

Challenges in the Management of Hemophilia B with Inhibitor

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Abstract

Development of factor IX (FIX) inhibitor is a rare but challenging complication in hemophilia B. In addition to inefficacy of specific replacement therapy, FIX inhibitors increase morbidity due to serious allergic reactions/anaphylaxis upon treatment with FIX. Limited experience with immune tolerance induction (ITI) shows a high risk of nephrotic syndrome development and poor ITI outcomes. Recently, immunomodulation therapy has been used in ITI regimens in hemophilia B; however, relevant guidelines for ITI in hemophilia B are still lacking. We describe a 7-year-old hemophilia B patient with “null” mutation Arg29 stop who underwent surgery and massive transfusion therapy in the neonatal period and developed an FIX inhibitor after consecutive 20 exposures to FIX concentrate. At the age of 6 years, a high-dose ITI was commenced combined with immunomodulation therapy including rituximab, dexamethasone, and intravenous immunoglobulin. Allergic reactions that occurred in the third week of ITI were resolved by premedication with antihistamines and continued immunomodulation protocol without any need for ITI interruption. Inhibitor was negative from week 10; however, doses of FIX continued unchanged until pharmacokinetic criteria for success were met at month 9 of ITI. One year after the start of ITI, the patient started regular prophylaxis with FIX 41 IU/kg three times a week. No further allergic reactions or any signs of nephrotic syndrome have occurred.

Keywords

- hemophilia B
- FIX inhibitor
- allergic reactions
- immune tolerance induction
- immunomodulation therapy
- rituximab

At present, the most challenging complication of hemophilia therapy is the development of inhibitors against coagulation factor VIII (FVIII) and factor IX (FIX), affecting 10 to 30% of patients with severe hemophilia A^{1,2} and 1 to 3% of patients with hemophilia B,^{3,4} respectively. Although not yet fully understood, several risk factors for inhibitor development in hemophilia A, either patient-related or therapy-related,^{1,5–7} as well as predictors of success of immune tolerance induction (ITI)^{6,8} have been recognized and effective immune tolerance induction regimens identified.^{2,9,10} In contrast, the possibility to study inhibitors in hemophilia B is very limited because of a

lower prevalence of this disorder and a low incidence of FIX inhibitors.³ Since the 1990s, several case reports and several cohorts of hemophilia B patients with inhibitor have been published in the literature.^{11–14} Similar to FVIII inhibitors in hemophilia A, FIX inhibitors in hemophilia B cause an ineffectiveness of the specific hemostatic therapy. Unlike hemophilia A, however, FIX inhibitors also lead to serious morbidity due to severe allergic reactions upon administration of FIX as well as the development of nephrotic syndrome.^{2,11,13,14}

Allergic phenotype was reported in 10 of 16 (63%) hemophilia B patients in the North American Immune Tolerance

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Registry (NAITR) and in 59 (60%) of a total of 94 individuals registered in the International FIX Inhibitor Registry,¹⁴ with a greatest risk in patients with large deletions and major rearrangements of *F9* gene.¹² ITI for patients with hemophilia B and inhibitors is recognized to be particularly difficult to conduct and achieves a low success rate ranging between 13 and 33%.^{13–15} Association of allergic reactions with both the risk of development of nephrotic syndrome and a poor ITI outcome is often observed. In the NAITR, 3 of 10 patients with previous anaphylaxis developed nephrotic syndrome and 8 of 10 patients failed ITI.¹² Similarly, in the International Registry of FIX Inhibitors, of 39 patients undergoing ITI, 13 developed nephrotic syndrome (11 patients had a history of anaphylaxis) and only 5 (13%) patients were successfully tolerated.¹⁴ In view of these findings, a traditionally reserved approach to inhibitor eradication has been recommended in hemophilia B.^{3,10}

Recently, an initial desensitization with gradually increasing amounts of FIX was reported in several patients with a history of anaphylaxis, enabling successful continuation of the ITI.^{16–19} To increase the chance of inhibitor eradication, several immunosuppressive/immunomodulation schemes have been employed as a part of ITI in hemophilia B, including dexamethasone and intravenous immunoglobulins (IVIG), sometimes in combination with cyclosporin A²⁰ or mycophenolate mofetil^{21,22}, or most recently with rituximab.^{19,23–26} However, the data on optimal dosing regimens, immunomodulation combinations, and the outcomes of ITI in hemophilia B are still limited.^{3,10} There is no clear consensus on how to effectively treat hemophilia B with inhibitors and recommendations for ITI in hemophilia B are substantially lacking.^{9,10,15}

Here, we report the case of a hemophilia B boy with inhibitor, who was successfully treated with a high-dose ITI regimen and immunomodulation therapy including dexamethasone, IVIG, and rituximab.

