

ITI with high-dose FIX and combined immunosuppressive therapy in a patient with severe haemophilia B and inhibitor

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Keywords

Haemophilia B, inhibitor, immune tolerance induction, immunosuppression

Summary

Inhibitor development is a rare but serious event in hemophilia B patients. Management is hampered by the frequent occurrence of allergic reactions to factor IX, low success rates of current inhibitor elimination protocols and the risk of development of nephrotic syndrome. Single cases of immune tolerance induction (ITI) including immunosuppressive agents like mycophenolat mofetil (MMF) or rituximab have been reported. We present a case of successful inhibitor elimination with a combined immune-modulating therapy and high-dose factor IX (FIX). This boy had developed a FIX inhibitor at the age of 5 years and had a history of allergic reactions to FIX and to FEIBA®. Under on-demand treatment with recombinant activated FVII the inhibitor became undetectable but the boy suffered from multiple joint and muscle bleeds. At the age of 11.5 years ITI was attempted with a combination of rituximab, MMF, dexamethasone, intravenous immunoglobulins and high-dose FIX. The inhibitor did not reappear and FIX half-life normalized. No allergic reaction, no signs of nephrotic syndrome and no serious infections were observed.

Schlüsselwörter

Hämophilie B, Hemmkörper, Immuntoleranz-induktion, Immunsuppression

Zusammenfassung

Die Hemmkörperentwicklung bei Hämophilie B-Patienten stellt eine seltene, aber schwere Komplikation dar. Die Behandlung wird durch das häufige Auftreten von allergischen Reaktionen auf Faktor IX (FIX), geringe Erfolgsraten der gängigen Eliminations-Protokolle und das Risiko der Entstehung eines nephrotischen Syndroms erschwert. Es existieren einzelne Berichte über Immuntoleranzinduktionen (ITI) mit Immunsuppressiva wie Mycophenolat-Mofetil (MMF) oder Rituximab. Wir berichten über eine erfolgreiche Hemmkörperelimination mit einer kombinierten immun-modulierenden Therapie und hochdosierter FIX-Gabe. Der Junge hatte mit 5 Jahren einen Inhibitor entwickelt und zeigte allergische Reaktionen auf FIX und FEIBA®. Unter der Bedarfsbehandlung mit rekombinantem aktiviertem FVII war der Inhibitor nicht messbar, aber der Junge erlitt multiple Gelenk- und Muskelblutungen. Mit 11,5 Jahren wurde eine ITI mit einer Kombination aus Rituximab, MMF, Dexamethason, Immunglobulinen und hochdosiertem FIX begonnen. Der Inhibitor wurde nicht geboostert und die FIX-Halbwertszeit normalisierte sich. Es wurden weder allergische Reaktionen, Zeichen eines nephrotischen Syndroms oder schwere Infektionen beobachtet.

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Immuntoleranzinduktion mit hoch-dosiertem FIX und kombinierter immunsuppressiver Therapie bei einem Patienten mit schwerer Hämophilie B und Inhibitor

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Inhibitor development is one of the major adverse events of factor replacement in haemophilia patients. Whereas the inhibitor incidence in haemophilia A is estimated to be as high as 33%, it appears to be less frequent in haemophilia B, occurring in about 1–3% of haemophilia B patients (8, 18). Management of these patients is even more complicated by allergic reactions to factor IX infusions which accompany or precede inhibitor development. Eradication of inhibitors is not only impeded by anaphylaxis but also involves the risk of development of nephrotic syndrome during ITI. These factors account for an overall reluctance to attempt ITI in those patients and, subsequently, for a lack of data on inhibitor elimination in the literature.

Case reports and small series have shown successful and safe ITI with protocols that include desensitization, immunoadsorption and/or immunosuppressive treatment with cyclophosphamide (3, 10, 13, 14, 16). Only recently, new immunosuppressive drugs have evolved. Rituximab, a humanized monoclonal anti-CD20 antibody, is used in a variety of antibody-mediated diseases. Its efficacy in the treatment of acquired haemophilia A has already been demonstrated (15). Mycophenolate mofetil (MMF) is an inhibitor of T- and B-cell proliferation which serves as immunosuppressive agent for organ transplantation. Wermes et al. (19) have reported a successful ITI in a haemophilia B patient with a combination of MMF, dexamethasone (Dexa) and intravenous immunoglobulin (IVIG).

We present a case of successful ITI in a boy with haemophilia B and inhibitor combining rituximab with MMF, Dexa, IVIG and high-dose FIX.

A boy with haemophilia B

The patient is a Caucasian boy in whom severe haemophilia B was diagnosed at the age of 10 months. An underlying mutation with a high risk of inhibitor development was found (ins/del 6379–6384delAATTCainsG in exon B of the FIX gene). He was initially treated on-demand with a plasma-derived FIX product (Immunine®).

