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CASE REPORT

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Portal vein thrombosis in a patient with severe hemophilia B: A challenging balanced management

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Key Clinical Message

The increased life expectancy in patients with hemophilia (PwH) over the last years has raised the incidence of comorbidities, including thromboembolic events. Thromboembolic events are rare in PwH and most of them occur in the presence of exogenous risk factors. There is still scarce scientific evidence on the optimal antithrombotic treatment and management approach in this population.

Abstract

In the hemophilic population thromboembolic events are rare. Most of them are often multifactorial and occur in the presence of both exogenous (orthopedic surgery, intensive replacement therapy, use of central venous catheters...) and endogenous (cardiovascular diseases) risk factors. We describe the case of a 43-year-old patient with severe hemophilia B (sHB) receiving prophylaxis with eftrenonacog alfa (rFIXFc) and antithrombotic treatment due to portal vein thrombosis. The patient was treated with extended half- life factor IX (EHL-FIX) prophylaxis maintaining higher trough levels to avoid new bleeding episodes associated to the underlying disease and the use of antithrombotic therapy with low molecular weight heparin. EHL-FIX concentrates allow prolonged intervals between intravenous infusions and higher hemostatic protection thanks to increased factor trough levels. This current case report provides clinical evidence in antithrombotic management in a patient with severe hemophilia B.

KEYWORDS

chronic diseases, hematology, pharmacology and pharmacy

1 | INTRODUCTION

Hemophilia B is a rare genetic bleeding disorder characterized by a FIX deficiency. Patients with severe hemophilia B (FIX <1 IU/dL) are more prone to develop spontaneous or traumatic bleeds mainly in joints or deep muscular tissues.

Thrombotic events in these patients are rare and occur mostly in the presence of multiple exogenous risk factors

such as orthopedic surgery, intensive replacement therapy, use of central venous catheters, etc., and/or in the presence of endogenous cardiovascular risk factors.[1–3]

Due to the increase in life expectancy of this population, these risks have become more frequent in patients with hemophilia (PwH)[1]; hence the need for guidelines on how to manage thromboembolic risk factors and thromboembolic events has become more relevant.

Recently, a guideline about antithrombotic treatment in PwH has been published. This guideline provides evidence and expert-opinion-based recommendations. The authors underlined that the occurrence of acute venous thromboembolisms (VTE) in PWH is very heterogeneous; hence a simple recommendation is not feasible.[2] In addition, many data on this field stems from PwH A.[2] Therefore, evidence in PwH B is required.

2 | CASE REPORT

We hereby describe the case of a 43-year-old patient with severe hemophilia B treated with plasma-derived FIX (pdFIX) on demand and no history of inhibitors. His annualized bleeding rate (ABR) was 9.27 and annualized joint bleeding rate (AjBR) was 3.71.

He had a history of hepatitis C (HCV) and human immunodeficiency virus (HIV) infections, caused by transfusions of contaminated blood products during his adolescence. The patient developed Child-Pugh A liver cirrhosis with portal hypertension and grade II esophageal varices, so primary prophylaxis with beta-blockers propranolol 20 mg every 12 h was started. The patient was monitored by the hepatologist. Liver enzymes were evaluated and liver ultrasound and elastography performed every 6 months since the diagnosis of cirrhosis.

He had received sofosbuvir in combination with simeprevir and ribavirin as HCV treatment. These therapies were effectives.

2.1 | Bleeding episode management

More than 8 years after the diagnosis of cirrhosis with portal hypertension and grade II esophageal varices, the patient visited the emergency room because of an acute upper gastrointestinal bleeding, which persisted despite the administration of pdFIX 40 IU/kg at home. No other symptoms were reported.

Physical examination revealed a 2–3 cm splenomegaly and the rectal examination, dark haematic-fecal remains without palpable hemorrhoids or masses. Blood test showed mild anemia (10.5 g/dL), with a hemoglobin decrease of 3 g/dL compared to previous.

An urgent gastroscopy was done after the administration of 50 IU/kg of pdFIX and somatostatin. Two grade III varicose cords with bleeding stigmata were identified. During the procedure, after the gagging effort, active bleeding from one of the varicose veins (which resolved spontaneously) was observed. Two elastic bands were placed on the varicose veins. Hemostatic treatment with pdFIX 50 IU/Kg every 12 h was continued to maintain trough FIX levels between 60 and 80 IU/dL.