Case Description

This presently, 7-year-old patient with hemophilia B who had no family history of hemophilia underwent urgent abdominal surgery after his birth because of a congenital jejunal atresia. The operation was performed without knowledge of a diagnosis of hemophilia and was complicated with serious bleeding that was controlled by a massive replacement of fresh frozen plasma and red blood cells. Severe hemophilia B was subsequently diagnosed (FIX, 0.2%; FIX inhibitor negative). Genetic testing, performed at the Department of Hematology, Transfusion and Hemophilia Center, Castelfranco Veneto, Italy by Conformational Sensitive Gel Electrophoresis (CSGE) and DNA sequencing, revealed as causative mutation in *F9* gene a C > T transition in nucleotide 6460, codon 29 in exon B, resulting in the stop codon TGA instead of the normal codon CGA coding for amino acid arginine (Arg-R). This nonsense mutation g.6460 C > T Arg29 stop resulted in the absence of both FIX coagulant activity and FIX antigen. The boy successfully underwent a second surgical intervention (occlusion of the jejunostomy and jejunal anastomosis) at the age of 2 months under the replacement of plasma-derived FIX

(pd-FIX) (Octanine F; Octapharma, Langenfeld, Germany), receiving a total dose of 4,000 IU (1,142 IU/kg) that was administered during 11 exposure days (ED).

Over the next year, the patient was treated on demand and FIX inhibitor (which was checked after every 2–3 ED of FIX concentrate) was negative. At 15 months of age, after a total of 20 ED to FIX, an inhibitor of 5.6 Bethesda units (BU/mL) was detected, with a peak titer of 15 BU/mL. On demand, treatment of bleeding episodes with recombinant activated factor VII (rFVIIa) was commenced. At the age of 2 years, in the absence of detectable inhibitor, the patient developed an episode of generalized severe urticarial exantema, associated with an increase of IgE and circulating immune complexes. The reason of this reaction remained unrevealed; food, drug, and infectious etiology of allergy were all excluded and the event was resolved by the use of antihistamines. Over the subsequent 4 years, the patient did not experience any joint bleeds or other serious bleeding episodes. From the age of 5.5 years, severe recurrent muscle bleedings occurred, the management of which was impeded by a poor venous access and decreasing efficacy of rFVIIa therapy. Severe mucosal bleeding in the oral cavity not responding to 4 mega-doses of rFVIIa (222–278 µg/kg) was stopped by the administration of FEIBA (Factor Eight Bypassing Activity) in a dose 50 IU/kg; this however also resulted in a strong anamnestic response with an inhibitor peak titer of 74 BU/mL. Nevertheless, the inhibitor disappeared spontaneously within 5 months and we proposed an early start of the ITI. Port-A-Cath (Smiths Medical, Watford, United Kingdom) was implanted under hemostatic treatment with a bolus of rFVIIa (300 µg/kg) followed by continuous infusion at initial infusion rate of 50 µg/kg/h, which was gradually reduced to 24 µg/kg/h within consecutive 6 days. To avoid the risk of allergic reactions and/or nephrotic syndrome, we commenced combined immunomodulation therapy 1 week before the start of a high-dose ITI with a pd-FIX concentrate (Octanine F 100 IU/kg every 12 hours).

