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CASE REPORT

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Successful immunosuppressive drug-free immune tolerance induction in hemophilia B with inhibitor and anaphylaxis to factor IX: A case report

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Key Clinical Message

Recommendations advise factor IX desensitization before immune tolerance induction in severe hemophilia B, supported by immunosuppression. A child with inhibitor and anaphylaxis to factor IX showed successful immunosuppression-free immune tolerance induction using very low and slowly increasing doses of a factor IX extended-half-life product. Immune tolerance to factor IX based on this protocol merits further study.

KEYWORDS

anaphylaxis reaction, desensitization protocol, factor IX-extended half-life product, immune tolerance induction, inhibitors, severe hemophilia B

1 | INTRODUCTION

Hemophilia B (HB) is a rare, inherited, X-linked, recessive, hemorrhagic disorder caused by mutations in the coagulation factor IX (FIX) gene. Subjects with severe HB (SHB) have FIX levels below 1 IU/dL and may develop spontaneous bleeding in joints, muscles, and other soft tissues.[1]

Since the introduction of safer and more effective treatments for HB, joint bleeding in patients with SHB has decreased considerably. However, the development of inhibitors against FIX concentrates continues to be the most serious complication associated with FIX administration.[2]

The development of inhibitors in HB is a rare adverse event observed almost exclusively in patients with SHB.[1] Inhibitors are often detected during the first 20 exposures to FIX. They make replacement therapy ineffective and increase not only the morbidity and mortality of the condition but also the cost of treatment, with a net loss of quality of life for patients and their families.[2] Immunotolerance induction (ITI) to FIX, therefore, continues to be one of the most important objectives in the treatment of patients with SHB and inhibitors.[2]

Efforts in this direction are hampered by the low prevalence of SHB (1.1/100,000 men)[3] and the low cumulative incidence of inhibitors in this group of patients (9%–23%),[4–10] limiting the collection of clinical evidence to support the design of effective ITI protocols in SHB. Moreover, the lower rates of efficacy of ITI in SHB (around 30%)[9] and the development of severe adverse events, such as allergic and/or anaphylactic reactions and nephrotic syndrome,[10–13] also make ITI difficult to address in this type of patients.

Large deletions or null mutations in the F9 gene increase the risk of developing FIX inhibitors, which, in turn, may increase the likelihood of anaphylactic or allergic reactions to FIX.[14] For SHB patients with inhibitors

and anaphylaxis/allergic reaction to FIX, previous desensitization by the administration of gradual FIX dose increments before undertaking ITI may be considered, although data on the efficacy or safety of this approach are limited.[2] Immunotolerance induction protocols suggest the combined use of high doses of FIX and immunosuppressive agents as first-line treatment.[15] However, groundbreaking FIX-extended half-life products, combined with the accumulated experience on desensitization protocols to chemotherapeutic agents in children, are paving the way for the design of less aggressive and risky ITI protocols in young SHB patients with inhibitors and anaphylaxis/allergic reaction to FIX. In line with this concept, we present here the case of a child with SHB and inhibitors, in whom we decided to apply a less aggressive, innovative immunosuppressive drug-free ITI strategy outside the current standards, given his young age and history of anaphylaxis/allergic reaction after exposure to FIX.

2 | CASE PRESENTATION

A young child was diagnosed with SHB at 10 months of age (baseline levels: 1.1 IU/dL FIX and F9 gene large deletion) after evidence of anemia (8.9 g/dL) and several mild subcutaneous hematomas.

3 | METHODS

Due to moderate to severe muscle hematomas, the patient initiated on-demand treatment with recombinant FIX (rFIX) (Benefix®, Pfizer®) (35 IU/kg) at 12 months of age. At the 6th exposure day (ED) (FIX 60 IU/kg), 6 months after starting treatment with FIX, anaphylaxis/allergic reaction (skin rash, cyanosis, and hypotension) to FIX was observed, accompanied by undetectable FIX levels and an inhibitor titer of 3.6 BU/mL. FIX treatment was suspended, and on-demand treatment with recombinant activated FVII (rFVIIa; Novoseven®) (120 mcg/kg) was started (inhibitor titers and 1-h postinfusion FIX recovery during the observation period are depicted in Figure 1).

