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CASE REPORT

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Extended half-life rFIX in major surgery—How to improve clinical practice: An intraindividual comparison

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Abstract

Practical, safe, and effective hemostatic approach to orthopedic surgery using Extended Half-Life factor IX in hemophilia B. By intraindividual comparison, we found a lower FIX consumption, number of infusions, and cost compared to plasma-derived FIX.

KEYWORDS

extended half-life FIX, hemophilia B, major surgery, orthopedic, pharmacokinetic, real-life experience

1 | INTRODUCTION

Hemophilia is the most common bleeding disorder, related to a congenital or acquired deficiency of factor VIII or IX. The most common complication is the musculoskeletal bleeding, particularly in specific joints, the so-called "*target joints*". Patients with hemophilia, particularly those suffering from moderate-to-severe hemophilia often develop a serious joint involvement, the so-called "hemophilic arthropathy". The most commonly affected joints are knees, elbows, and ankles,[1] and nonetheless, shoulders and hips can be damaged to some extent.[2] Orthopedic surgery experiences in patients with hemophilia are limited.[3-5] Like all invasive procedure in this kind of patients, orthopedic surgery requires prophylactic administration of the missing factor both at preoperative and postoperative level. Recently, extended half-life (EHL) concentrates for hemophilia A and B are being introduced in the prophylaxis and treatment of bleeding.[6] Nevertheless, their use is still limited and surgery guidelines are quite conservative and suggest caution.[7] In this regard, various relevant issues are under debate, such as cost-effective treatment and cost-saving pharmacokinetic (PK) approach.[8]

2 | CASE REPORT

Here, we report our replacement strategy population PK-guided with EHL recombinant factor IX Fc fusion product (rFIXFc,eftrenonacog alfa) in a 68-year-old male patient with moderate-severe hemophilia B (FIX 0.029 U/dL) and

needle phobia, who underwent left hip replacement. We also assessed the total burden of surgery in terms of hemophilia-related therapy and performed a comparison with a previous knee replacement under plasma-derived FIX (pdFIX) prophylaxis effectuated 5 years before in the same patient.

Genetic mutation had been previously characterized: The patient carried a point mutation with missense effect Cys28Tyr. Of note, this mutation is present in patients with moderate/severe hemophilia B. In 2017, he was treated successfully with direct antiviral agents for HCV infection. No other coinfections were known.

Hemophilia Joint Health Score (HJHS) was 15 at the time of surgery. Central venous access was positioned some days before surgery after a single infusion of 70 U/kg rFIXFc. Data from PK with rFIXFc are depicted in Figure 1

Based on PK data, a bolus of 80 IU/Kg rFIXFc was infused before surgery, followed by 12 IU/kg at +8 hours after surgery. From day +1 to day +5, 60 IU/kg/d rFIXFc was infused on average and then from day +6, 70 IU/kg every 48 hours. From day +11 to +21, rFIXFc was infused three times a week and afterward once a week until the end of the rehabilitation period. Thromboprophylaxis was started at +12 hours from surgery because of old age and leg varices, and it was stopped at patient discharge.

We evaluated trough FIX levels during perioperative period using one-stage assay (Synthasil-Werfen) at +8 hours, day +1, +2, +5, +10, and +39, and we verified that they were consistent with expected values based on the PK analysis performed before surgery. Trough levels were kept between 40% and 60% from day +1 to +8 and between 20% and 30% from day +9 to the end of physiotherapy.

According to surgeon assessment, hemostasis was excellent.[9] Median rFIXFc consumption was 57U/kg/d from day 0 to +10, and it was 10U//Kg/d from day +11 to +40. Three red blood cell units were transfused in day +2. The total number of infusions was 9 from day 0 to +11 and 6 from day +12 to +40. No adverse events occurred. The patient was discharged on day +16 and started physiotherapy as an outpatient. His compliance was good, thanks to the low need for infusions.

Prophylaxis with eftrenonacog alfa 75 U/kg every 14 days is still ongoing both during hydro-kinesitherapy and long-term prevention of bleeding, keeping a trough level of 0.07 U/dL, with no adverse events, after six months from surgery.

3 | DISCUSSION

According to published data, rFIXFc improves both long-term prophylaxis and surgery management compared with conventional FIX therapy.[10] To confirm such data, we matched intraindividual total FIX consumption, the number of infusions and time to patient discharge for the hip replacement (THR) and the knee replacement (TKR) performed 5 years before, which was also PK-guided. This comparison allows to reduce confounding factors such as individual pharmacokinetics features and different bleeding phenotype.

During the left TKR, median pdFIX consumption was 90 U/kg from day 0 to +10 and 50 U/kg from day +11 to +40; burden of infusions was higher, with 14 infusions from day 0 to +10 and 20 from day +11 to +40; the patient was discharged on day +21 due to difficulties in infusing replacement therapy. No transfusion was needed, and no differences were observed in the number of FIX dosing. Despite an initial functional good recovery, the patient stopped prophylaxis early because of needle phobia and in the following months he experienced new bleeding events with partial loss of flection (from 75° to 40°).

Figure 2 shows a cost analysis of both surgeries, as well as a comparison in terms of replacement therapy, hospitalization, and other procedures.