The treatment protocol and dynamics of inhibitor are shown in ►Fig. 1. Four doses of the anti CD-20 monoclonal antibody (rituximab 375 mg/m²) were given at weekly intervals. Three day pulses of dexamethasone (12 mg/m² twice daily) and two-day cycles of IVIG infusions (1 g/kg/day) were repeated every 4 weeks during a consecutive 4 months. Anamnestic response of inhibitor culminated on day 10 of ITI at a peak titer of 35 BU/mL. On days 18 to 20, the patient experienced skin urticaria after FIX injections without any systemic symptoms. Treatment was reduced to one FIX dose of 100 IU/kg per day, given after the premedication with oral antihistamine desloratadine 2.5 mg and intravenous hydrocortisone. At this time, the patient received the last infusion of rituximab and the second cycle of dexamethasone and IVIG. Under this treatment, allergic reactions disappeared and two daily doses of FIX were resumed. The residual level of FIX before the next dose was satisfactory from week 10, suggesting the inhibitor negativity; however, because of insufficient in vivo recovery (18–26%), the ITI was continued with unchanged dose regimen. The treatment success was confirmed at month 9 of ITI by the 48-hour pharmacokinetic study, which showed an in vivo recovery of 58%, incremental

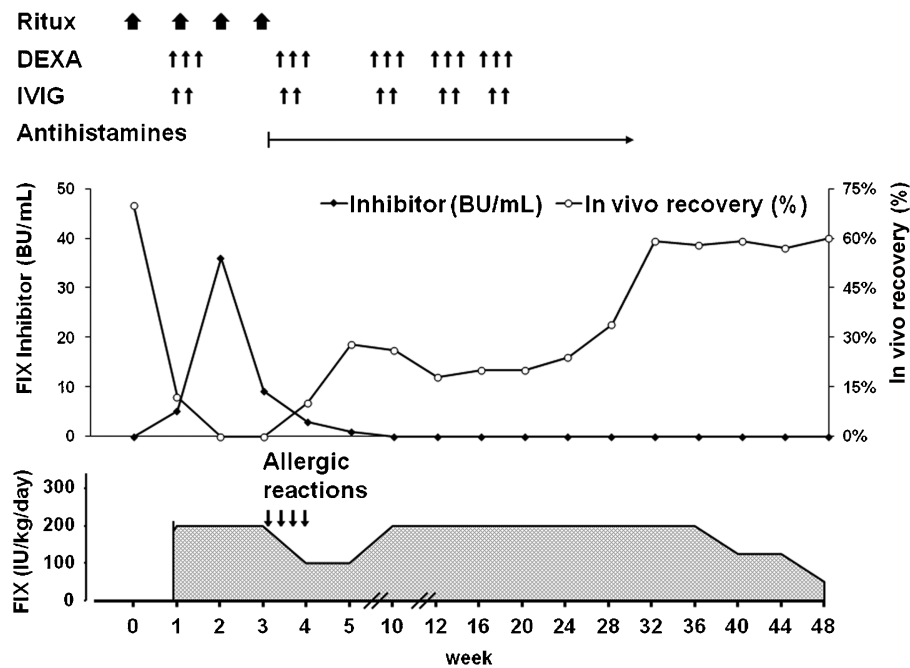


Fig. 1 Immune tolerance induction (ITI) protocol and the dynamics of inhibitor and in vivo recovery during the ITI course. Ritux, rituximab 375 mg/m² (week 0, week 1, week 2, and week 3); DEXA, dexamethasone 12 mg/m² every 12 hours for 3 days monthly; IVIG, IV immunoglobulin 1 g/kg/day for 2 days monthly; antihistamines, premedication with desloratadine 2.5 mg 1 hour before factor IX administration.

response of 1.1%/1 IU/kg, biological half-life of 13.9 hours, and FIX clearance of 4.7 mL/kg/h (►Table 1). In the next 3 consecutive months, the dose of FIX was gradually reduced to 50 IU/kg/day and now, 1 year after the initiation of the ITI, the patient is on regular prophylaxis at a dose of 41 IU/kg three times a week. Except for urticaria at the beginning of ITI, no other allergic reactions have been observed.

At no time during the ITI did the patient develop proteinuria or any other biochemical or clinical evidence of nephrotic syndrome. Immunomodulation therapy was uneventful and well tolerated, no clinical sequelae of the temporary complete suppression of CD19⁺, CD20⁺, and CD22⁺ lymphocytes were present. The lymphocyte subpopulations were fully normalized within 8 months after the treatment with rituximab. FIX concentrate was administered in a home setting using the Port-A-Cath system without any adverse events. Absence of

bleeding led to radical improvement of patient's quality of life, and the boy was able to complete his first year of the regular school attendance without any day lost because of bleeding episodes.

