

Inhibitors in hemophilia B in the era of extended half-life FIX concentrates: a case report

Inhibidores en hemofilia B en la era de los concentrados de FIX de vida media extendida: a propósito de un caso

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Introduction

The development of inhibitors is currently recognized as the most important complication of replacement therapy in patients with hemophilia. In patients with hemophilia B (HB), the risk of developing an inhibitor is lower than in patients with hemophilia A (HA). The reported frequency of inhibitor development is less than 5% among all patients with HB and between 9% and 23% in cases with severe disease. Approximately 80% of the inhibitors that develop in HB are high-responding.¹

Inhibitors develop as a consequence of a multifactorial process in which both genetic and non-genetic risk factors are involved; however, in HB – and probably due to the small number of patients who develop an inhibitor – there is limited information establishing a relationship between their occurrence and non-genetic risk factors.

Objective

To report the experience with the use of recombinant FIX concentrate fused to recombinant albumin in the management of a patient diagnosed with severe HB who, after developing an inhibitor and after three failed attempts at immune tolerance induction (ITI) therapy with standard half-life recombinant FIX concentrate

(SHL-rFIX), including the use of immunosuppression, achieved complete success after switching to Idelvion® (albutrepenonacog alfa, an extended half-life FIX concentrate fused to recombinant albumin, rFIX-FP).

Case description

This is the case of a 17-year-old adolescent diagnosed with severe HB (FIX 0,6%) at 6 months of age in the context of a spontaneous cerebral hemorrhage. Intensive treatment with SHL-rFIX was initiated for 21 days, which required the placement of a first port-a-cath. After this period, the patient was discharged and recovered without sequelae. At that time, prophylaxis with SHL-rFIX was initiated at a dose of 40 IU/kg, 3 times per week. The result of the genetic study revealed a mutation (guanine deletion in exon 2 [nucleotide 6403] of the *F9* gene) resulting in a stop codon. During childhood, the patient exhibited a severe hemorrhagic phenotype with multiple bleeding episodes up to the age of 7 years, particularly in the left ankle, despite maintaining trough levels > 1-2%. Until that time, all inhibitor determinations had been persistently negative. At the age of 7 years, and after more than 500 exposure days (ED), a high-titer inhibitor was detected (32 Bethesda units [BU]) with type 2 kinetics. At that time, daily ITI therapy was initiated (dose of 100 IU/kg).

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Date of reception: 09-09-2024

Date of acceptance: 23-05-2025

DOI: 10.24875/RHT.M25000073

Available online: 04-05-2026

Hemost Trombos (Eng). 2026;3(1):29-33

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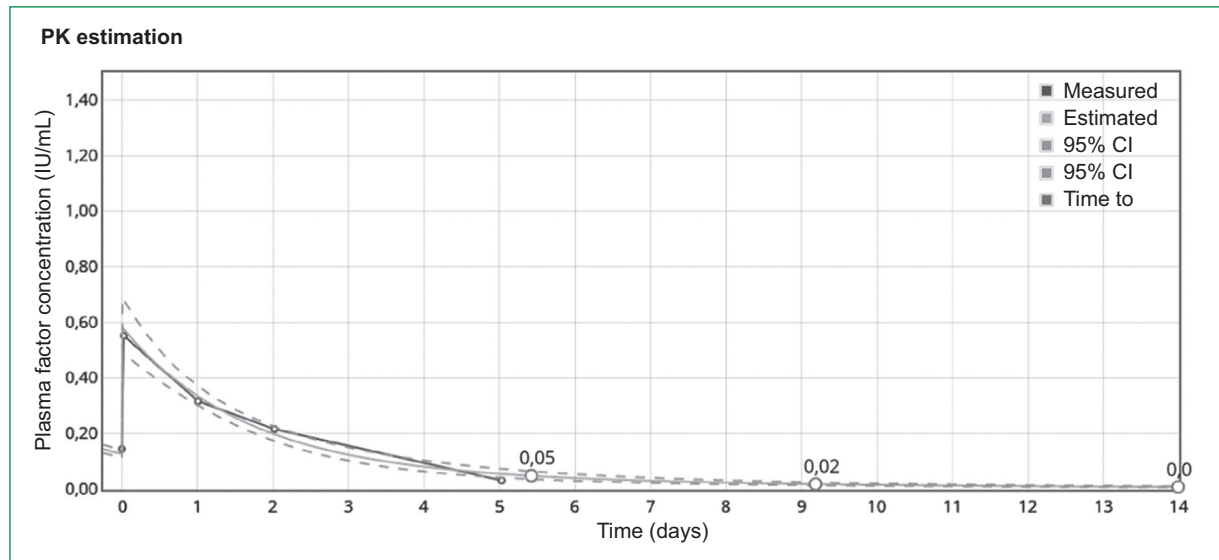


Figure 1. First pharmacokinetic evaluation with rFIX-FP (July 2023). Balanced estimation. CFIX: FIX concentrates; 95% CI: 95% confidence interval.

