Treatment of high-risk bleeding with susoctocog alfa in a patient with acquired haemophilia A and a nosocomial severe acute respiratory syndrome coronavirus 2 infection

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SUMMARY

We report the case of a man in his early 70s with idiopathic acquired haemophilia A and persistent high-titre type II inhibitors on immunosuppressive treatment to eradicate the inhibitor. As complications, he had a nosocomial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which caused severe pneumonia and an explosive inflammatory reaction that required tocilizumab and remdesivir treatment, and a high-risk retroperitoneal haematoma. Recombinant porcine factor VIII, susoctocog alfa, was requested from the Pharmacy Service in view of the extreme risk of thromboembolism resulting from the concomitant inflammatory storm caused by SARS-CoV-2. Improvement in the SARS-CoV-2 infection made it possible to complete the immunosuppressive treatment with rituximab. The patient was discharged with mycophenolate mofetil as immunosuppressive treatment after 89 days in hospital and 22 days of treatment with susoctocog alfa. His SARS-CoV-2 infection resolved and the haematoma evolved favourably.

BACKGROUND

Acquired haemophilia A (AHA) is an autoimmune disease resulting from the development of inhibitory autoantibodies targeted against endogenous human coagulation factor VIII (FVIII). These autoantibodies affect FVIII activity and predispose to severe, potentially fatal, bleeding episodes.[1]

Unlike alloantibodies against exogenous FVIII, which are seen in patients with congenital haemophilia, these autoantibodies are characterised by not fixing complement, having an in vitro time- and temperature-dependent action and a low incidence of cross-reactions with heterologous sources of FVIII such as porcine. Disease control is based on controlling and preventing bleeding episodes, eradicating the inhibitor and treating the underlying disease.[2] Bypassing agents such as activated prothrombin complex concentrate (APCC) or recombinant activated factor VII (rFVIIa) are the first-line treatment for acute bleeding, although it has drawbacks such as the technical inability to measure its activity levels and its association with the development of thrombosis, with a similar incidence for both bypassing agents (2.9% for rFVIIa and 4.8% for APCC).[1 3]

In the present case, specialists of the Haematology Service composed a multidisciplinary team comprising specialists of the Internal Medicine Service and Pharmacy Service. Acute treatment of the retroperitoneal haemorrhage with susoctocog alfa was proposed, in view of the condition and the extremely high risk of thromboembolic phenomena resulting from the concomitant inflammatory storm caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4]

CASE PRESENTATION

We report the case of a man in his early 70s weighing 66 kg with permanent atrial fibrillation (AF) treated with apixaban, who attended the Emergency Department for mucocutaneous ecchymosis. He denied a history of coagulopathies and was admitted to the hospital for a clotting study. He was diagnosed with idiopathic AHA with high-titre type II inhibitors (prothrombin time 1.16 s (0.85–1.2), activated partial thromboplastin time 2.12 s (0.81–1.3), thrombin time 1.0 s (0.96–1.25), fibrinogen 359.0 mg/dL (170.0–470.0), coagulative assay FVIII (FVIII:C) 1.8 IU/dL (54.0–155.0), chromogenic assay FVIII (FVIII:Cr) 5.0 IU/dL (54.0–155.0), FVIII inhibitor 21.0 BU/dL (0.0–0.4), von Willebrand (vWF) antigen 157.4 IU/dL (41.0–156.0), vWF:ristocetin cofactor 162.8 IU/dL (50.0–158.0)). In view of the clinical data, rFVIIa (90 μg/kg every 3 hours) was initiated but was stopped for the management of skin haemorrhagic diathesis and immunosuppressive treatment for inhibitor eradication (1 mg/kg daily prednisone and 375 mg/m^2 weekly rituximab). Over 14 days, 407 mg of rFVIIa were administered.

Prior to the completion of the fourth dose of rituximab, the patient was nosocomially infected with SARS-CoV-2. Clotting control showed FVIII:C 4.2 IU/dL, D-dimer (DD) 302.0 ng/mL (0.0–500.0) and FVIII:Cr 7.6 IU/dL, so immunosuppressive treatment was maintained with prednisone. SARS-CoV-2 treatment with lopinavir/ritonavir and hydroxychloroquine was initiated, applying the validated protocol at that time. Mild spontaneous bleeding in the lip appeared so clotting control was repeated, showing persistent AHA: FVIII:C 4.9 IU/dL, FVIII:Cr 6.9 IU/dL and FVIII inhibitor 47.0 BU/dL. Restarting bypass therapy was considered, without eventually becoming necessary. Despite antiviral treatment for 10 days,

