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COVID-19 can be associated with coagulopathy (CAC, COVID-19-associated coagulopathy) with a high prothrombotic risk based on an intense inflammatory response to viral infection leading to immunothrombosis through different procoagulant pathways. Emerging evidence suggests that the use of heparin in these patients could be associated with lower mortality. Emicizumab is a bispecific humanized monoclonal antibody that bridges activated factor IX (FIX) and factor X (FX), thereby restoring the function of missing factor VIIIa (FVIIIa) in hemophilia A. The use of emicizumab has been associated with thrombotic events in patients who also received high cumulative amounts of activated prothrombin complex concentrates. Although this risk is extremely low, there is a lack of evidence on whether CAC increases the thrombotic risk in patients on emicizumab prophylaxis. We present the case of a patient with severe hemophilia A in prophylaxis treatment with emicizumab; due to the potential thrombotic risk we decided to administer low molecular weight heparin as prophylaxis treatment without any thrombotic or bleeding complications.

**KEYWORDS**
COVID-19, emicizumab, hemophilia, thromboprophylaxis, thrombosis
He had human immunodeficiency virus (HIV) infection with antiretroviral treatment (lamivudine and darunavir-cobicistat) with good HIV virologic response and immunologic recovery. He had also been treated with antivirals for hepatitis C virus (HCV).

In November 2018 he was diagnosed with non-Hodgkin’s diffuse large activated-B cell lymphoma stage IV. He received six cycles of R-CHOP achieving a complete remission in May 2019.

In April 2020 he attended the emergency department with malaise, cough, myalgia, a feverish sensation, anosmia, and dysgeusia of 4 days’ duration. He had no dyspnea or chest pain. SARS-COV-2 polymerase chain reaction (PCR) was positive. The chest angio-TC showed no COVID-19-compatible disease or pulmonary thromboembolism. Because of the mild disease and respiratory stability, the patient was discharged with domiciliary follow-up by the hemophilia unit. He did not receive hydroxychloroquine as he had no radiological evidence of COVID-19 disease and because he was on HIV antiretroviral therapy.

Due to uncertainty about the risk of an increased prothrombotic state in CAC in association with emicizumab prophylaxis, thromboprophylaxis with low molecular weight heparin (LMWH), enoxaparin 40 mg once daily, was started. The patient’s clinical course was good without any bleeding or thrombotic complications and he continued on the same regimen of emicizumab prophylaxis; LMWH prophylaxis was stopped after the first negative SARS-CoV-2 PCR on day 26 of onset of symptoms and after 21 days of LMWH treatment. The patient consented to the use of his data and has been approved by the local Ethics Board of our center.

1 | DISCUSSION

Emicizumab prophylaxis is associated with great efficacy in patients with hemophilia without inhibitors.6 It has a good safety profile, the commonest side effect being injection site reactions in about 15% of patients. However, some very uncommon adverse events, such as thrombotic microangiopathy (TMA) and venous and arterial thrombosis, have been described, especially in patients with inhibitors and in association with bypassing agents.5

Emicizumab as a bispecific antibody with two binding regions, one recognizing FIX/factor IXa (FIXa) and the other recognizing FX/factor Xa (FXa), promotes FIXa-mediated FX activation. Both FVIIIa and emicizumab increase FXa generation, but with emicizumab, the factor that is limiting FXa generation is no longer FVIIIa but the amount of FIXa that is being generated.5 This is important because tenase activity is limited by its cofactor activity, so FXa generation is controlled by FVIIIa inactivation, which suggests, as proposed by Lenting et al, that emicizumab has no on/off mechanism.3 Furthermore, as emicizumab does not need previous activation to work as a cofactor, an increase in FIXa could contribute to thrombin generation.6 Regarding the location of FXa generation by emicizumab, it has been postulated that this is re-localized to areas of increased phosphatidyl-serine exposure.3 Finally, there is little data on patients receiving prophylaxis in the context of sepsis or major trauma.6

Emerging evidence shows that severe COVID-19 can be complicated by CAC.1,7 Inflammation is present in severe COVID-19 patients, with a subgroup exhibiting exacerbation in the inflammatory response with a cytokine storm. This inadequate inflammatory reaction is responsible for the progression of CAC with increased D-dimer, associated with a poorer prognosis.8 SARS-CoV-2 attacks the endothelial cells, expressing high levels of ACE2.9 This endotheliopathy leads to microvascular thrombosis and endothelial damage exposing phosphatidyl-serine.5

Available data on the management of thrombotic risk are limited and based on case series.10,11 Recommendations suggest that in cases in which an increased thrombotic risk is suspected, pharmacologic venous thromboembolism (VTE) prophylaxis in all hospitalized COVID-19 patients should be initiated as long as there is no contraindication.12 The ideal dose and type of heparin remains unclear, pending randomized trials on this subject.