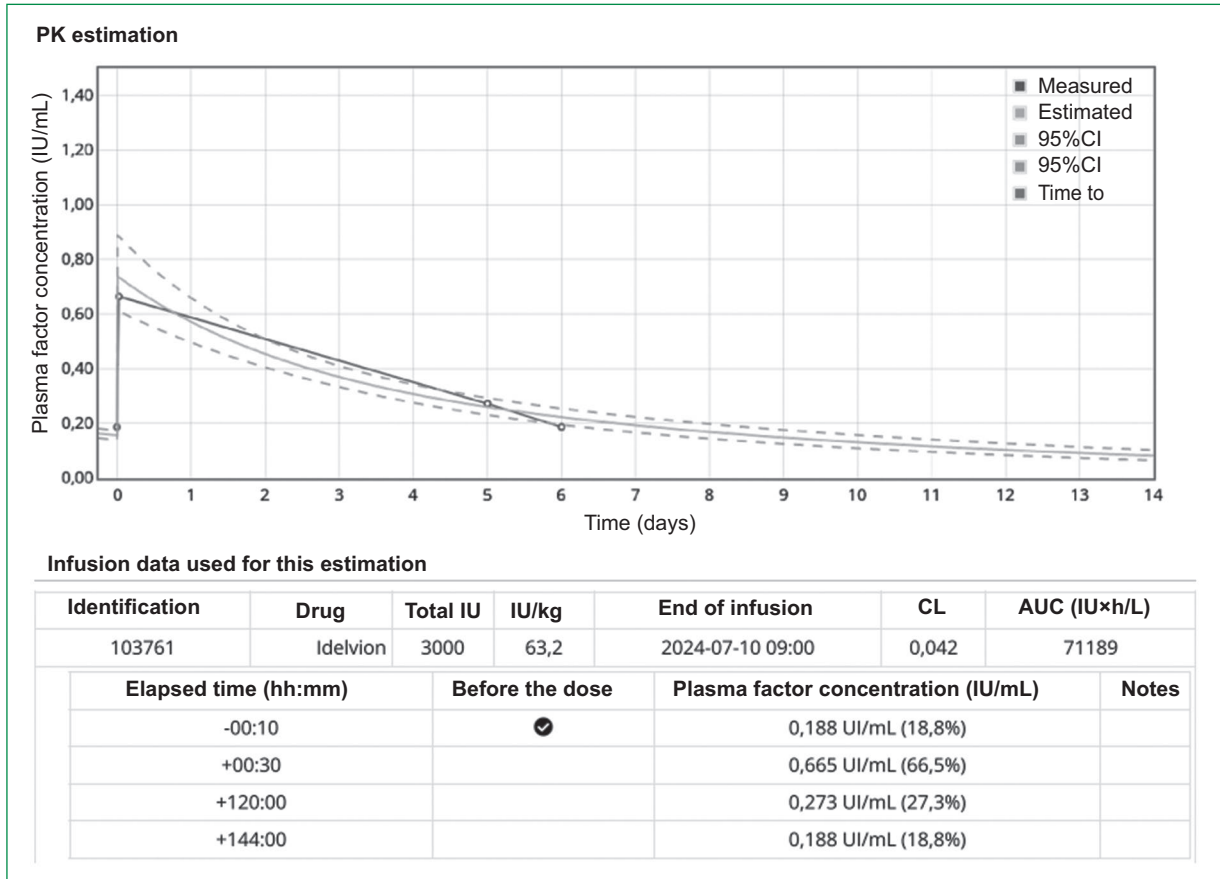
Analytical monitoring was scheduled every 4 weeks: 24-hour urine testing initially monthly and later quarterly, monthly biochemical analysis, urine dipstick testing after each administration (to monitor the appearance of proteinuria and signs of nephrotic syndrome), and monthly inhibitor determination. Approximately 6 months later, due to persistence of the inhibitor (8 BU), an anti-CD20 monoclonal antibody was added (4 doses; 375 mg/m²/week), resulting in inhibitor negativization but without normalization of recovery or half-life (partial success). A gradual dose reduction was attempted until reaching 50 IU/kg every 48 h, at which point the inhibitor rebounded (4 BU). The SHL-rFIX dose was increased to 50 IU/kg/day and, 2 months later, the inhibitor was negative. Bleeding episodes were treated with recombinant activated FVII (when the inhibitor was positive) and with SHL-rFIX when it was negative. The year 2020 was particularly complicated. First, during removal of the port-a-cath due to infection, the patient developed an allergic reaction, although the causative agent could not be determined (antibiotic therapy used, SHL-rFIX, factitious urticaria). Therefore, a structured desensitization protocol was carried out by the Allergy Department. Second, the patient was proposed for participation in a clinical trial with a subcutaneously administered rebalancing agent, but was ultimately rejected because, according to the trial sponsor, the inclusion criteria were not met. After more than 4 years of daily administration of SHL-rFIX, in July 2023 mild proteinuria was detected in a 24-hour urine analysis (0,20 g/24 h; 0-0,15),