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the patient developed a fever and bilateral ground-glass opacities of the lungs were found on imaging. Analytical control showed a systemic inflammatory storm (DD 18 431.0 ng/mL, ferritin 8658.0 ng/mL (30.0–400.0), interleukin-6 379 pg/mL (0.0–5.9), C-reactive protein 12.01 mg/dL (0.0–1.0)). In this context, it was decided to administer tocilizumab (600 mg single dose), remdesivir in clinical trial (200 mg loading dose followed by 100 mg for 9 days), methylprednisolone and prophylactic enoxaparin (40 mg/day) owing to the high risk of thromboembolism.[5]

Clotting control at the start of the medication showed FVIII:C 8.7 IU/dL, DD 9646.0 ng/mL and FVIII:Cr 12.0 IU/dL. After 72 hours, a decrease in DD and ferritin was observed and enoxaparin was discontinued. The patient complained of pain in the lower left limb and clinical examination showed a haematoma in the psoas and iliac muscles and in the left retroperitoneal space. Clotting control (FVIII:C 8.9 IU/dL, DD 1193.0 ng/mL and FVIII:Cr 6.1 IU/dL) and its clinical stability guided conservative management, given the thromboembolic risk with both rFVIIa treatment and SARS-CoV-2 disease.[4 6]

INVESTIGATIONS

Considering the high risk of thrombosis in this patient as a result of non-anticoagulated AF during hospital admission, SARS-CoV-2 infection with increased DD and being bedridden, treatment was re-evaluated after an increase was seen in the size of the haematoma and FVIII:C 19.0 IU/dL.

In view of this situation, it was decided to request the use of susoctocog alfa, a B-domain deleted, recombinant porcine sequence FVIII concentrate that is licensed for AHA. It acts as a cofactor of activated factor IX, accelerating factor X conversion into activated factor X, which ultimately converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.[6 7]

Unlike bypassing agents, susoctocog alfa provides FVIII and can be monitored using existing assays, allowing individualised dosing.[8 9] Furthermore, the drug is effective even when inhibitor titres are high, the risk of thrombosis associated with it is lower than with rFVIIa[10] and its dosing schedule (every 12–24 hours instead of every 3–4 hours with rFVIIa) allows a reduced number of nursing staff contacts with the patient infected with SARS-CoV-2.

TREATMENT

Susoctocog alfa is not available in Spain, so the Pharmacy Service had to request and acquisition it through the application of medicines in special situations of the Spanish Agency of Medicines and Medical Devices. Pharmacists analysed the potential risks in its use and complex practical handling to prepare the total dose since each powder vial contains 500 units (13 vials for initial dose preparation), also taking into account the short stability of the drug after reconstitution (3 hours). According to the established requirements for the preparation of drugs and the recommendations of the pharmaceutical company, the Pharmacy Service prepared a ready-to-use syringe labelled with information on its correct administration.[11] All the treatment manipulation was performed in a laminar flow cabinet. As an additionally safety measure, the Pharmacy Service verified knowledge of administration of the drug by nursing staff for each dose and guaranteed traceability and dosage compliance within the stability interval of the preparation. This was the first time susoctocog alfa had been used in our hospital. Special attention was paid to the follow-up given the high complexity of the concomitant pathology and the large number of prescribed treatments, including a clinical trial product.

Although the recommended loading dose for recombinant porcine FVIII is 200 IU/kg,[7] in our case clinicians decided to use lower doses. The first dose prescribed (100 IU/kg, 6500 IU) was administered at least 4 hours after the last dose of rFVIIa, followed by a second dose 12 hours later (50 IU/kg, 3000 IU). FVIII levels were determined by coagulative and chromogenic assays, and dose adjustment of susoctocog alfa was made based on FVIII:C measured, as shown in figure 1.

Forty-eight hours after starting susoctocog alfa, antithrombotic prophylaxis with enoxaparin (40 mg/day) was restarted when FVIII levels were above 50 IU/dL.[10] After 22 days, susoctocog alfa was suspended due to good clinical and radiological evolution of the haematoma. Twenty-one doses of susoctocog alfa were administered, 40 500 IU in total, without any related adverse effects being detected.

