Received: 19 May 2021 | Revised: 15 June 2021 | Accepted: 13 July 2021

DOI: 10.1111/1744-9987.13710

LETTER TO THE EDITOR

Therapeutic Apheresis and Dialysis

WILEY

Additional eculizumab dose and tacrolimus discontinuation for treatment of COVID-19 in a kidney transplant recipient with aHUS

Dear Editor

The SARS-CoV-2 virus causes systemic complement activation, which can lead to the initiation of the "cytokine storm," considered to be the integral step for the development of ARDS and severe COVID-19.[1–3] Like COVID-19, complement activation and resultant endothelial cell injury are hallmarks of the atypical haemolytic uremic syndrome (aHUS). aHUS can be provoked by stressors, including infections, pregnancy, transplantation, and cancer.[4–6] In kidney transplant recipients (KTR), graft failure with aHUS relapses occurs in one-fifth of patients despite treatment with eculizumab.[7] Eculizumab is a monoclonal antibody against C5 and is an established treatment option for aHUS. However, there is no established method for the management of KTR with aHUS affected by COVID-19.

Our patient is a 37-year-old female KTR who was diagnosed with aHUS at the age of 33. She developed end-stage renal disease requiring hemodialysis until receiving a kidney transplant in 2019. Genetic analysis revealed two mutations (CFI c.−13G > A and CFHR5 p.P46S) and 4 SNPs/haplotypes, which might cause a predisposition to aHUS. She was on a once-monthly maintenance regimen of eculizumab since the transplantation with tacrolimus, prednisone, and mycophenolate maintenance. In March 2021, she presented with 6 days of myalgia, fatigue, and a positive nasopharyngeal swab polymerase chain reaction (PCR) test for SARS-CoV-2. She was admitted for evaluation and observation. A chest CT scan showed ground-glass opacities bilaterally, baseline laboratory workup showed normal inflammatory markers (C-reactive protein 2.6 mg/L, WBC 3.5×10^9/L, neutrophils 76.2%), normal blood counts (hemoglobin 129 g/L, platelets 223×10^{12}/L, BUN 5.4 mmol/L), and preserved renal function (creatinine 92 μmol/L). Empiric meropenem, LMWH, and remdesivir were started. Tacrolimus was stopped, MMF was continued, and intravenous methylprednisolone 125 mg was initiated. A 900 mg dose of eculizumab was given on the second day, and her scheduled dose was administered on the 18th day of the disease. On the 21st day, a control chest CT scan showed regression of lung infiltration, which enabled reinstitution of tacrolimus at reduced doses. The patient remained afebrile throughout the hospital stay, exhibited no signs of hemorrhage or respiratory distress, and the kidney function remained stable. Two consecutive negative PCR tests were obtained on hospital days 21 and 22, and she was discharged. On follow-up, 4 days later, she was asymptomatic. Laboratory tests were within reference ranges (hemoglobin 132 g/L, WBC 4.8×10^9/L, platelets 296×10^{12}/L, C-reactive protein 1.6 mg/L, D-dimers 0.56 mg/L, creatinine 84 μmol/L, creatinine clearance 102 mL/min). Serum protein electrophoresis showed no abnormalities, complement levels, free hemoglobin, and LDH were normal. Blood PCR for BK, JC, EBV, and CMV were negative, and urine PCR was positive for JC polyomavirus.

Trimarchi et al described a case of COVID-19 in a KTR with aHUS.[8] They opted for continuing tacrolimus and withholding MMF, together with eculizumab administration. This strategy failed to prevent respiratory failure and endothelial cell injury. However, the patient improved and was discharged home. We considered the potential risk of tacrolimus-associated thrombotic microangiopathy warranted a different approach to immunosuppression than reported in most KTRs with COVID-19.[9, 10] Cognard et al opted for almost the same strategy as was used in our case. However, they postponed the initially scheduled injection of eculizumab, and later administer eculizumab at a higher dose (1200 mg). They also ceased tacrolimus with a favorable outcome.[11]