Discussion

Inhibitors of FIX represent a rare complication of treatment in hemophilia B with much lower prevalence than in hemophilia A.³ The most recent Database of the Universal Data Collection (UDC) showed 75 of 3,785 hemophilia B persons registered in the US had an inhibitor in the period 1998 to 2011, with a prevalence of 2%.⁴ Our patient presented here is the only hemophilia B patient with inhibitor in Slovakia, representing a prevalence of FIX inhibitors of 1.3%. Major gene mutations have been shown to be an important predisposing factor in the

Table 1 Pharmacokinetics in our patient with hemophilia B on month 9 of the high-dose ITI with a plasma-derived FIX concentrate compared with noninhibitor patients

Parameter	Noninhibitor hemophilia B patients (range)	Patient (month 9 of the ITI)
In vivo recovery (%)	49–59	58
Incremental response (%/IU/kg)	0.6–1.1	1.13
Clearance (mL/kg/h)	3.8–5.3	4.7
MRT (h)	24–45	18.7
VDSS (mL/kg/mL)	110–150	82.8
Half-life (h)	18–34	13.9

Abbreviations: FIX, factor IX; ITI, immune tolerance induction; MRT, mean residence time; VDSS, volume of distribution at steady state.

Note: Normal values according to Poon 2006.³³

developing of inhibitors in both hemophilia A and hemophilia B. In hemophilia B, the missense point mutations are the most prevalent, whereas the “null” mutations are less frequent compared with hemophilia A. This difference may partially explain the lower incidence of FIX inhibitors.^{3,5} The development of antibodies against FIX is invariably associated with severe mutations, most frequently with large deletions and stop codon resulting in a loss of coding information.^{27,28}

In our patient, F9 gene mutation in exon B with nucleotide 6460 c.223 C > T; Arg29 stop was detected. This mutation is well known and until now has been reported in 73 unrelated hemophilia B individuals included in the FIX Mutation Database (<http://www.factorix.org>). FIX inhibitor was present in 7 (12%) of the total 68 individuals in the Database with Arg29 stop mutation, in whom, an inhibitor status was reported. In addition to gene mutations and severity of hemophilia, several other risk factors similar to those that are identified in hemophilia A (black race and age 11 years or less) were also found to be significantly associated with FIX inhibitors.⁴

Unlike hemophilia A, FIX inhibitors cause serious allergic reactions and/or anaphylaxis upon the administration of FIX.^{11,13,14} Several mechanisms may be involved in the pathogenesis of allergic reactions, including possible mast cells activation by extravascularly distributed small sized FIX molecules,^{3,13} IgE mediated hypersensitivity,¹⁶ immune complexes formation and complement activation by transient production of IgG1 subclass antibodies, which have been detected at the time of allergic events.²⁹ Several authors have observed allergic reactions before an inhibitor detection and suggest that allergic phenotype may herald inhibitor development.³ Our patient had no allergic reactions associated with FIX administration at the diagnosis of inhibitor. Inhibitor testing was performed after every 2 to 3 ED, so inhibitor was revealed early and the patient was not exposed to FIX administrations at the time of further progression of inhibitor titer. However, an episode of generalized urticaria of unknown reason associated with an increase of both IgE and immune complexes levels could have been a signal for future allergic phenotype in our patient. This was also a reason for our reluctant approach to ITI until the bleeding phenotype in our patient was mild. The worsening of the bleeding phenotype and unsatisfactory efficacy of rFVIIa influenced our decision to eradicate the inhibitor by ITI.