With good control of the haematoma and SARS-CoV-2 disease clearly improving, it was proposed that immunosuppressive treatment be completed for the eradication of FVIII inhibitor with the administration of the fourth dose of rituximab and oral

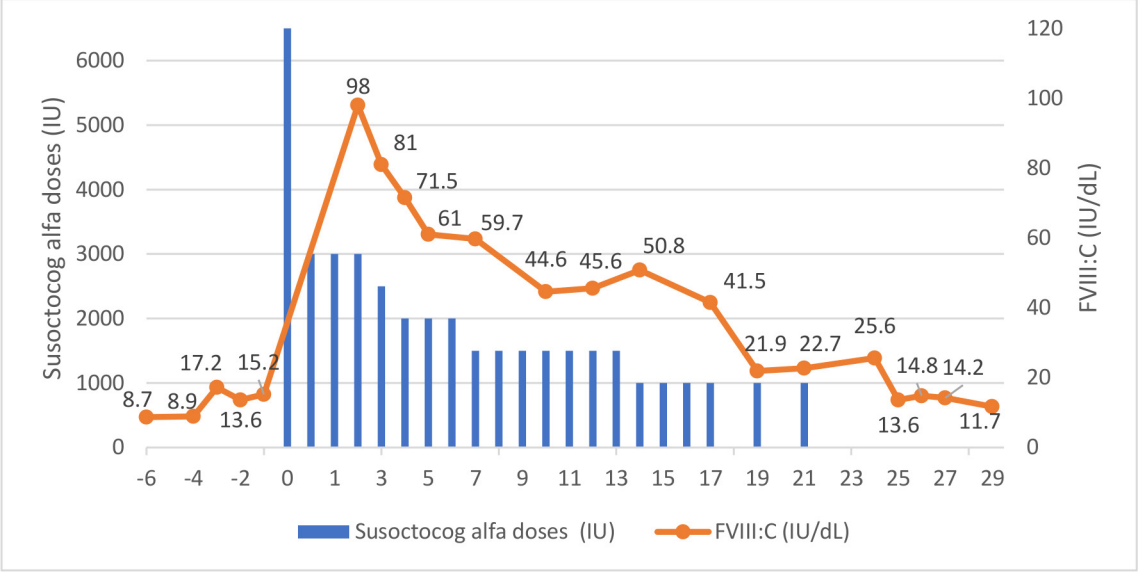

Figure 1 Adjustment of susoctocog alfa dosage and posology over time according to coagulative assay FVIII (FVIII:C) plasma levels.

prednisone (1 mg/kg/day). Since no increase in the FVIII level was observed as quickly as expected, the second line of immunosuppressive treatment with mycophenolate mofetil (MMF) was started.[10]

With SARS-CoV-2 infection resolved, bleeding controlled and clotting parameters in range (FVIII:C 23.1 IU/dL, DD 589.0 ng/mL, FVIII:Cr 24.4 IU/dL, fibrinogen 381.0 mg/dL), the patient was discharged on MMF (1000 mg every 12 hours). As it is an off-label indication, MMF was dispensed by the Pharmacy Service, where pharmacists still continue the pharmacotherapeutic follow-up.

OUTCOME AND FOLLOW-UP

AHA and chronic pathologies were stable and no susoctocog alfa-related adverse events have been observed since hospital discharge. Sustainable FVIII:C and FVIII:Cr levels above 30.0 IU/dL and a moderate thrombotic risk due to AF have allowed full-dose apixaban to be restarted while the dose of MMF continues to be reduced. Neither inhibitor titres nor immunity against SARS-Cov-2 have become evident 2 months after hospital discharge.

DISCUSSION

Susoctocog alfa is a safe and effective treatment in controlling severe acute AHA bleeding. In our clinical case, potential bleeding control involved a high risk of thromboembolic events owing to non-treated AF during hospital admission, prolonged period in bed and SARS-CoV-2 disease with acute phase reactants and elevated DD.[12]

In our case, as in other published experiences in real clinical practice, haemostatic effectiveness and absence of adverse events were observed, using lower starting doses than those used in pivotal clinical trials.[13 14] Moreover, although the inhibitor level was high at the beginning of the treatment, no cross-reactivity was observed between the inhibitor and susoctocog alfa. Data extracted from a prospective AHA cohort study showed that titres above 100.0 BU/mL predicted a cross-reactivity of 97.0%, although in our case the inhibitor titre was 47.0 BU/mL when susoctocog alfa was initiated.[15]

The economic impact of bypassing agents in AHA requires continuous evaluation during the therapeutic course.[16] In our case, the cost of 407 mg of rFVIIa and 40 500 IU of susoctocog alfa was 218 697.38 Euros and 63 180 Euros, respectively. Furthermore, the use of a lower initial dose of susoctocog alfa than that used in pivotal clinical trials contributed to a lower total consumption than initially expected.[13]

Learning points

- A multidisciplinary approach is essential for the dissemination of knowledge about AHA when dealing with highly complex and fragile patients.
- The ability to adjust susoctocog alfa dosage by determination of the levels of FVIII, activated partial thromboplastin time or prothrombin time, among others, is an important advantage in its monitoring compared with bypassing agents, the haemostatic effect of which is assessed clinically.
- Susoctocog alfa allowed haemostatic treatment without excessive thrombotic risk.

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