Received: 23 March 2021 | Revised: 9 April 2021 | Accepted: 14 April 2021

DOI: 10.1111/hae.14326

Haemophilia WILEY

LETTER TO THE EDITOR

Successful treatment of COVID-19 in a patient with severe haemophilia A on emicizumab prophylaxis in the intensive care unit

The course of infection with SARS-CoV-2 virus in patients with congenital bleeding disorders does not differ from the general population. COVID-19 in these patients can be mild but also can progress to severe pneumonia, respiratory failure and death.[1] The treatment of patients with COVID-19 and haemophilia A receiving emicizumab for bleeding prevention is particularly challenging because of the need to balance the increased risk of thrombotic events and bleeding, and reports in this population are scarce.[2] Emicizumab is a bispecific antibody that bridges factors X and IXa, which restores the function of missing factor VIII (FVIII) in haemophilia A. The recommended subcutaneous prophylactic dose is 3 mg/kg once weekly for the first 4 weeks, followed by a maintenance dose of usually 1.5 mg/kg once weekly. At the usual recommended dose of emicizumab, the FVIII equivalent is about 10%–15%. Observations from registration studies have shown a small number of cases displaying increased risk of thrombotic events and thrombotic microangiopathy, especially when combined with bypassing agents (aPCC).[3] Thus, it could be thought that when an additional prothrombotic factor is present, as COVID-19, increased prothrombotic activity may occur.[2] On the other hand, patients on emicizumab prophylaxis may also experience bleeding episodes. The literature is less clear on how the drug may interact with thrombosis in the course of COVID-19.[4]

We present a case of a 70-year-old male patient with severe haemophilia A on emicizumab prophylaxis that developed severe COVID-19. His haemophilia was diagnosed at age 5 with FVIII levels of 0.5% and complicated by an inhibitor at 50 years of age with maximum inhibitor titre up to 52 Bethesda units (BU). An inhibitor appeared as a consequence of intensive substitution treatment after right knee replacement surgery in 2000, and the patients underwent immune tolerance induction (ITI). After successful inhibitor eradication, the patient has received FVIII for secondary prophylaxis since 2013. In June 2017, the patient started emicizumab prophylaxis as a part of clinical trial, initially receiving a dose of 1.5 mg/kg weekly but because of recurrent bleeding episodes, the dose was increased to 3 mg/kg every week according to the protocol. Surgically, before starting emicizumab prophylaxis, the patient has undergone bilateral knee (1985, 2000) and hip replacements (1985, 2000) and synovectomies of bilateral elbows in 1990 and 2013 for haemophiliac arthropathy. His additional comorbidities include hypertension and HCV infection successfully treated with IFN and ribavirin in 2008. Prior to COVID-19, he was on emicizumab prophylaxis at a dose of 3 mg/kg once weekly and his weight was 85 kg; he had no history of bleeding episodes nor thromboembolic events.

