

Rituximab and Desensitization for a Patient With Severe Factor IX Deficiency, Inhibitors, and History of Anaphylaxis

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Summary: We report the case of a 9-year-old boy with severe hemophilia B with an inhibitor and a history of anaphylaxis to factor IX (FIX), who was successfully treated with immune tolerance (IT) that included rituximab (Genentech, San Francisco, CA) and desensitization. The patient began the first course of IT at age of 7 years with daily recombinant FIX infusions that was aborted at day 32 because of a systemic allergic reaction. A second course of IT was attempted 11 months later, initiated with a desensitization protocol with escalating doses of plasma-derived FIX in addition to therapy with rituximab. This was well tolerated without allergic symptoms and with eradication of the inhibitor and improvement in factor kinetics. A second course of rituximab was given 13 months later for worsening FIX kinetics again with an excellent response and without evidence of adverse effects.

Key Words: hemophilia, factor IX, inhibitors, anaphylaxis, desensitization, immune tolerance

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The development of an inhibitor in patients with hemophilia B is a rare and severe complication with limited therapeutic options. The incidence of inhibitors in individuals with severe hemophilia B is estimated to be between 1% and 6%.¹ Though the data are somewhat limited by small patient numbers, the response rate to immune tolerance (IT) is significantly lower for individuals with hemophilia B and inhibitors than for those with hemophilia A.² In addition, unique limitations to success of IT in patients with hemophilia B include allergic reactions and the development of nephrotic syndrome.^{3,4}

Recombinant activated factor VII (rVIIa; NovoSeven, Novo Nordisk, Bagsvaerd, Denmark) is a therapeutic

alternative for patients with factor IX (FIX) deficiency and inhibitors. The use of rVIIa for prophylactic therapy is limited by the agent's short half-life, a lack of experience with its use in this manner and prohibitive cost.⁵

The use of rituximab for IT in patients with hemophilia and inhibitors has been reported in multiple case reports and small case series, including a small number of patients with FIX deficiency.^{6,7} For individuals with FIX deficiency with a history of anaphylaxis, some success with desensitization protocols has been reported, including the use of plasmapheresis and antigen exposure as well as the use of escalating doses of FIX in addition to steroids.^{8–10}

In this case report, we describe successful IT therapy for a young boy with severe hemophilia B with inhibitors with a history of anaphylaxis to recombinant FIX.

CASE REPORT

The patient was diagnosed with severe FIX deficiency (< 1%) at 4 months of age after testing done because of a family history. He was treated on an as needed basis with his first dose of factor therapy at age of 6 months. He was initially treated with plasma-derived factor (Alphanine, Grifols, Los Angeles) and transitioned to recombinant factor (BeneFix, Wyeth, Philadelphia) at 2.5 years of life. At age of 3 years 11 months, he was found to have a low titer inhibitor of 1.6 Bethesda Units (BU) with rapid clearing of infused factor documented by a 30-minute postinfusion FIX level of < 1%.

After the detection of the inhibitor he was treated with activated rVIIa at a dose of 90 µg/kg. He had very frequent bleeding episodes including joint and soft tissue bleeds. Response to rVIIa was suboptimal, even to high-dose rVIIa (240 µg/kg every 6 h).

Owing to a declining quality of life secondary to frequent bleeding episodes, at the age of 7 years he was begun on an IT regimen with daily recombinant FIX at a dose of 80 U/kg. His first 15 infusions were done in the clinic. His 30-minute postinfusion factor levels were done weekly during this period and despite the fact that they remained < 1% he had no bleeding episodes. His highest pretherapy inhibitor titer was 1.6 BU and immediately before IT the inhibitor was 0. His inhibitor peaked at 109 BU on day 16 of therapy. On day 32 of IT he developed diffuse, severe pruritis with hives 15 minutes after his factor infusion. He was treated with epinephrine, methylprednisolone, and diphenhydramine with resolution of his symptoms. His IT was discontinued and treatment with rVIIa was resumed for frequent bleeding episodes.