As part of the study, an abdominal ultrasound was requested, detecting an ambiguous portal vein thrombosis. Therefore, the study was expanded with an abdominal computed tomography angiography (CTA), which confirmed partial thrombosis of the main portal vein and intrahepatic branches with significant signs of portal hypertension and esophageal varices, as well as paraoesophageal, fundic, coronary vein territory, and in the perisplenic area. Due to recent gastrointestinal bleeding, treatment with pdFIX concentrates was continued, as well as the monitoring of FIX levels monitoring. No antithrombotic treatment was initiated. He continued treatment for 1 week after the onset of symptoms.

Once the bleeding episode was resolved, the patient got discharged to continue his follow-up as an outpatient.

2.2 | Antithrombotic management

Due to the high risk of portal thrombosis progression and consequently worsening of portal hypertension and esophageal varices, antithrombotic treatment with low molecular weight heparin (LMWH) was initiated once the bleed was resolved and the hemostatic treatment was stable.

Since there was a clear need for therapeutic anticoagulant treatment, it was decided to start prophylaxis with pdFIX 60 IU/Kg three times a week to avoid increasing his bleeding risk during the anticoagulation treatment. The aim was to maintain FIX plasma levels above 15 IU/dL. Patient complaint about intravenous (i.v) injection difficulties, hence other treatment alternatives were explored and switching to extended half-life (EHL) FIX was suggested.

Once EHL FIX products were available, the patient was switched to eftrenonacog alfa (rFIXFc) aiming to reduce the number of weekly i.v. infusions and maintaining the target trough levels of FIX. The switch was guided by pharmacokinetics using the Web Accessible Population Pharmacokinetic Service-Hemophilia (WAPPS-Hemo). In this case, the initial dose of rFIXFc was 50 IU/kg and was administered 1 month after the bleeding episode.

Blood samples were collected after 4, 48 h, 5, and 7 days after the first infusion of rFIXFc, as well as before. The terminal half-life equilibrated estimated by WAPPS-Hemo was 109.5 h, clearance was 0, 12 L/h and apparent volume

of distribution at steady state was 15,70 L. Following WAPPS-Hemo's estimates, rFIXFc prophylaxis was established at 58 IU/kg iv every 7 days.

Regarding antithrombotic treatment, given the recent haemorrhagic symptoms, the decision was taken to start subcutaneous LMWH with enoxaparin at a prophylactic dose (0.5 mg/kg/24 h), which was increased to intermediate doses (1 mg/kg/24 h) after 1 week, after making sure there was no rebleed. Thereafter, anti-Xa activity was monitored to maintain values between 0.4 and 0.5 IU/mL.

Two weeks after initiating the antithrombotic treatment, the patient developed painless haematuria, therefore, according to the pharmacokinetics parameters, prophylactic treatment with rFIXFc was adjusted to 58 IU/kg i.v every 4 days. No further bleeding events were experienced since the dose adjustment.

After 3 months of anticoagulant treatment with LMWH at an intermediate dose, a new abdominal ultrasound was ordered, which revealed signs of chronic liver disease, portal hypertension, and persistent thrombosis. Due to the lack of improvement in the portal thrombosis despite anticoagulation with intermediate doses of LMWH, it was decided, in a multidisciplinary session, to suspend the antithrombotic treatment, since the benefit–risk balance of continuing the current antithrombotic therapy or increasing the LMWH doses did not seem favorable. It is well known that anticoagulation and fibrinolytic therapies are more effective in treating acute rather than chronic thrombosis so in that notice, the decision was to stop anticoagulation to avoid any additional bleeding risk since the possibilities of gaining any benefit for the patient were low.

After suspending antithrombotic treatment, the patient continued receiving prophylactic treatment with rFIXFc adjusted to pharmacokinetics, at a dose of 58UI/kg i.v every 14 days (trough levels 5.6 IU/dL). From the beginning of the prophylaxis, the patient did not experience any bleeding episodes even when he was receiving lower doses than the one recommended in the summary of product characteristics (SmPC).

Currently, the patient continues to be monitored for hepatology, infectious diseases, and hematology every 6 months where a new ultrasound, fibroscan and blood test are perfomed. No progression of the thrombosis has been observed.