In conclusion, we reported a practical surgical approach to major surgery using EHL-FIX. Previous data on FIX concentrate consumption during surgery are heterogeneous in terms of hemophilia severity and type of surgery,[11,12] and cannot drive directly the clinical practice. However, our approach

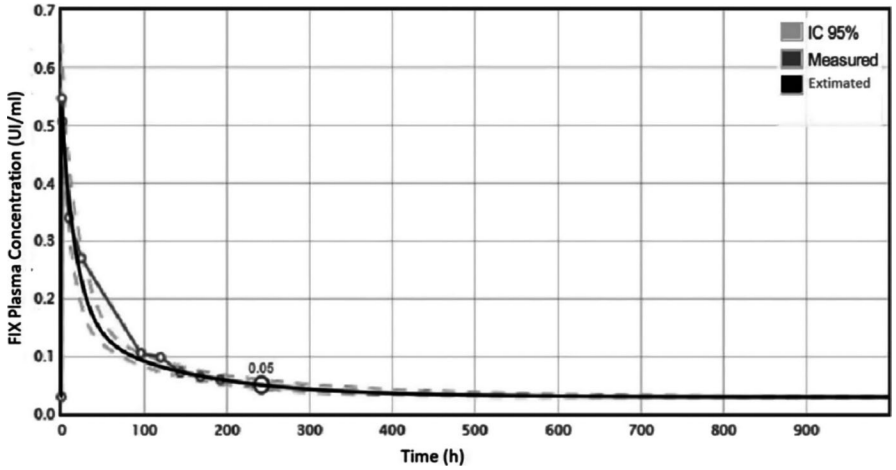

FIGURE 1 Trough Level at 241.75 h postinfusion of 48.2 UI/kg of rFIXc

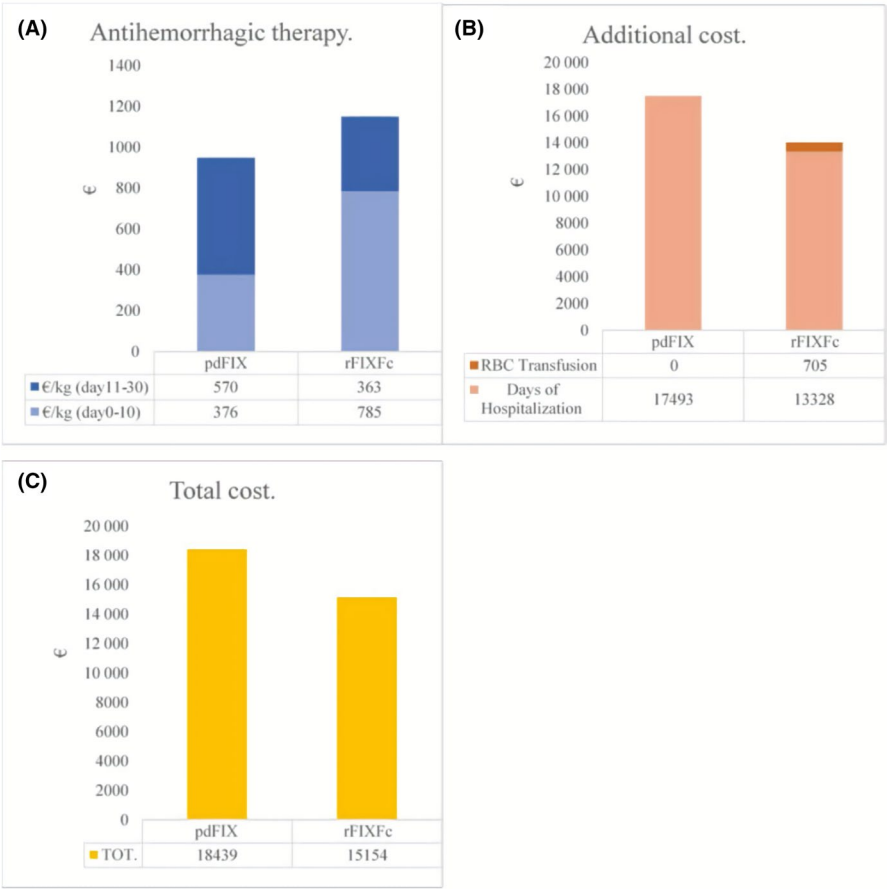

FIGURE 2 Comparison in terms of cost between the two surgical procedures: cost of antihemorrhagic therapy (A), cost of hospitalization and RBC transfusions (B), and total cost (C)

proved to be safe and effective. Furthermore, in agreement with the retrospective OPTI-CLOT study,[13] target trough levels can be safely kept at a lower level than previously suggested.[14] By an intraindividual comparison, our case showed a reduction in total FIX consumption using eftrenonacog alfa versus pdFIX and switching from the standard half-life to the EHL product did not increase costs, in contrast with data from real-world analysis during prophylaxis.[8] Finally, EHL allowed higher compliance in long-term prophylaxis and helped to maintain the benefit from surgery, which is the main issue with orthopedic procedure in patients with hemophilia [4].

CONFLICT OF INTEREST

FV: is an accommodation consultant bureau for Roche and Bayer. AB: is an accommodation consultant bureau for Roche, Kedrion, Bayer, and Novo Nordisk. JAG: is an accommodation consultant bureau for Kedrion and received honoraria from Pfizer. CD: is an accommodation consultant bureau for Novo Nordisk.

AUTHOR CONTRIBUTIONS

FV: is the primary investigator for this case report and wrote this manuscript. JAG and CD: provided critical feedback and helped shape the manuscript. AV and ED: made pharmacokinetic study and FIX assays during physiotherapy and follow-up. BM: made FIX assays during surgery. ED: MB: is Head of the Hematology Division where the patient received treatment. AB: wrote and supervised the manuscript. All authors discussed the results and contributed to the final manuscript.

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