confirmed 7 days later (0,30 g/24 h). After reviewing the literature,² we decided to switch to recombinant albumin-fused FIX (rFIX-FP) at a dose of 60 IU/kg (total, 3.000 IU), adjusted according to pharmacokinetics (WAPPS-Hemo®) every 5 days (plasma level at 120 h 3,3%, recovery at 30 minutes 66%) (Fig. 1). The patient presented accelerated clearance and a reduced half-life vs the estimates reported by Zhang et al.,³ who suggested that with a dose of 50 IU/kg in a child older than 12 years, FIX levels > 5% should be maintained for 12,5 days, > 3% for 15,5 days, and > 1% for a total of 23 days.

After presenting two traumatic muscle hematomas within the first 2 months, in the context of sports practice (soccer), which responded well to the administration of two additional doses of 3.000 IU of rFIX-FP spaced 48 h apart, the infusion regimen was reduced to every 4 days for 2 months. Due to the patient's favorable clinical course and the progressively higher trough levels recorded, the infusion interval was gradually extended, remaining for 4 months on a regimen every 4 days and then for 6 months every 5 days. At 10 months, after documenting a trough level of 27%, weekly prophylaxis was initiated. At the 1-year follow-up, the patient can be considered to be "in remission"; with an infusion regimen of 55,5 IU/kg every 7 days, trough FIX levels of 18% were observed (recovery 88%) (Table 1 and Fig. 2) (for FT4, in children aged 12 to < 18 years, 88,8 h; 51,5-130,0). In addition, the patient has remained free of bleeding during the last

Table 1. Comparison between the balanced estimates of WAPPS-Hemo[®]

Parameter	Time to reach 0,05 IU/dL	Time to reach 0,02 IU/dL	Time to reach 0,01 IU/dL	Half-life
July 2023	130 h	220.5 h	335.75 h	78 h
September 2024	447.75 h	672.75 h	898 h	142.25 h

**Figure 2.** Pharmacokinetics with rFIX-FP (September 2024). Balanced estimation. AUC: area under the curve; CL: clearance; PK: pharmacokinetics; 95%CI: 95% confidence interval.

10 months, with a substantial improvement in quality of life and a degree of independence and autonomy that had not previously been achieved. The most recent joint evaluation performed using HEAD-US (October 2024) showed a score of 1, with synovial hypertrophy in the left ankle (the previous score in 2023 was 2). For the remaining joints, the score was 0.

Discussion

Risk factors for the development of inhibitors include the presence of large deletions (as in this patient) and

null mutations in the *F9* gene, as well as early and intensive exposure to FIX concentrates, as occurred in our patient. Male et al.⁵ described a cumulative incidence of inhibitors of 10,2% at 500 exposure days (ED) in a well-defined, unselected cohort of previously untreated patients with severe HB. Our patient developed the inhibitor after more than 500 ED despite having received intensive treatment at diagnosis.

ITI in patients with HB and high-titer inhibitors is performed less frequently than in patients with HA due to the lower success rate reported and the risk of severe complications such as anaphylactic reactions or the

Table 2. Pharmacokinetic comparison before and after 12 months following the initiation of prophylaxis with rFIX-FP

Date	Recovery	FIX levels	Predicted levels at 14-15 days (WAPPS, balanced)
July 2023	66%	At 120 h: 3,3%	1%
September 2024	88%	At 144 h: 18,8%	7.4%

rFIX-FP: recombinant FIX concentrate fused to recombinant albumin.

development of nephrotic syndrome. Therefore, the available evidence on inhibitor eradication in patients with HB is very limited, and management is generally carried out in a manner similar to that used for inhibitors against FVIII. At the same time, the criteria for defining immune tolerance success are not clearly established. On the other hand, new subcutaneously administered molecules such as Concizumab® or Mastarcimab®,^{6,7} inhibitors of the tissue factor pathway, have demonstrated the safety and efficacy profile in preventing bleeding in patients with inhibitors in both HA and HB. In the field of HB, they could change the prognosis, even survival, of patients who develop inhibitors against FIX and are not candidates for ITI. They may even call into question the use of ITI in those few patients with HB who develop inhibitors against FIX.