After 2.7 months of intensive treatment with rFVIIa due to repetitive muscle and subcutaneous hematomas, prophylaxis with rFVIIa (90 mcg/kg) on Monday/Wednesday/Friday was initiated via a central catheter to overcome difficult venous access. Inhibitor titer decreased to undetectable levels over a period of 5.6 months.

4 | CONCLUSION AND RESULTS

Based on previous desensitization strategies to other drugs by the administration of low and repeated doses of the allergen,[12,13] we restarted FIX administration on a 72- to 96-h schedule in the intensive care unit (ICU) using an extended half-life FIX concentrate (Idelvion®, CSL Behring®) (rIX-FP), in order to space out the doses as long as possible. After the third rIX-FP dose of 56 IU/kg (first dose of 23 IU/kg and second dose of 46 IU/kg), neither allergic/anaphylactic reaction nor nephrotic syndrome was observed, but inhibitor titer reached 12.8 BU/mL, so rIX-FP administrations were suspended, while rFVIIa prophylaxis was continued for bleeding prevention. Once undetectable titer at 6 months after the last rIX-FP infusion was reached (2.5 years of age), a new ITI protocol was initiated, consisting of ICU-monitored twice-weekly administration of very low doses of rFIX-FP with

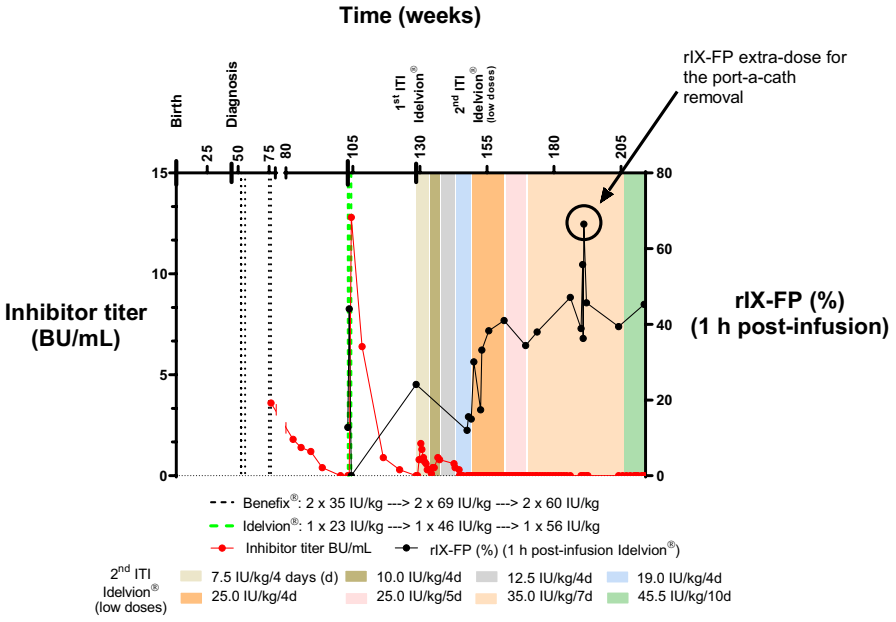

FIGURE 1 Inhibitor titers and factor (F) IX recovery during treatment with FIX concentrates. ITI, immunotolerance induction.

slow dose increase (Table 1). The protocol began at rIX-FP 7.5 IU/kg every 4 days and was incremented after 10 ED. FIX recovery, inhibitor titer, and clinical response were evaluated before the administration of every new FIX dose. The patient tolerated all doses without presenting any allergic/anaphylactic reaction. The patient has had no joint bleeding since starting this second ITI course. He required only rFVIIa administration on two occasions due to two mild hematomas, one in the gastrocnemius muscle and the other in the subcostal area, while receiving the dose of 10 IU/kg every 4 days. The patient is now 4 years old and is receiving a prophylactic regimen with rIX-FP doses of 44.6 IU/kg every 10 days with a FIX trough level of 5.5 IU/dL, an rIX-FP recovery of 45.3 IU/dL, a "balanced" half-life of 103.5 h (Wapps-Hemo analysis is described in Table 2), and undetectable inhibitor titer.