Eleven months later, IT was again attempted. The patient was evaluated for allergic sensitization and anaphylactic reaction to FIX. He underwent skin testing with both

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TABLE 1. Results of FIX Skin Testing*

Reagent	Patient	Control No. 1	Control No. 2
Saline			
Prick	Negative	Negative	Negative
ID 1:10	Negative	Negative	Negative
Histamine			
Prick	12 × 15/20 × 20	20 × 20/30 × 35	10 × 12/25 × 20
Mononine			
Prick	Negative	Negative	Negative
ID 1:10	3 × 3/6 × 7	Negative	Negative
ID 1:1	8 × 10/15 × 15	Negative	Negative
FEIBA			
Prick	Negative	Negative	Negative
ID 1:10	Negative	Negative	Negative
ID 1:1	5 × 3 (equivocal)	3 × 3 (irritant)	Negative
BeneFix			
Prick	5 × 6/12 × 12	Negative	Negative
ID	Not done	Not done	Not done

*Results measured at 20 min, reported in mm, wheal/flare format.

Prick positive: wheal of 3 × 3 mm; ID (intradermal) positive: wheal 5 × 5 mm.

epicutaneous and intradermal methods to several FIX containing products [Mononine (ZLB Behring, Kankakee IL), BeneFix and FEIBA]. He showed positive reactions to Mononine and BeneFix and an equivocal reaction to FEIBA. After providing informed consent, 2 adult controls were used to validate this testing who did not show any skin reaction to these agents (Tables 1, 2).

Starting 3 days before the initiation of his desensitization protocol, the patient received his first of 4 weekly doses of rituximab at a dose of 375 mg/m². The desensitization protocol was initiated using plasma-derived FIX (Mononine). He received a continuous dose escalation over 10 hours from 0.01 U/kg/20 min to a final rate of 4 U/kg/h (100 U/kg/d) successfully and without any premedication. Over the next 6 days his total daily dose was compressed into shorter infusion times (24, 8, 4, 2, 1, and 0.5 h). He tolerated this process without evidence of adverse reactions. He then continued with daily factor therapy, infused in a standard manner at a dose of 100 U/kg/d, which was subsequently decreased to 80 U/kg/d. He completed his 4 planned doses of rituximab without incident.

At the initiation of this course of therapy his inhibitor was again 0. It peaked at day 21 to 77 BU and subsequently fell to 0 by day 42. He remained clinically well through this period without bleeding episodes.

Four months after the desensitization, the patient experienced an episode of break-through hives following his factor infusion. His inhibitor titer remained 0. He was treated with antihistamines and continued daily factor infusions. After discontinuation of antihistamines, skin testing was repeated to Mononine (both via epicutaneous and intradermal methods), which was found to be negative indicating maintenance of the desensitization status and hives to be anaphylactoid in nature. Thereafter, he has not reported any further adverse reactions.

Thirteen months after his second course of IT, at which point he was being treated with a factor dose of 80 U/kg every other day, he again began to have symptomatic bleeding. Evaluation of his FIX kinetics revealed a 30-minute postdose level of < 1% despite an inhibitor of 0 BU. Repeat administration of 4 weekly doses of rituximab at a dose of 375 mg/m² together with daily FIX infusions again restored normal kinetics concurrent with the resolution of bleeding episodes by week 4 of therapy. He was subsequently again able to be transitioned to every other day factor therapy at a dose of 80 U/kg.

He was monitored with at least twice weekly urine analysis during each initial 4-week course of IT and otherwise at approximately every 2-month intervals. His urine remained negative for protein.

His school attendance and performance from preschool through grade 2 were significantly impacted by his hemophilia, primarily related to frequent bleeding episodes. He was absent an average of 41 days per year during this period, which contributed to his needing to repeat grade 1 and the development of school avoidance behaviors. With resolution of frequent bleeding episodes postimmune therapy his attendance has been near perfect and he is working at grade level.

