were administered without new or recurring symptoms. She had positive SARS-CoV-2 antibody test 49 days after the first eculizumab infusion. *ED* emergency department, *PCR* polymerase chain reaction

There is no consensus on the safe administration of eculizumab in the context of COVID-19, although recommendations exist [11]. Extrapolating from other autoimmune diseases treated chronically with eculizumab, there is no evidence to prompt its suspension in the context of a SARS-CoV-2 infection [12]. Considering the debilitating and severe nature of NMO, it is important to balance the benefits of preventing a relapse with the potential risk of rendering a patient more susceptible to SARS-CoV-2 infection.

We also demonstrate that antibody formation to SARS-CoV-2 occurs following PCR-confirmed COVID-19 in a patient treated with eculizumab, implying immunity to SARS-CoV-2 could occur during ongoing complement inhibitor therapy. Despite ongoing treatment with eculizumab, this patient's immune system was able to mount an antibody response to COVID-19. Antibody formation implies an immunogenic vaccine response in eculizumab-treated patients will likely occur. Meanwhile, we recommend that patients with NMO continue adopting all preventive measures against COVID-19, including vaccination, and those on eculizumab treatment should not suspend or discontinue it if exposed to SARS-CoV-2.

Table 1 Published case reports of COVID-19 infections on patients being treated with eculizumab or ravulizumab

Disease	Country	Anti-complement therapy	Age/sex	Comorbidities	Duration of anti-complement therapy	Dose	Days from anti-complement therapy to diagnosis of COVID-19	COVID-19 treatments received	Ventilatory support	Hospitalized, duration of stay (days)	Outcome	References
NMOSD	USA	Eculizumab	56F	Lupus, Sjögrens, myositis	1 y	900 mg every month	10	None	No	No	Resolved	***
PNH	UK	Eculizumab	37F	None	11 y	1500 mg every 2 weeks	NA	None	No	No	Resolved	[4]
PNH	UK	Ravulizumab	35F	None	6 y	3300 mg every 8 weeks	NA	None	No	No	Resolved	[4]
PNH	UK	Eculizumab	47M	Myelodysplastic syndrome, psoriasis, hypercholesterolemia	2 y 7 m	1200 mg every 2 weeks	6	None	No	Yes, 5	Recovered	[5]
PNH	UK	Eculizumab	43M	Type 2 diabetes mellitus, aplastic anemia	4 y 4 m	900 mg every 2 weeks	5	None	Yes	Yes, 23	Died	[5]
PNH	UK	Eculizumab	77F	Parkinson's disease, iron overload	6 y 7 m	900 mg every 2 weeks	8	None	No	Yes, 12	Recovered	[5]
PNH	US	Ravulizumab (recent change from eculizumab)	39F	None	11 y	NA	NA	None	No	No	Recovered	[6]
Thrombotic microangiopathy following kidney transplant	USA	Eculizumab	54F	Lupus nephritis	7 m	NA	NA	None	No	Yes, 4	Recovered	[6]
PNH	USA	Eculizumab	60F	NA	8 y	NA	14	None	No	No	Recovered	[6]
PNH	Germany	Eculizumab	68F	Hypertension, chronic hepatitis C	13 y	900 mg every 2 weeks	13	NA	No	Yes, 15	Recovered	[2]
PNH	France	Eculizumab	45M	Hypertension, obesity, obstructive sleep apnea	12 y	1200 mg every 12 days	3	Hydroxychloroquine, lopinavir + ritonavir, tocilizumab	Yes	Yes, 31	Recovered	[1]

Table 1 (continued)

Disease	Country	Anti-complement therapy	Age/sex	Comorbidities	Duration of anti-complement therapy	Dose	Days from anti-complement therapy to diagnosis of COVID-19	COVID-19 treatments received	Ventilatory support	Hospitalized, duration of stay (days)	Outcome	References
Kidney transplant recipient with aHUS	Argentina	Eculizumab	24M	NA	6 y	900 mg every 2 weeks	11	Dexamethasone, convalescent plasma	No	Yes, 17	Recovered	[3]

Only patients with a positive RT-PCR test were included

aHUS atypical hemolytic uremic syndrome, *NA* not available, *US* United States of America, *UK* United Kingdom, *PNH* paroxysmal nocturnal hemoglobinuria

***Current case report

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Informed consent Informed consent was obtained from the patient included in this study.

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