He was admitted to the Department of Internal Medicine, Wroclaw Medical University on 28 November 2020 due to one week of cough, dyspnoea and fever. On admission, SARS-CoV-2 infection was confirmed by PCR assay. Laboratory tests revealed: low lymphocyte count 0.38 × 10^3/μL (1.5–3.5), D-dimers 2.65 μg/mL (<0.5), aPTT 25.7 s (26–38) and ferritin 1450 μg/L (15–400) (Table 1). On the 4th day of hospitalization, the patient's dyspnoea worsened requiring high flow oxygen therapy and ventilation in the supine position. Despite these measures, the patient's respiratory status deteriorated requiring intubation and ICU admission. Chest X-ray showed numerous bilateral ground-glass opacities and consolidations. The patient received remdesivir (5 days), dexamethasone and convalescent plasma (two doses of 300 mL with an S-RBD-specific IgG titre greater than 1:1000 in serum) for COVID-19. During the first two days in the ICU, the patient periodically required norepinephrine for circulatory stabilization. Prophylactic low-molecular-weight heparin (LMWH) was administered from the time of ICU admission. The patient received enteral nutrition until day 3 when parenteral nutrition was instituted due to a vomiting episode. The clinical examination revealed abdominal tenderness, and an increase in total bilirubin level to 2.1 mg/dL was detected while liver enzymes, amylase and lipase levels were normal. Abdominal CT showed oedematous pancreas in the distal part of the body and tail, surrounded by hyperdense fatty tissue and bands of fluid consistent with pancreatitis. Broad-spectrum antibiotics were administered, resulting in improvement of the general condition. On the 10th day of treatment, a spike in inflammatory parameters was observed C-reactive protein (CRP) levels from 93.3 to 312.2 mg/L, procalcitonin (PCT) from 0.07 to 8.55 ng/mL. Repeat chest X-ray showed progression of lung lesions. Chest CT scan revealed confluent areas of consolidation, with peripheral and posterior localization, ground-glass opacification of 40%–50% of the lung parenchyma. Cardiac ultrasound did not show any pathological changes. Bronchial aspirate culture was positive for extensively drug-resistant *Acinetobacter baumannii* (XDR) and methicillin-resistant *Staphylococcus aureus* (MRSA). Vascular catheter tip and blood cultures were positive for *Acinetobacter baumannii* XDR. A diagnosis of ventilator-associated

TABLE 1 Laboratory results during hospitalization

Time intervals	Hgb g/dL	WBC x10^3/μL	Lymphocytes x10^3/μL	Granulocytes x10^3/μL	Platelet x10^3/μL	Dimer-D μg/mL	Factor VIII IU/dL	CRP mg/L	PCT ng/mL	Anti- Xa IU/mL	aPTT s	Ferritin μg/L
On admission to the hospital	14.3	7.3	0.38	6.7	212.0	2.65	15.5	93.3	0.07	2.02	25.7	1450
On admission to the ICU	9.6	7.01	0.54	5.7	93.0	4.205	86.1	312.1	0.45	0.11	28.9	1010
Before discharge	9.4	6.8	0.64	5.9	187.0	1.207	59.3	15.94	0.07	0.07	28.4	523

Abbreviations: aPTT, activated partial thromboplastin time; CRP, C-reactive protein; Hgb, haemoglobin; ICU, intensive care unit; PCT, procalcitonin; s, second; WBC, white blood count.

bacterial pneumonia and secondary sepsis was made. Colistin and linezolid were administered and guided by susceptibility testing. Emicizumab at weekly dose of 3 mg/kg was continued. Additionally, LMWH doses were increased to therapeutic doses due to patient deterioration and further increase in D-dimer levels (4.5 μg/mL). During therapy with LMWH, regular injections of plasma-derived (pd) FVIII concentrate at a dose of 4000 IU (47 IU/kg) per day were administered (Figure 1). To monitor FVIII plasma levels, a chromogenic method with bovine reagents (ELECTRACHROME Factor VIII, Werfen Instrumentation Laboratory) was used. FVIII plasma levels ranged between 59.3 and 86.1 IU/dL. On day 21 of hospitalization, tracheostomy was performed still under FVIII protection. During ICU treatment, including invasive procedures (intubation, central and intravenous catheter placement, bladder catheter placement, tracheostomy, enteral feeding tube), no bleeding or thrombotic incidents have been observed. On days 19 and 20 of hospitalization, the patient had two negative SARS-CoV-2 test results. CRP (15.0 mg/L) and procalcitonin (0.07 ng/mL) levels as well as dimer-D level (1.2 μg/mL) gradually decreased, abdominal complaints resolved, lung X-ray showed a partial regression of inflammatory changes, and the clinical condition improved. Gradual weaning from the mechanical ventilator was carried out, and on day 30, the patient was breathing independently. At present, the patient is at home, his dyspnoea and cough have resolved, and he is undergoing physical and respiratory rehabilitation. Replacement therapy with pdFVIII was stopped on day 30 and since then the patient is again on emicizumab prophylaxis.