ITI in hemophilia B patients remains a major clinical challenge. Allergic reactions and anaphylaxis are often associated with ITI failure and, in particular, with nephrotic syndrome that develops mostly between the months 8 and 9 of high-dose ITI.^{11,13,14} Nephrotic syndrome presents with periorbital edema, proteinuria, hypoalbuminemia and oliguria and in some patients may be irreversible.¹¹ Histology and electron microscopy of renal biopsy confirmed segmental membranous glomerulonephritis in these patients.^{11,30} Concerns about these serious complications and a poor success rate, in particular, also supported the traditionally conservative approach to ITI in hemophilia B. Indeed, in the International FIX Inhibitor Registry only 39 of 94 patients underwent ITI.¹⁴ To reduce the risk of immunologic complications, the desensitization with FIX before ITI^{16–19} or immunosuppres-

sive regimens concomitantly with ITI were used in several patients.³¹ These procedures however, were not shown to have an impact on ITI outcomes in the International FIX Inhibitor Registry, where only 5 of 39 (13%) patients achieved successful inhibitor eradication regardless to immunosuppressive therapy.¹⁴ Recently, corticosteroids and IVIG have been successfully used in combination with mycophenolate mofetil^{21,22} or now with increasingly used rituximab as a part of ITI attempts in hemophilia B.^{23–26} However, whether these regimens may have real impact on the overall ITI success rate is not clear. Paradoxically, Klukowska et al reported recently on successful ITI in two hemophilia B patients without the use of immunosuppressive therapy and any adverse immunological events.³²

As to the inhibitor eradication in hemophilia B, there is no consensus or recommendation on the optimal ITI regimen. Various schemes have been used employing daily doses of FIX ranging between 50 and 200 IU/kg/day. In our patient, we used a high-dose protocol with regard to a high historical peak of inhibitor as potentially poor prognostic factor. Because of a history of circumstantial evidence of allergic reactions, the combined immunomodulation therapy was commenced 1 week before the start of ITI. Despite this, the patient developed several skin allergic reactions after injection of FIX in the first month of the ITI course. The problem was resolved by the premedication with antihistamines and continued immunomodulation according to the protocol. We hypothesize that immunomodulation therapy including rituximab used at the start of the high-dose ITI successfully suppressed the full development of allergic phenotype in our patient and possibly prevented anaphylaxis and/or the development of nephrotic syndrome.

In hemophilia A, the criteria of successful immune tolerance include a negative titer of inhibitor, in vivo recovery of factor VIII (FVIII) more than 66% and a half-life more than 6 hours.^{3,9,10} However, recent ITI guidelines consider that half-life of less than 6 hours may underestimate inhibitors even in small children, who usually have a shorter half-life. Thus, these guidelines suggest values more than 7 hours as a criterion of inhibitor negativity.¹⁰ In hemophilia B, the criteria of the ITI success are not clearly defined.^{2,9,10} Given the biological properties of FIX molecule resulting in different pharmacokinetics, these criteria should differ from those in hemophilia A. In particular, the in vivo recovery hardly exceeds 60% after administration of pd-FIX, and is even lower after recombinant FIX.^{33,34} Similarly, the half-life of FIX ranges widely, so this parameter cannot be used as a simple criterion for the exclusion of inhibitor. In addition, a low in vivo recovery despite a negative Bethesda assay may suggest a persistence of undetectable inhibitor. In our patient, the inhibitor was negative from the week 10 of the ITI, with gradually increased preinfusion FIX levels. Despite this, a persisting low in vivo recovery (18–24%) led us to continue unchanged the high-dose ITI protocol. The pharmacokinetic study performed after an increase in in vivo recovery above 50% on month 9 of the ITI showed results compatible with a complete remission of inhibitor; however, the value of the half-life was still below the lower limit of the range reported in the literature^{33,34} (► **Table 1**).

Conclusion

On the basis of our experience with this inhibitor hemophilia B patient, we support a frequent testing of inhibitor after the initiation of replacement therapy in hemophilia B children. Immunomodulation therapy as a part of the ITI in some patients with a known disposition to allergic reactions enables continuation of a high-dose regimen without therapy interruption. During the ITI, in addition to monitoring of inhibitor and preinfusion levels of FIX, the determination of *in vivo* recovery may also be of value, as it may alert persisting undetectable inhibitor and prevent premature reduction in the FIX dosage. The pharmacokinetic criteria for evaluating the success of ITI in hemophilia B should be adapted to the specific characteristics of FIX. However, to reach a consensus about optimal strategies of ITI and criteria for success in this setting a larger, preferably prospective international collection of data on the management of inhibitors in hemophilia B patients is needed.

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