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Severe COVID-19 infection in a patient with paroxysmal nocturnal hemoglobinuria on eculizumab therapy

COVID-19 in PNH patient on eculizumab

Authors: Alexis Genthon1*, Thibault Chiarabini2*, Pierre Baylac2, Nadia Valin2, Tomas Urbina3, Jérome Pacanowski2, Arsène Mekinian4, Eolia Brissot1, Fella M.'Hammedi-Bouzina1, Simona Lapusan1, Mohamad Mohty1, Karine Lacombe5 and Patrick Ingiliz2

1. Service d'Hématologie Clinique et Thérapie Cellulaire, Hôpital Saint-Antoine, Sorbonne Université, INSERM UMRs 938, Paris, France.
2. Service de Maladies Infectieuses et Tropicales, Saint-Antoine Hospital, Paris, France.
4. AP-HP, Hôpital Saint Antoine, service de médecine interne et Inflammation (DHU i2B), Faculté de Médecine Sorbonne Université, F-75012, Paris, France, UMR 7211, F-75005, Paris, France
5. Sorbonne Université, Inserm U1136, Hôpital Saint-Antoine, AP-HP, Paris, France

*AG and TC contributed equally.

Corresponding author:
Alexis Genthon, MD
Service d'Hématologie Clinique et Thérapie Cellulaire
Hôpital Saint-Antoine, Sorbonne Université
184 rue du Faubourg Saint-Antoine
F-75012 Paris
E-mail: alexis.genthon@gmail.com
Tel: +33 (0) 1 49 28 34 38 - Fax: +33 (0) 1 49 28 32 00

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The course of the COVID-19 infection has been better understood since the first identification of a novel beta-coronavirus (SARS-CoV-2) in early January 2020 in Wuhan, China [1]. Some individuals will develop after the first “viral phase”, as a predictor of a severe outcome, a second “immunological” phase that appears to be mediated by strong complement activation and can lead to a state of thrombotic microvascular injury [2]. Several antiviral or immune -modulatory drugs have been used in clinical trials or as experimental therapy in COVID-19 patients all over the world. Among the latter are several biologicals such as interleukine 6 (IL-6) antagonists (tocilizumab) [3,4] and IL-6 receptor antagonists (sarilumab) or TNF-alpha-antagonists [5]. A beneficial effect from the off-label use of the complement antagonist eculizumab has been reported in patients with severe [6] or critical [7] COVID-19 infections and in combination with ruxolitinib in 7 patients in a controlled study [8]. Eculizumab is a monoclonal antibody currently approved for the treatment of paroxysmal nocturnal hematuria (PNH) and some other conditions. It specifically binds to complement C5, thereby inhibiting its cleavage to C5a and C5b and preventing the generation of the terminal complement complex C5b-9 [9]. It is hypothesized that treatment with eculizumab could improve outcome by reducing immune-mediated lung injury during the course of COVID-19 pneumoniae. Eculizumab is currently used as an investigational and experimental [6] agent to treat COVID-19 but its efficacy is yet to be proven. Here, we report a case of patient who received eculizumab to treat underlying PNH while he became infected with SARS-CoV-2.

A 45-year old man was referred to our emergency department in Saint-Antoine Hospital, Paris, France with a 3-day history of dry cough, myalgia, and diarrhea (figure 1). He also reported anosmia. He had been diagnosed with PNH when he
was 18 years old. The patient had no history of thrombosis and had been treated with eculizumab since 2008 at the dose of 1200 mg every 12 days with partial response. He was obese with a body mass index of 42.6 kg/m² and had obstructive sleep apnea.

Three days before his referral, he had come to our outpatient department to receive his eculizumab infusion. A few hours later, he developed myalgia and fever. The patient was started on antibiotic treatment with amoxicillin/clavulanate and ciprofloxacin with no improvement and was then referred to the hospital. Physical examination revealed a blood pressure of 156/81 mmHg, a pulse of 104 beats per minute, a body temperature of 37.2°C, respiratory rate of 18 breaths per minute, and oxygen saturation of 100% while the patient was breathing ambient air. Chest radiography revealed interstitial lung infiltrates. A posterior nasopharyngeal swab was tested positive for SARS-CoV-2 nucleic acid by RT-PCR. Laboratory findings revealed macrocytic anemia with hemolysis: hemoglobin: 89 g/L, MCV: 110 µ3, reticulocytes: 272 G/L (11.3 %), LDH: not measurable due to hemolysis, haptoglobin <0.01 g/L, total bilirubin: 63 µmol/L and conjugated bilirubin: 28 µmol/L (figure 2).