SARS-CoV-2 infection results in COVID-19–associated coagulopathy (CAC) with increased levels of prothrombotic factors, mainly factor VIII, von Willebrand factor and elevated D-dimer values, prolonged prothrombin time and thrombocytopenia.[5] Thromboinflammation occurs during the course of SARS-CoV-2 infection leading to microthrombosis within pulmonary vessels. Evidence suggests that pulmonary thrombosis in situ may be one of the leading causes of death in COVID-19.[6] The pathophysiology of SARS-CoV-2 infection in patients with haemophilia is complex.[7] Haemophilia is characterized by a defect in thrombin production, resulting in reduced fibrin formation. For obvious reasons, in severe haemophilia A, marked elevation of factor VIII levels is not seen like that in patients without severe haemophilia. Therefore, it could be hypothesized that this might attenuate the potentiating effect of CAC in people with haemophilia A. However, many of the mechanisms described above, including the impact of endothelial damage leading to microvascular dysfunction, are not solely dependent on thrombin production.[7] According to Dorgaleh et al[1], patients with severe congenital bleeding disorders are less susceptible to hypercoagulability associated with SARS-CoV-2 infection. On the other hand, additional factors, such as sepsis which was diagnosed in our patient and complex adaptive haemostasis present in the course of sepsis, may enhance different prothrombotic pathways, resulting in the activation of coagulation factors and may worsen the course of infection.[5] Finally, patients with severe haemophilia on regular prophylaxis with FVIII and/or emicizumab have their baseline