It is important to note that no evidence-based recommendations for immunosuppression management in COVID-19 exist. Eculizumab is currently under evaluation, and its role in COVID-19 will be further elucidated (National Library of Medicine [NLM], NCT04288713). The complex interplay of the prothrombotic state caused by COVID-19, potential alternative pathway activation in aHUS, and the need to preserve graft function required

unprecedented treatment decisions. We describe a KTR with COVID-19 who was treated with an additional dose of eculizumab to prevent recurrence of aHUS. This case indicates that our treatment strategy may have contributed to the absence of pneumonia progression and complications of either COVID-19 or aHUS, resulting in a mild clinical course. According to our experience and currently available data, due to the risk of aHUS exacerbation, it is safe to give eculizumab in the setting of COVID-19.

CONFLICT OF INTEREST

The authors have declare no conflict of interest.

Nikolina Bašić-Jukić
Armin Atić

Department of Nephrology, Arterial hypertension, Dialysis and Transplantation, Clinical Hospital centre Zagreb, Zagreb, Croatia

Correspondence
Nikolina Bašić-Jukić, Department of Nephrology, Arterial Hypertension, Dialysis and Transplantation, University Hospital Centre Zagreb, Kispaticeva 12, 10000 Zagreb, Croatia.
Email: nina_basic@net.hr; nbasic@kbc-zagreb.hr

ORCID

Nikolina Bašić-Jukić https://orcid.org/0000-0002-0221-2758
Armin Atić https://orcid.org/0000-0003-2487-6878

REFERENCES

1. Song WC, FitzGerald GA. COVID-19, microangiopathy, hemostatic activation, and complement. J Clin Invest. 2020;130:3950–3.
2. Lo MW, Kemper C, Woodruff TM. COVID-19: complement, coagulation, and collateral damage. J Immunol. 2020;205:1488–95.
3. Risitano AM, Mastellos DC, Huber-Lang M, Yancopoulou D, Garlanda C, Ciceri F, et al. Complement as a target in COVID-19? Nat Rev Immunol. 2020;20:343–4.
4. Raina R, Krishnappa V, Blaha T, Kann T, Hein W, Burke L, et al. Atypical hemolytic-uremic syndrome: an update on pathophysiology, diagnosis, and treatment. Ther Apher Dial. 2019; 23:4–21.
5. Afshar-Kharghan V. Atypical hemolytic uremic syndrome. Hematol Am Soc Hematol Educ Progr. 2016;2016:217–25.
6. Ville S, Le Bot S, Chapelet-Debout A, et al. Atypical HUS relapse triggered by COVID-19. Kidney Int. 2021;99:267–8.
7. Gonzalez Suarez ML, Thongprayoon C, Mao MA, Leeaphorn N, Bathini T, Cheungpasitporn W. Outcomes of kidney transplant patients with atypical hemolytic uremic syndrome treated with Eculizumab: a systematic review and meta-analysis. J Clin Med. 2019;8:919.
8. Trimarchi H, Gianserra R, Lampo M, Monkowski M, Lodolo J. Eculizumab, SARS-CoV-2 and atypical hemolytic uremic syndrome. Clin Kidney J. 2020;13:739–41.
9. Vanikar AV, Kanodia KV, Suthar KS, Nigam LA, Patel RD, Thakkar UG, et al. Thrombotic microangiopathy in a renal allograft: single-center five-year experience. Saudi J Kidney Dis Transplant. 2020;31:1331–43.
10. Cravedi P, Mothi SS, Azzi Y, Haverly M, Farouk SS, Pérez-Sáez MJ, et al. COVID-19 and kidney transplantation: results from the TANGO international transplant consortium. Am J Transplant. 2020;20:3140–8.
11. Cognard N, Gautier-Vargas G, Perrin P, Benotmane I, Caillard S. COVID-19 in a kidney transplant recipient treated with eculizumab for atypical hemolytic uremic syndrome: a case report. J Nephrol. 2021;17:1–4.