DISCUSSION

This patient has received 3 courses of IT, 2 of which involved rituximab and is currently without evidence of an inhibitor. He has tolerated his second and third courses of IT without complications, specifically without evidence of allergic reactions or proteinuria.

TABLE 2. Summary of Patient Course

Age	IT Regimen	Inhibitor Titer (Immediately Pre-IT/Peak Titer Post-IT)	Time to Resolution of Inhibitor and/or Normalization of Expected Factor Recovery	Clinical Impact of IT
7 y, 5 mo	Daily recombinant FIX	0/106	NA	Anaphylactic response on day 32, return to frequent bleeds with suboptimal response to rVIIa
8 y, 4 mo	Rituximab and plasma-derived FIX initiated with desensitization regimen	0/77	6 wk	Well, without bleeding episodes for 13 mo, followed by return of frequent bleeding episodes despite alternate day prophylactic therapy with plasma-derived FIX
9 y, 5 mo	Rituximab and daily plasma-derived FIX	0/1	4 wk*	Well, without bleeding episodes with ongoing alternate day prophylactic therapy with plasma-derived FIX

Inhibitor measured in Bethesda units.

*Before and during the third course of IT the patients' inhibitor remained 0-1 BU however the 30 min recovery studies after 80 U/kg of plasma-derived FIX were < 1% immediately before and at weeks 1 and 2 of therapy but normalized with a postlevel of 96% by week 4.

Anaphylaxis to FIX containing products is a potentially life threatening complication of the therapy for hemophilia B. There is a limited literature on the use of desensitization to FIX containing products.^{9,10} The use of desensitization protocols for various drugs, including antibiotics, aspirin and various chemotherapy agents is well described.^{11,12}

On the basis of the clinical history and skin testing, it was concluded that the patient had IgE-mediated sensitization to FIX. The mechanism by which clinical tolerance is induced during drug desensitization is complex but depends fundamentally on achieving antigen-specific mast cell desensitization.^{13–15} Desensitization is an active and reversible process, which depends on the continuous presence of drug. Since the initiation of his desensitization protocol our patient has received FIX on an uninterrupted daily or every other day schedule (compatible with half life of 22 h) without any evidence of allergic reaction. Finally, desensitization does result in reduced skin sensitivity in most patients^{16,17} as is seen in our patient in whom skin testing 4 months postdesensitization was found to be negative, thereby documenting maintenance of desensitization.

Nephrotic syndrome has been recognized as a complication of IT therapy in patients with FIX deficiency, often temporally associated with anaphylactoid reactions and in some cases associated with gene deletions.^{3,4} Our patient was at risk of this complication and therefore was monitored intensively.

Rituximab has been shown to be effective in the treatment of some individuals with acquired hemophilia.¹⁸ In addition, there are now multiple case reports and small case series reporting mixed efficacy with the use of rituximab in patients with congenital factor VIII deficiency and inhibitors.^{6,7,19–21} The experience in patients with FIX deficiency remains more limited, also with mixed results.^{6,7}

In this patient, a second course of therapy with rituximab 13 months after the initial therapy was well tolerated and had a beneficial effect on bleeding symptoms and factor kinetics. A Canadian group reported the use of a more prolonged course of rituximab with monthly dosing after 4 weekly doses.²¹ Use of a single second dose of rituximab with partial success has also been described.⁶

To date the success of IT therapy for patients with FIX deficiency and inhibitors has been fairly limited. The complicating factor of anaphylactic responses further confounds therapy and is associated with significant risks. The use of desensitization protocols for those with anaphylactic reactions has the potential to be beneficial. Rituximab may have an impact on the rate of success in obtaining IT for these patients. This drug is not licensed for the use in children and is associated with the risks of severe side effects including anaphylaxis and multifocal leukoencephalopathy related to JC virus reactivation.²²

The role of rituximab in the therapy for patients with FIX deficiency and inhibitors, and the safest and most efficacious way in which to administer it, will need to be evaluated in well designed multicenter trials.