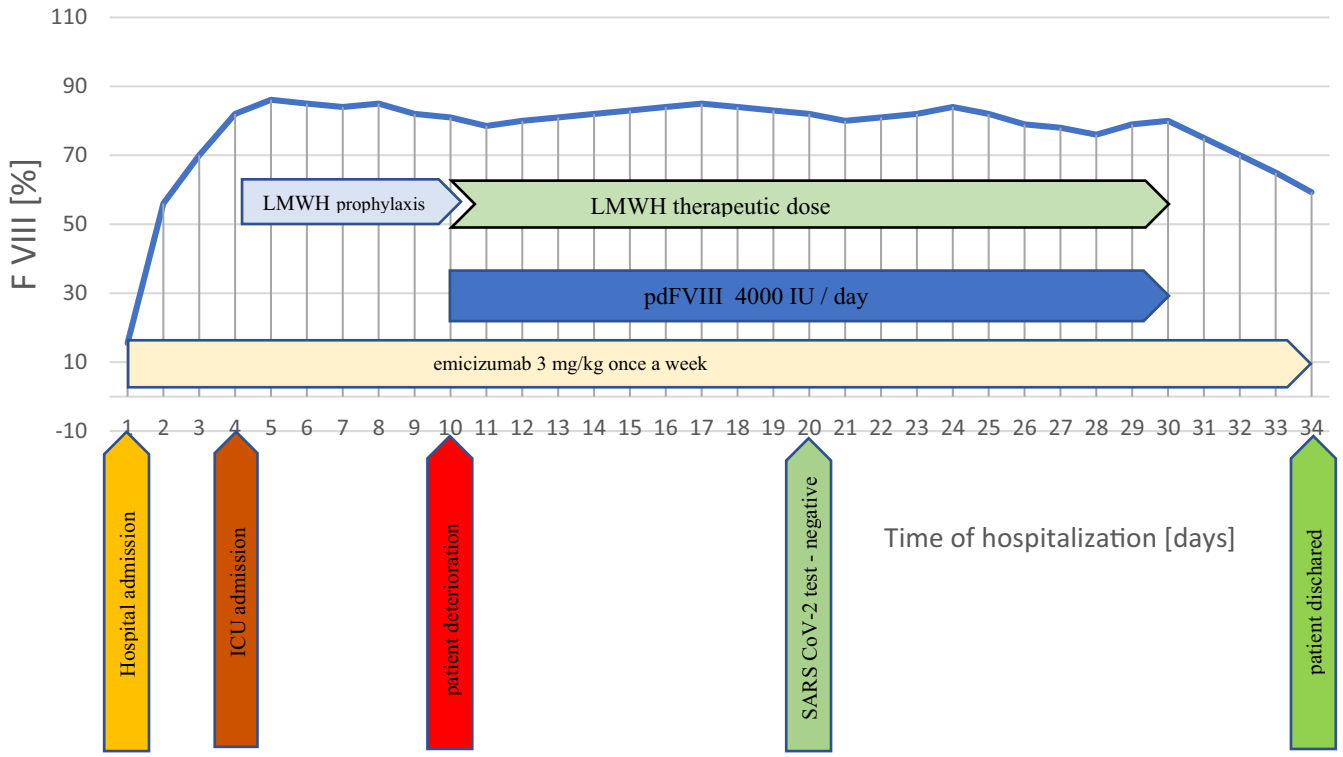

FIGURE 1 Bleeding prevention and thromboprophylaxis in patient with severe hemophilia A during hospitalization for COVID-19. LMWH- low molecular weight heparin, pdFVIII- plasma-derived Factor VIII, ICU- Intensive Care Unit, SARS-CoV-2- Severe acute respiratory syndrome coronavirus 2

haemostasis improved and therefore seem to be at higher risk of thrombotic complications as compared with severe haemophilia patients not treated prophylactically. The role of thromboprophylaxis in COVID-19 patients with haemophilia is debated. Pipe et al[8] recommend against the routine use of thromboprophylaxis in haemophilia A patients with mild COVID-19. Additional FVIII replacement therapy is not recommended in stationary patients on emicizumab prophylaxis as the level of haemostatic protection with emicizumab can support standard anticoagulant treatment without significant bleeding risk.[9] However, the use of thromboprophylaxis may be considered in combination with FVIII administration in severe cases and in precaution for invasive procedures.[8] Our patient had the following risk factors for severe COVID-19: age > 70 years, hypertension, history of numerous surgeries, immobilization, late hospitalization (advanced inflammatory changes in the lungs on admission) and intubation with subsequent tracheostomy. It is suggested that heparin's anti-inflammatory properties when used in patients with severe haemophilia A on emicizumab can prevent cytokine storm by acting as a protective agent against CAC.[9] As our patient's condition worsened, the dose of LMWH was increased, and additionally, pdFVIII was used under laboratory monitoring of FVIII plasma activity levels. According to the recommendations, the FVIII trough level was maintained within 80 IU/dL, avoiding increases above 100 IU/dL.[8,10] Rapid SARS-CoV-2 negativity was achieved despite the severe course, occurrence of complications and unfavourable prognostic factors. It is not entirely clear which of used drugs or perhaps a combination of remdesivir, dexamethasone, heparin and convalescent plasma as well as a complex supportive care had a decisive impact on the cure of the patient highlighting the need for additional research to optimize COVID-19 therapy.

The case presented here is, to our knowledge, the first in the literature documenting successful evolution of severe COVID-19 in a patient with severe haemophilia A on emicizumab prophylaxis. The case demonstrates the importance of close cooperation of physicians of many specialties, including a haematologist, anaesthesiologist, radiologists and infectious disease specialist as well as experienced laboratory specialists in the diagnostic and therapeutic process. Moreover, close monitoring of coagulation parameters and maintenance of appropriate FVIII levels were crucial in the therapy ensuring optimal haemostasis.

FUNDING INFORMATION

No funding was obtained for this study.

ACKNOWLEDGEMENTS

We thank native speakers of English from Ecorrector for the correction of the manuscript. The authors have received permission from the sponsor to publish the case report.

CONFLICTS OF INTEREST

D. Urbaniak-Kujda received speaker fees from Takeda, MM. Biernat received speaker fees from Takeda and Pfizer, outside the

submitted work. J. Windyga reports grants and honoraria for lectures from Baxalta/Shire/Takeda, Novo Nordisk, Octapharma, Rigel Pharmaceuticals, Roche, Alexion, CSL Behring, Sobi, Sanofi, Siemens, Werfen, Kedrion, LFB, outside the submitted work. The remaining authors declare no competing financial interests. The funders had no role in the design of the study; in the collection, analyses or interpretation of data; in the writing of the manuscript or in the decision to publish the results.