3 | DISCUSSION

There is not much data available in the literature on the challenging management of thrombosis in PwH B.[2] We describe a case about a patient with hemophilia B who develops a thrombosis and requires a balanced treatment between anticoagulation and prophylaxis with FIX concentrates.

In the hemophilic population thromboembolic events have been considered rare. Most of them are often multifactorial and occur in the presence of multiple risk factors.[1,7] Among the exogenous factors in PwH is orthopedic surgery, which confer risk due to the procedure itself as well as for the bed-resting period and perioperative intensive replacement therapy.[1–3,6] Most cases described in the literature are in this context, although their incidence is much lower than what described in the general population (0.5% vs. 4.3%).[1–3] Other exogenous risk factors are the use of central venous catheters, treatment with bypass agents in PwH with inhibitors, and patients with acquired immunodeficiency syndrome (AIDS).[7]

Although our patient has HIV and received treatment for it, he does not have AIDS which is considered a risk factor.

Regarding endogenous factors, the presence of various hereditary thrombophilias has been described in patients with congenital coagulation deficits, which in the presence of one or more of the aforementioned risk factors, could facilitate the appearance of thrombosis in these patients.[7]

Concerning portal thrombosis, liver cirrhosis is the main predisposing factor in the general population, regardless of its etiology, with an annual incidence that ranges between 0.6%–1.6%, being higher in patients with greater liver damage.[5] While in non-cirrhotic patients, hereditary or acquired thrombophilias have been described as a relevant predisposing factor.[8]

In our case, the patient had a history of HCV with known liver cirrhosis and portal hypertension associated to grade II esophageal varices. These concomitant conditions might have predisposed the patient to develop the mentioned a portal vein thrombosis since hereditary thrombophilia and other risks factors were ruled out.

It is described in the literature that in the 1980s, both arterial and venous thrombotic complications were observed in hemophilia B patients undergoing treatment with prothrombin complex concentrates. Such concentrates have been successfully used for the treatment of bleeding episodes of hemophilia B patients over the past 30 years. However, they have been replaced by highly purified factor IX concentrates, significantly reducing thrombosis in these patients.[7]

The patient in question did not received treatment with prothrombin complex concentrates or any other bypass agent ever since he does not have history of inhibitors. Neither, he had not received intensive replacement therapy prior to the VTE diagnosis.

There is no consensus in the literature on the target level of FIX to start anticoagulation, type of antithrombotic treatment and its duration. Some authors state that bleeding phenotype of the patient, characteristics of the

anticoagulant, intensity of anticoagulant therapy and its duration should be individually balanced and holistically approached.[2,3,4]

In our patient, the aim was to maintain FIX plasma levels above 15 IU/dL. Regarding the antithrombotic treatment, LMWH was chosen, due to its short half-life, easy monitoring and easy reversal if needed.

4 | CONCLUSION

In conclusion, we present a case of portal vein thrombosis in a patient with severe hemophilia B with a recent bleeding episode and the challenges finding the balance between antithrombotic treatment and FIX prophylaxis. The patient was treated with FIX-EHL prophylaxis which was guided with pharmacokinetic tool WAPPS-Hemo, which enabled less frequent FIX infusions maintaining higher trough levels to avoid new bleeding episodes associated to the underlying disease and the use of antithrombotic therapy. For the antithrombotic treatment, LMWH was chosen, due to its short half-life, easy monitoring and easy reversal if needed. The treatment was started once the recent bleeding episode was resolved and the prophylactic treatment with FIX was stable. This case was considered relevant due to the potential increase in thromboembolic events in people with hemophilia due to the current increase in their life expectancy and because there is still scarce scientific evidence on the optimal management approach.

AUTHOR CONTRIBUTIONS

Olga Benitez-Hidalgo: Conceptualization; methodology; project administration; writing – original draft. **Milagros Suito Alcántara:** Writing – review and editing. **Maria Fernanda Martnez Garcia:** Writing – review and editing. **Desiree Campoy:** Writing – review and editing. **Pavel Olivera:** Writing – review and editing. **Mercedes Gironella Mesa:** Writing – review and editing. **Juan Carlos Juarez-Gimenez:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

The data related to this study are available from the corresponding author upon reasonable request.

CONSENT

We confirm that the written informed patient consent has been collected for publication of this case report.

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