Recently, Palomo Bravo et al.⁸ reported their experience in the treatment of a pediatric patient who developed a high-titer inhibitor to SHL-rFIX associated with an anaphylactic reaction. In that case, successful immune tolerance induction without immunosuppression was achieved using very low doses of rFIX-FP that were gradually increased. In our case, this was the first report of such an experience, which encouraged us to proceed with the switch. Although several mechanisms involved in the development of inhibitors against FIX have been hypothesized, it has been suggested that mast cells present in the extravascular space, upon contact with extravasated FIX, could trigger an IgE-mediated hypersensitivity reaction.⁹ The influence of the larger volume of distribution of SHL-FIX or complement activation due to the formation of transient IgG1 antibodies has also been proposed¹⁰. In the case of rFIX-FP, whose pharmacokinetics appear to follow a bicompartamental model,^{4,11} the molecule shows a small volume of distribution and minimal extravascular distribution, which could reduce the risk of anaphylaxis. These allergic reactions have been associated with the

development of nephrotic syndrome. Typically, this condition appears around 8 or 9 months after the start of ITI with high doses of FIX and presents with symptoms such as periorbital edema, proteinuria, hypoalbuminemia, and oliguria. Our patient had been receiving daily SHL-rFIX at doses of approximately 40-50 IU/kg/day for more than 4 years following desensitization, with regular 24-hour urine monitoring and urine dipstick testing after each infusion. Although it seemed unlikely, the mere “threat” (proteinuria confirmed by two determinations even in the absence of hypoalbuminemia or oliguria) was considered sufficient to propose a change of product. Although the etiology remains unknown, it appears to be related to immune complex deposition, although this has not yet been fully elucidated. In published cases, renal biopsy has described membranous glomerulonephritis without the presence of FIX immune complexes.¹² In some cases, the syndrome resolves after discontinuation of treatment with FIX concentrates (CFIX); in others, corticosteroid therapy has been required, and irreversible cases have also been reported.

The success of this individual case is evident: first, proteinuria disappeared and therefore the risk of developing nephrotic syndrome was reduced due to the lower dose received and the lower protein content of the new molecule. A progressive normalization of pharmacokinetic parameters was observed without inhibitor rebound. The first study, in July 2023, showed a recovery of 66%, FIX plasma levels of 3,3% at 120 h, and the balanced prediction in relation to FIX levels at 14 days was 1%. Pharmacokinetic evaluation one year later showed a recovery of 88,3%, FIX plasma levels of 18% at 144 h, and a predicted level at 15 days of 7,4%, values within the normal range for a patient of this age (Tables 1 and 2).

Furthermore, rFIX-FP achieved adequate clinical control and substantially reduced the treatment burden (approximately 80%). The economic cost decreased slightly, although the difference is expected to become more noticeable after one year of treatment. Nevertheless, this case is not generalizable; however, it is important to report experiences of this type to “open the door to new hypotheses regarding the doses required to achieve immune tolerance with other factor concentrates,” as stated by Dr. Palomo Bravo.⁸

Conclusions

The management of patients with severe HB who develop inhibitors remains one of the major challenges

faced by healthcare professionals involved in their care. As with the publication by Palomo Bravo et al., this case reinforces the potential of rFIX-FP as a viable alternative for immune tolerance induction, highlighting the possibility of avoiding immunosuppression and the risk of its associated adverse effects in patients who develop complications such as anaphylactic reactions or a potential risk of nephrotoxicity. The experience obtained suggests that the use of extended half-life products could be key to improving clinical outcomes in difficult-to-treat patients through personalized therapies, reducing the need for frequent infusions and improving patients' quality of life. Further studies are needed to establish standardized protocols that include these extended half-life concentrates, similar to what has been done in HA with certain extended half-life FVIII concentrates, in the management of inhibitors in HB, especially in patients at high risk of immunological complications.

We believe that this case provides some evidence regarding its efficacy and safety, although we emphasize the need for future research and the development of treatment protocols.

Acknowledgments

To Dr. Ma. Fernanda López-Fernández and her team (Hematology and Hemotherapy Department, Complejo Hospitalario Universitario A Coruña) for their invaluable support, and to Dr. Jaime Megias-Vericat (Hospital Pharmacy Department, Hospital Policlínico Universitario La Fe, Valencia) for his invaluable collaboration in performing the pharmacokinetic studies.

Funding

None.

Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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