At the age of 22 months (after 6 exposure days) urticaria was observed twice shortly after infusion of the drug which responded to treatment with steroids. No inhibitor was detected at that time. On-demand treatment was continued with another plasma-derived FIX (Berinin®). At the age of 5/10/12 years prophylaxis twice a week was started. Two months later a type I inhibitor of 5.44 BU (Bethesda units) was detected which subsequently increased to a peak titer of 6.2 BU. FIX infusions were stopped and bleedings were treated with a bypassing agent (FEIBA®). After a few uneventful infusions a severe allergic reaction to FEIBA® occurred resulting in hypovolemic shock. On-demand treatment with recombinant activated FVII (rFVIIa, NovoSeven®) was initiated. The inhibitor decreased gradually to an undetectable level but the boy suffered from multiple joint and muscle bleeds consuming enormous amounts of rFVIIa.

In 2005, at the age of 11,5 years finally ITI was attempted after informed consent had been obtained. A port-a-cath had been implanted two years before because of difficulties in venous access. The boy received mycophenolate mofetil 2×300 mg/m²/d continuously for seven weeks and $4 \times$ rituximab 375 mg/m² once a week. Pulses of dexamethasone

(2×12 mg/ml/d) and immunoglobulin infusions were given in week 2, 4 and 7. Treatment with high-dose factor IX (Immunine® 2×100 U/kg/d) was started in the second week. The treatment protocol is shown in ►Figure 1.

No allergic reaction was observed nor was there a booster of the inhibitor. ►Figure 2 shows FIX activities measured 12–17 hours after application. FIX dosage was gradually decreased from day +51 on. After two months the FIX half-life was 11 hours. The patient presently receives 30 IU/kg FIX twice a week.

No major bleedings have occurred since the start of ITI. B-cells have been depleted for about a month. Normal values have only been reached after seven months. No serious infections have been observed during the whole follow-up of 3.5 years. Urine analysis at regular intervals has never revealed proteinuria. The boy has finally resumed normal life.

Discussion

Due to the low frequency of haemophilia B inhibitor patients only limited data on their management is available. Old registries include 12–16 patients who have undergone ITI with a failure rate of up to 80% and a similar frequency of adverse events. Risk factors for failure are thought to be adverse reactions, a positive family history for inhibitors and high historical peak titre and pre-induction titre (7, 17, 18). About half of the protocols used in those patients included immune modulating agents and/or plasmapheresis. Freiburghaus et al. reported on successful ITI with the so-called Malmö protocol in 6/7 patients. However, data on history of anaphylaxis and development of nephrotic syndrome is lacking

(10). Current recommendations therefore conclude that ITI in haemophilia B patients should be considered very carefully (2, 6, 11).

Cyclophosphamide is a chemotherapeutic agent which was commonly applied in former protocols but should be used carefully in children due to its possible long-term consequences. Before 2005 only few cases using new approaches with immunosuppressive drugs like rituximab and MMF were presented (13, 19). At that time our patient suffered from multiple bleeds which required frequent and prolonged treatment with rFVIIa leading to heavy restrictions in his daily life.

We therefore proposed an ITI regime which takes into account the prior critical immune response of this patient and which therefore included a combined immunosuppressive/immune modulating therapy. High-dose FIX was only given in the intensive care unit after one week of immunosuppressive treatment with MMF and prior steroid application. After repeated uneventful infusions the treatment was continued in our outpatient clinic. Antimicrobial prophylaxis with cotrimoxazole and topic antimycotics was given until six weeks after cessation of immunosuppressive treatment. Delayed recovery of B cell depletion after rituximab treatment which may pose patients at a considerable risk for infections was fortunately not seen in our patient. No cytopenia which is a major side effect of MMF was found in regularly blood counts of our patient. We therefore conclude that our protocol was safe. However, we recommend that these regimens should only be used in centres with experience in immunosuppressive therapy and management of the adverse events.

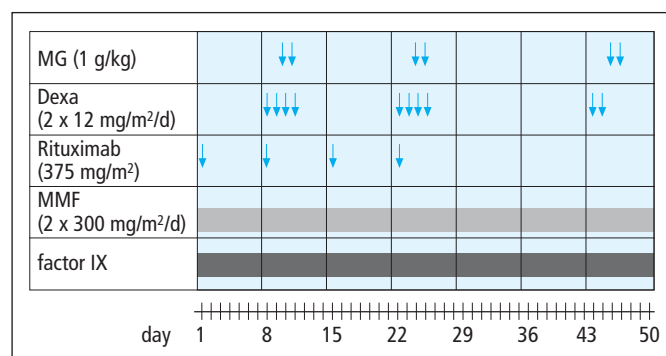


Fig. 1 ITI protocol (IVI: intravenous immunoglobulins; Dexa: dexamethasone; MMF: mycophenolate mofetil)

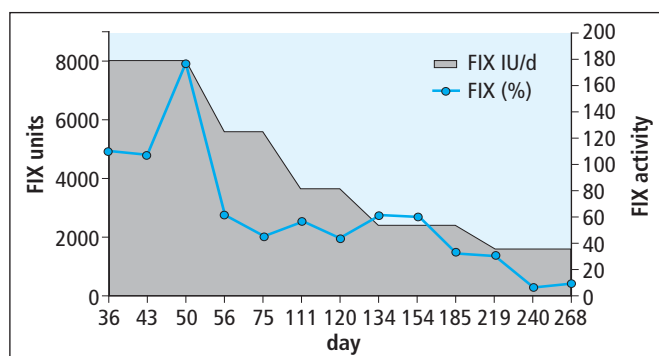


Fig. 2 Factor IX activity determined 12–18 hours after replacement in correlation to administered daily doses of FIX (IU/d).