INFORMED CONSENT STATEMENT

Informed consent was obtained from subject involved in the study. Written informed consent has been obtained from the patient to publish this paper.

AUTHOR CONTRIBUTIONS

M.M. Biernat and D. Urbaniak-Kujda. involved in study concept and design; J. Jacków-Nowicka, T. Skalec contributed to resources; D. Urbaniak-Kujda wrote—original draft preparation, M.M. Biernat. wrote—review and editing; J. Windyga involved in critical supervision and T. Wróbel. supervised the study. All authors have read and agreed to the published version of the manuscript. ”

Donata Urbaniak-Kujda[1]
Monika Maria Biernat[1]
Tomasz Skalec[2]
Jagoda Jacków-Nowicka[3]
Jerzy Windyga[4]
Tomasz Wróbel[1]

[1]*Department of Haematology, Blood Neoplasms and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland*
Email: monika.biernat@umed.wroc.pl
[2]*Department of Anaesthesiology and Intensive Therapy, Wroclaw Medical University, Wrocław, Poland*
[3]*Department of Radiology, Wroclaw Medical University, Wrocław, Poland*
[4]*Department of Hemostasis Disorders and Internal Medicine, Laboratory of Hemostasis and Metabolic Diseases, Institute of Hematology and Transfusion Medicine, Warsaw, Poland*

ORCID

Monika Maria Biernat https://orcid.org/0000-0003-3161-3398
Jerzy Windyga https://orcid.org/0000-0001-7877-4784

REFERENCES

1. Dorgalaleh A, Dabbagh A, Tabibian S, et al. Patients with congenital bleeding disorders appear to be less severely affected by SARS-CoV-2: Is inherited hypocoagulability overcoming acquired hypercoagulability of coronavirus disease 2019. *Semin Thromb Hemost*. 2020;46:853–855.
2. Rivas-Pollmar MI, Álvarez-Román MT, Butta-Coll NV, Martín Salces M, García-Barcenilla S, Jiménez-Yuste V. Thromboprophylaxis in a patient with COVID-19 and severe hemophilia A on emicizumab prophylaxis. *J Thromb Haemost*. 2020;9:2202–2204. https://doi.org/10.1111/jth.14954.
3. Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. *N Engl J Med*. 2017;9:809–818.
4. Noun P, Ibrahim A, Hodroj MH, Fakhredin RB, Taher AT. COVID-19 in benign hematology: emerging challenges and special considerations for healthcare professionals. *Expert Rev Hematol*. 2020;10:1081–1092.
5. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood*. 2020;23:2033–2040.
6. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;2:120–128. https://doi.org/10.1056/NEJMoa2015432.
7. Pereira JP, Hantson P, Gerard L, et al. Management of COVID-19 coagulopathy in patient with severe haemophilia A. *Acta Haematol*. 2020;25:1–3.
8. Pipe SW, Kaczmarek R, Srivastava A, Pierce GF, Makris M. Hermans C : interim guidance; coagulation products safety, supply and access (CPSSA) Committee of the World Federation of Hemophilia Management of COVID-19-associated coagulopathy in persons with haemophilia. *Haemophilia*. 2021;27(1):41–48. https://doi.org/10.1111/hae.14191.
9. Weyand AC, Dorfman AL, Shavit JA, Pipe SW. Emicizumab prophylaxis to facilitate anticoagulant therapy for management of intra-atrial thrombosis in severe haemophilia with an inhibitor. *Haemophilia*. 2019;3:e203–e205.
10. World Federation of Hemophilia. *COVID-19 (coronavirus disease 2019) pandemic caused by SARS-CoV-2: practical recommendations for people with hemophilia*. Available at. https://news.wfh.org/covid-19-coronavirus-disease-2019-pandemic-caused-by-sars-cov-2-practical-recommendations-for-hemophilia-patients/. Accessed 21 Feb, 2021.