At the age of 3.7 years, the patient required removal of the central reservoir. A prophylactic dose of rIX-FP 45.5 IU/kg was used to cover the surgery (66.5 IU/dL FIX 30 min postinfusion). The efficacy of rIX-FP was excellent and the patient developed neither adverse events nor inhibitor rebound. No additional doses of rIX-FP were required apart from the prophylactic doses.

TABLE 1 Number of recombinant factor IX doses administered during the immunosuppressive drug-free immunotolerance induction with very low doses of rIX-FP (Idelvion®, CSL Behring®) and slow dose increment.

Dose (IU/kg)	Frequency	Total number of doses
7.5	Every 4 days	10
10.0		10
12.5		10
19.0		10
25.0		20
25.0	Every 5 days	10
35.0	Every 7 days	36
45.5	Every 10 days	12[a]

[a]At time of article writing.

5 | 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, which did not occur in our patient since he was receiving treatment on demand and did not receive more than two consecutive doses of FIX before inhibitor detection. The reasoning behind the application of desensitization in this patient was based on the development of an anaphylaxis/allergic reaction after the administration of FIX concentrate (Benefix®, Pfizer®) associated with the development of inhibitors against FIX. Thus, we hypothesized that avoiding an anaphylactic/allergic response after the administration of FIX would, in turn, prevent the rise of the inhibitor titer. We modeled our approach on the evidence of success described in desensitization protocols to chemotherapy drugs and antibiotics.[13,15] In our case, we obtained a good outcome. We were able to avoid the use of immunosuppressants by relying on rIX-FP (Idelvion®, CSL Behring®) that could be administered using low doses spaced over time, thus reducing the number of infusions and generating lower costs. We describe here the experience of a single patient, so our results cannot be extrapolated to others. However, given his history of anaphylaxis and allergic reaction associated with the administration of FIX, followed by his good response to our novel desensitization protocol, our case may serve as a guide to other clinicians who wish to reattempt ITI in this group of difficult-to-treat subjects for whom scant data are available. Our report adds to the body of knowledge that might contribute to the design of ITI protocols for inhibitor clearance and improve the quality of life of children with SHB who develop inhibitors and allergic/anaphylactic reactions to FIX. It opens the door to new hypotheses on

TABLE 2 Pharmacokinetic study performed using the Wapps-Hemo platform.

Parameter	Estimated (hours)		
	Conservative	Balanced	Optimistic
Time to 0.05 IU/mL	218.3	250.8	288.3
Time to 0.02 IU/mL	364.8	415.0	472.0
Time to 0.01 IU/mL	510.8	579.0	656.5
Half-life	92.0	103.5	116.8

Note: Administered dose Idelvion® 1000 IU (44.6 IU/kg); first point of evaluation: time from infusion (hh:mm) +240:15, 0.055 IU/mL (5.5%) of plasma rIX-FP activity; second point of evaluation: time from infusion: +1:55, 0.453 IU/mL (45.3%) of plasma rIX-FP activity. Assay Type: One-stage clotting assay.

the doses required to achieve immune tolerance to other factor concentrates, such as FVIII.

AUTHOR CONTRIBUTIONS

Ángeles Palomo Bravo: Conceptualization; formal analysis; writing – original draft; writing – review and editing. **Rosario Prieto Bonilla:** Formal analysis; writing – review and editing. **Daniel Bardan Rebollar:** Formal analysis; writing – review and editing. **Francisco José López-Jaime:** Writing – review and editing. **Ihosvany Fernández-Bello:** Formal analysis; writing – original draft; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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