Success in ITI can be defined as absence of the inhibitor and normalization of recovery and half-life after factor replacement. In our patient, half-life was determined only once in the course of dose reduction of FIX. We did not calculate recovery. However, because the patient has not experienced major bleedings anymore and trough levels of FIX are above 1% under prophylaxis twice a week, we assume that there is no clinical activity of the inhibitor. Low historic peak titre and undetectable pre-ITI inhibitor might have contributed to the favourable outcome.

During the past years more cases on ITI in haemophilia B patients including rituximab with varying outcome have been reported (1, 4, 9). The encouraging experience with MMF in two patients has also been published recently (12). In addition, Cross et al. demonstrated a case of successful ITI with cyclosporine A (5).

Conclusion

There is growing evidence of the efficacy and safety of immunosuppressive drugs in the elimination of inhibitors in haemophilia B patients.

References

- Alexander S, Hopewell S, Hunter S, Chouksey A. Rituximab and desensitization for a patient with severe factor IX deficiency, inhibitors, and history of anaphylaxis. *J Pediatr Hematol Oncol* 2008; 30: 93–95.
- Astermark J, Morado M, Rocino A et al. Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors. *Haemophilia* 2006; 12: 363–371.
- Barnes C, Rudzki Z, Ekert H. Induction of immune tolerance and suppression of anaphylaxis in a child with haemophilia B by simple plasmapheresis and antigen exposure. *Haemophilia* 2000; 6: 693–695.
- Chuansumrit A, Moonsup Y, Sirachainan N et al. The use of rituximab as an adjuvant for immune tolerance therapy in a hemophilia B boy with inhibitor and anaphylaxis to factor IX concentrate. *Blood Coagul Fibrinolysis* 2008; 19: 208–211.
- Cross DC, van der Berg HM. Cyclosporin A can achieve immune tolerance in a patient with severe haemophilia B and refractory inhibitors. *Haemophilia* 2007; 13: 111–114.
- Dimichele D. The North American Immune Tolerance Registry: contributions to the thirty-year experience with immune tolerance therapy. *Haemophilia* 2009; 15: 320–328.
- DiMichele DM, Kroner BL. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. *Thrombosis and haemostasis*. 2002; 87: 52–57.
- Ehrenforth S, Kreuz W, Scharrer I et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet* 1992; 339: 594–598.
- Fox RA, Neufeld EJ, Bennett CM. Rituximab for adolescents with haemophilia and high titre inhibitors. *Haemophilia* 2006; 12: 218–222.
- Freiburghaus C, Berntorp E, Ekman M et al. Tolerance induction using the Malmo treatment model 1982–1995. *Haemophilia* 1999; 5: 32–39.
- Hay CR, Brown S, Collins PW et al. The diagnosis and management of factor VIII and IX inhibitors: a guideline from the United Kingdom Haemophilia Centre Doctors Organisation. *Br J Haematol* 2006; 133: 591–605.
- Klarmann D, Martinez Sagner I, Funk MB et al. Immune tolerance induction with mycophenolate-mofetil in two children with haemophilia B and inhibitor. *Haemophilia* 2008; 14: 44–49.
- Mathias M, Khair K, Hann I, Liesner R. Rituximab in the treatment of alloimmune factor VIII and IX antibodies in two children with severe haemophilia. *Br J Haematol* 2004; 125: 366–368.
- Shibata M, Shima M, Mitsu H et al. Management of haemophilia B inhibitor patients with anaphylactic reactions to FIX concentrates. *Haemophilia* 2003; 9: 269–271.
- Stasi R, Brunetti M, Stipa E, Amadori S. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. *Blood* 2004; 103: 4424–4428.
- Suzuki N, Watanabe J, Kudoh T et al. Successful induction of immune tolerance in a patient with haemophilia B with inhibitor. *Haemophilia* 2003; 9: 340–342.
- Warrier I. Management of haemophilia B patients with inhibitors and anaphylaxis. *Haemophilia* 1998; 4: 574–576.
- Warrier I, Ewenstein BM, Koerper MA et al. Factor IX inhibitors and anaphylaxis in hemophilia Br J Pediatr Hematol Oncol 1997; 19: 23–27.
- Wermes C, von Depka Prodzinski M, Welte K KW S. New strategy for the treatment of factor IX inhibitors in severe haemophilia B. *Blood* 2000; 96: 647a.