The antibiotic treatment was stopped and a hydroxychloroquine treatment was started outside of clinical trial (200 mg TID). Seven days after the first symptoms, the patient developed a severe hypoxemic syndrome with PaO₂ of 68 mmHg. Oxygen supplementation delivered by nasal cannula at 6 liters per minute was started. A chest computed tomography imaging was performed and showed bilateral ground-glass opacities. An association of ritonavir and lopinavir, based on in vitro efficacy on SARS-CoV and middle-east respiratory syndrome (MERS) viruses available at this time [10,11], as well as venous thromboembolism prevention by enoxaparin 6000 IU OD was added. The eculizumab treatment was continued at the dose of 1200 mg on day 7, day 19, and day 29 of the hospitalization. The patient’s condition continued to
worsen and he developed a fever of 40ºC. Laboratory findings showed an inflammatory syndrome with C-reactive protein: 204.2 mg/L (<5 mg/L) and interleukin-6 at 68.1pg/mL (<12.5 pg/mL). The decision was made to stop lopinavir/ritonavir and hydroxychloroquine and to administer i.v. tocilizumab (8 mg per kg). He was transferred to the ICU on day 10 since first symptoms. A second line of antibiotics, cefotaxime and azithromycin was also administered. On day 12, he developed an acute respiratory distress syndrome (ARDS) with a PaO$_2$/FiO$_2$ ratio of 78 and was placed under lung-protective mechanical ventilation with neuromuscular blockade. Three sessions of prone positioning were required before respiratory parameters gradually improved and fever ultimately disappeared. A percutaneous tracheostomy was performed after 25 days of mechanical ventilation to facilitate weaning.

The SARS-CoV-2 PCR was finally negative on day 31 and the patient was discharged from the ICU. Hemoglobin was stable at 95 g/L with no sign of hemolysis. A new chest computed tomography imaging was performed on June 24 showed disappearance of ground-glass opacities.

We here report the case of a male individual treated for PNH by repeated eculizumab infusions since 2008 that developed a severe SARS-CoV-2 infection, while his treatment was pursued. Although being on a stable eculizumab regimen for PNH, we saw an increased hemolysis during the COVID-19 infection, as it has been described with other viral infections. While the induction of auto-immune hemolytic anemia has been described in COVID-19, the underlying pathomechanism in our case was most likely complement activation. Eculizumab is not suspected to have the potential to prevent SARS-CoV-infection, and likewise, in our case, the administration did not serve him as pre-exposure prophylaxis. Few agents such as hydroxychloroquine
have been suggested for pre- and post-exposure prophylaxis in COVID-19 but have not proven efficacy yet [12]. Biologicals, such as eculizumab, may not be suitable due to their deleterious impact on the immune response and even facilitate infection. However, eculizumab is investigated in clinical trials such as the SOLID C-19 trial (NCT number: 04288713) or the CORIMMUNO-ECU trial (NCT number: 04346797) for the treatment of moderate to severe pneumonia related to COVID-19.

Eculizumab is an inhibitor of the complement factor C5. The complement system plays a crucial role in the host defense system against bacterial, fungal, or viral infections. It is further related to a pro-inflammatory state associated with ARDS in SARS-CoV-infection [13], and its inhibition may therefore lead to a favorable disease outcome. In mice with MERS and acute respiratory failure high concentrations of C5 have been detected and blockage of C5a led to a reduced alveolar macrophage infiltration [14].

Our patient developed a severe course requiring mechanical ventilation despite repeated administration of 1200mg i.v. eculizumab at day 1 and 10 of COVID-19 related symptoms, and the drug did not seem to have an effect on the course of the disease. Several risk factors for severe outcomes have been identified in COVID-19 patients, such as arterial hypertension, diabetes mellitus, coronary heart disease, age [1], or obesity. Our patient was hypertensive and had a BMI of 42.6 kg/m2, and this may explain the severity of his disease, and these factors may outweigh the beneficial effect of a complement C5 blockade. Interestingly, this very high-risk patient experienced no thrombotic complication. The i.v. administration of the IL-6 receptor antagonist tocilizumab was followed by a remarkable decrease in inflammatory blood markers such as C-reactive protein or lactate dehydrogenase, while his IL-6 levels remained strongly elevated. It is noteworthy that both C-reactive
protein and lactate dehydrogenase levels abruptly rose 14 days after infusion. Tocilizumab is currently evaluated in randomized-controlled trials to treat the cytokine-release syndrome associated to COVID-19 [15], and reduced risk of mechanical ventilation or death have been reported [3,4].

For eculizumab as for tocilizumab, the accurate dose in COVID-19 ARDS is unknown. In the CORIMMUNO-ECU trial, much higher doses of eculizumab are administered (1200mg i.v. at day 1, 4, and 8, then again at day 15, 18, and 22), as pharmacokinetics are likely to differ in the septic state. Considering the high body weight of our patient, he was potentially underdosed to reach drug levels that may be sufficient to induce sufficient complement blockade.

Although tocilizumab was associated with a transient decrease in inflammatory biomarkers, further reports are needed to identify whether this anti-IL6 receptor agent or eculizumab itself could have modified the course of the severe Sars-Cov2 infection for this overweight individual with PNH.

In conclusion, we may speculate that eculizumab administered in a classical schedule for PNH did not contribute, in our case, to control a severe course of COVID-19 ARDS in an overweight individual. Tocilizumab may have played a role in reversing the course of the disease. Controlled studies are needed and awaited to understand the benefit and eventually the optimal administration of immunomodulating drugs during Sars-Cov2 infections.
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References


Figures

- **Figure 1.** Evolution from first symptoms to ICU discharge.
- **Figure 2.** C-reactive protein, haptoglobin, hemoglobin and lactate dehydrogenase evolution during COVID-19 infection.