REFERENCES

1. Briet E, Reischer HM, Roberts HR. Inhibitors in Christmas disease. *Prog Clin Biol Res.* 1984;150:123–129.
2. DiMichelle DM, Kroner BL. The North American immune tolerance registry: practices, outcomes, outcomes predictors. *Thromb Haemost.* 2002;87:52–57.
3. Tengborn L, Hansson S, Fasth A, et al. Anaphylactoid reactions and nephritic syndrome—a considerable risk during factor IX treatment in patients with hemophilia B and inhibitors: a report on the outcome in two brothers. *Haemophilia.* 1998;4:854–859.
4. Warrior I, Ewenstein BM, Koerper MA, et al. Factor IX inhibitors and anaphylaxis in hemophilia B. *J Pediatr Hematol Oncol.* 1997;19:23–27.
5. Matthew P, Young G. Recombinant factor VIIa in paediatric bleeding disorders: a 2006 review. *Haemophilia.* 2006;12:457–472.
6. Fox RA, Neufeld EJ, Bennett CB. Rituximab for adolescents with hemophilia and high titer inhibitors. *Haemophilia.* 2006;12:218–222.
7. Mathias M, Khair K, Hann I, et al. Rituximab in the treatment of alloimmune factor VIII and IX antibodies in two children with severe hemophilia. *Br J Haematol.* 2004;125:366–368.
8. Barnes C, Brewin T, Ekert H. Induction of immune tolerance and suppression of anaphylaxis in a child with hemophilia B by simple plasmapheresis and antigen exposure: progress report. *Haemophilia.* 2001;7:437–438.
9. Shibata M, Shima M, Misu H, et al. Management of hemophilia B inhibitor patients with anaphylactic reactions to FIX concentrates. *Haemophilia.* 2003;9:269–271.
10. Dioun AF, Ewenstein BM, Geha RS, et al. IgE-mediated allergy and desensitization to factor IX in hemophilia B. *J Allergy Clin Immunol.* 1998;102:113–117.
11. Castells M. Desensitization for drug allergy. *Curr Opin Allergy Clin Immunol.* 2006;6:476–481.
12. Castells M. Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol.* 2006;6:271–277.
13. Naclerio RM, Mizrahi EA, Adkinson NF Jr. Immunologic observations during desensitizations and maintenance of clinical tolerance to penicillin. *J Allergy Clin Immunol.* 1983;71:294–301.
14. Sobotka AK, Dembo M, Goldstein B, et al. Antigen specific desensitization of human basophils. *J Immunol.* 1979;122:511–517.
15. Sullivan TJ. Antigen specific desensitization of patients allergic to penicillin. *J Allergy Clin Immunol.* 1982;69:500–508.
16. Stark BJ, Earl HS, Gross GN, et al. Acute and chronic desensitization of penicillin allergic patients using oral penicillin. *J Allergy Clin Immunol.* 1987;79:523–532.
17. Graybill JR, Sande MA, Reinartz JA, et al. Controlled penicillin anaphylaxis leading to desensitization. *South Med J.* 1974;67:62–64.
18. Green D. The management of acquired hemophilia. *Haemophilia.* 2006;12(suppl 5):32–36.
19. Linde E, Ettinghausen CE, Voigt B, et al. First successful inhibitor elimination with a new protocol in a high responding hemophilia. A patient after failure of various immune tolerance induction regimens. *Blood.* 2001;98:534A.
20. Carcao M, St Louis J, Poon MC, et al. Rituximab for congenital haemophiliacs with inhibitors: a Canadian experience. *Haemophilia.* 2006;12:7–18.
21. Mateo J, Badell I, Forner R, et al. Successful suppression using rituximab of a factor VIII inhibitor in a boy with severe congenital hemophilia: an example of a significant decrease of treatment costs. *Thromb Haemost.* 2006;95:386–387.
22. FDA. Rituxan warning. *FDA Consum.* 2007;4:3.