Our case had an initial mild presentation of COVID-19 disease but presented an uncertain risk of CAC due to the prophylaxis with emicizumab. Bearing in mind the low risk of thrombosis with emicizumab in SHA without inhibitors, but because some of the mechanisms associated with the risk of thrombosis described above could be risk factors for the development of CAC, and in the absence of literature or guidelines for the management of such patients, our consensus clinical decision was to administer prophylactic doses of LMWH and to monitor laboratory parameters to follow up the disease and cytokine release storm.

LMWH inhibits mainly FXa, which cleaves factor II (FII) to factor IIa (FIIa), but like unfractionated heparin it also has indirect inhibition of FIIa itself. Some authors suggested that activated partial thromboplastin time (aPTT) could reflect the real clinical effect of LMWH under specific conditions.12 In our case the aPTT was always below the normal range, which corresponds to emicizumab treatment, so we decided to monitor thromboprophylaxis with anti-FXa levels, as these describe pharmacokinetics rather than pharmacodynamics, but to be sure not to exceed prophylactic levels.

The patient had no bleeding complications, but it was unclear when was the ideal time to stop thromboprophylaxis in the absence of guidelines: taking into account that the laboratory parameters had all been stable since the diagnosis (Table 1), we decided to stop thromboprophylaxis based on negative SARS-CoV-2 PCR. Fortunately, the laboratory findings of our patient did not worsen and the clinical course was also favorable.

This mild and favorable course of our patient with SHA on emicizumab prophylaxis could be interpreted in the same way as for approximately 85% of COVID-19 patients, ie, neither the hemophilia nor the emicizumab treatment has a significant influence on the course of the disease, or that, however SHA and/or emicizumab and/or HIV status has any protective effect against inflammation and immunothrombosis per se.

Otherwise, heparin has an anti-inflammatory effect and its use in a SHA patient on emicizumab prophylaxis could help to prevent a cytokine storm, having protective effect against CAC.
We do not know to what extent the protective effect of LMWH counteracts the potential prothrombotic state of COVID-19 and emicizumab. But we proposed the use of prophylactic dose of LMWH in SHA on emicizumab treatment at diagnosis, based on the low rate of bleeding complications associated with its use, the lack of predictive parameters of CAC development, and the potential prothrombotic state of emicizumab treatment in the context of sepsis induced coagulopathy.

CONFLICTS OF INTEREST
Victor Jimenez Yuste has received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Takeda, Bayer, CSL-Behring, Grifols, NovoNordisk, Sobi, Roche, Octapharma, and Pfizer. María Teresa Álvarez Román has received fees as an advisor for Bayer, Takeda, Roche, Pfizer, CSL Behring, Novartis, Novonordisk, and Amgen, and as a speaker at several meetings. This work was supported by FIS-Fondos FEDER FIS19/00631.

AUTHOR CONTRIBUTIONS
MIRP, MTAR, MMS, and VJY were responsible for the clinical management of the patient; SGB was the nurse who administered the treatment; and NBC was responsible for the laboratory tests.

REFERENCES
1. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033-2040.
2. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094-1099.
3. Lenting P-J, Denis C-V, Christophe O-D. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? Blood. 2017;130(23):2463-2468.
4. Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med. 2018;379(9):811-822.
5. Oldenburg J, Mahlangu J-N, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med. 2017;377(9):809-818.
6. Makris M, Hermans C. A golden age for haemophilia treatment? Haemophilia. 2018;24(2):175-176.
7. Kollia A, Kyriakoulis K-G, Dimakakos E, Poulakou G, Stergiou G-S, Syrigos K. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. Br J Haematol. 2020;189(5):846-847.
8. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost. 2020;18(6):1324-1329.
9. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. Lancet. 2020;395(10235):1517-1520.
10. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. Intensive Care Med. 2020;46:1089-1098.
11. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-1026.
12. Thomas O, Lybeck E, Strandberg K, Tynngård N, Schött U. Monitoring low molecular weight heparins at therapeutic levels: dose-responses of, and correlations and differences between aPTT, anti-factor Xa and thrombin generation assays. PLoS One. 2015;10(1):e0116835.