

Successful second ITI with factor IX and combined immunosuppressive therapy

A patient with severe haemophilia B and recurrence of a factor IX inhibitor

K. Holstein¹; R. Schneppenheim²; J. Schrum²; C. Bokemeyer¹; F. Langer¹

¹II. Medizinische Klinik und Poliklinik, Universitätsklinikum Eppendorf, Hamburg, Germany;

²Pädiatrische Hämatologie und Onkologie, Universitätsklinikum Eppendorf, Hamburg, Germany

Keywords

Haemophilia B inhibitors, immune tolerance induction, immunosuppression

Summary

Immune tolerance induction (ITI) in patients with haemophilia B and inhibitors may be complicated by anaphylactic reactions and nephrotic syndrome with lower success rates than in haemophilia A (25% vs. 50–90%). According to case reports, immunosuppressive therapy in addition to high doses of factor IX (FIX) appears to be promising.

We report an 18-year-old patient with severe haemophilia B and a FIX inhibitor with a maximum titre of 2.6 Bethesda units and allergic skin reactions to FIX infusions. At 5 years of age, this patient already had a FIX inhibitor with allergic reactions to FIX and activated prothrombin complex concentrate. ITI at 11 years of age with high-dose FIX, dexamethasone, rituximab, mycophenolate

mofetil and intravenous immunoglobulins had induced a sustained response until the current presentation.

The patient was restarted on the same ITI regimen with aforementioned immunosuppressants, which were initiated one week before high-dose FIX. No allergic reactions, nephrotic syndrome or serious infection occurred during ITI. The FIX inhibitor was undetectable after five weeks of treatment and remained so until 19 months of follow-up.

Schlüsselwörter

Hämophilie B, Inhibitor, Immuntoleranzinduktion, Immunsuppression

Zusammenfassung

Im Vergleich zu Inhibitorpatienten mit Hämophilie A führt die Immuntoleranzinduktion (ITI) bei Patienten mit Hämophilie B und Inhibitor

seltener zum Erfolg und häufiger zu Komplikationen wie allergischen Reaktionen oder nephrotischem Syndrom. Nach Fallberichten scheint die zusätzliche Immunsuppression vielversprechend.

Wir berichten über einen 18-jährigen Patienten mit schwerer Hämophilie B und einem Faktor IX (FIX)-Inhibitor von maximal 2,6 Bethesda-Einheiten sowie allergischer Hautreaktion auf FIX-Infusion. Bereits im Alter von 5 Jahren hatte dieser Patient einen FIX-Inhibitor mit allergischer Reaktion auf FIX und aktiviertes Prothrombinkomplex-Konzentrat. Im Alter von 11 Jahren führte eine ITI mit hochdosiertem FIX, Rituximab, Dexamethason, Mycophenolat-Mofetil (MMF) und intravenösen Immunglobulinen zu einer sieben Jahre anhaltenden Remission.

Aktuell wurde eine erneute ITI mit o. g. immunsuppressiver Therapie, die eine Woche vor FIX-Gabe begonnen wurde, durchgeführt, ohne dass es erneut zu Allergie, Infektion oder nephrotischem Syndrom kam. Der FIX-Inhibitor war nach fünf Wochen negativ und die Remission anhaltend über den Beobachtungszeitraum von 19 Monaten.

Correspondence to:

Dr. Katharina Holstein
II. Medizinische Klinik und Poliklinik
Universitätsklinikum Eppendorf
Martinistr. 52, 20246 Hamburg, Germany
Tel. +49/(0)40/741 05-2453, Fax -5193
E-mail: k.holstein@uke.de

Erfolgreiche zweite Immuntoleranzinduktion mit Faktor IX und kombinierter Immunsuppression bei einem Patienten mit schwerer Hämophilie B und Inhibitor-Rezidiv

Haemostaseologie Supplement 2014;34: S5–S8

<http://dx.doi.org/10.5482/HAMO-14-01-0010>

received: January 31, 2014

accepted in revised form: September 17, 2014

Development of inhibitory antibodies against the lacking clotting factor is still a major complication of replacement therapy in haemophilia. The highest risk for inhibitor development is reported during the first 50 exposure days with an incidence of

20–35% and 2–6% in haemophilia A and B, respectively.

In haemophilia B, patients with major deletions, gene rearrangements or frame shift mutations are at highest risk (16).

As the incidence of haemophilia B itself is about tenfold lower than that of haemophilia A, inhibitor development in haemophilia B is a very rare event.

Inhibitor eradication is the goal of immune tolerance induction (ITI), and ITI

regimens similar to those in haemophilia A are usually applied in haemophilia B, some of which include additional immunomodulation.

Success rates for ITI seem to be lower in haemophilia B (13–70%) than in haemophilia A (50–90%).

Moreover, ITI-associated complications such as allergic reactions, anaphylaxis or nephrotic syndrome are reported more frequently in haemophilia B (10, 12, 18).

Data on ITI regimens and outcomes in haemophilia B is sparse, but two studies with registry data, one retrospective multicentre case series and single case reports are available to provide guidance.

The North American Immune Tolerance Registry (NAITR) (10, 11) collected data from 68 haemophilia centres in Northern America and Canada. A past or current history of inhibitor development was reported in

- 2.4% (n = 32) of all haemophilia B patients and
- 6.3% (n = 30) of those with severe factor IX (FIX) deficiency.

17 patients started, and 16 patients completed ITI. Five (31%) of these ITI procedures have been successful with sustained remissions obtained in four (25%). The median FIX dose was 100 IU/kg of body weight daily and in eight patients (47%) additional immunomodulation and immunosuppression were used. Ten pa-

tients experienced allergic reactions, and this resulted in ITI termination in three of them. Of the ten patients with allergic reactions, eight were ITI failures and three developed nephrotic syndrome.

The ISTH-SCC international FIX inhibitor registry (6) focussed on haemophilia B patients with an allergic phenotype associated with the inhibitor. A total of 94 patients were retrospectively reported, 39 of whom underwent ITI. Outcome in this high-risk cohort was poor with only five patients (13%) being successfully tolerated. In 25 patients (64%), FIX alone was used for ITI, while 14 patients received additional immunosuppression, including cyclophosphamide, intravenous immunoglobulins (IVIg) and prednisone. Seven patients were additionally treated with plasmapheresis. ITI-associated nephrotic syndrome was reported in 13 patients, eleven of whom were treated with high-dose FIX concentrate alone.

A recently published multicentre retrospective survey from Italy (3) reported data from the National Registry of Haemophilia and Allied Disorders of the Italian Association of Haemophilia Centres (AICE) involving 282 patients with severe haemophilia B. Of the ten patients who developed an inhibitor (2.8%), three patients experienced allergic reactions to FIX. Five patients underwent ITI with FIX at a median daily dose of 80 IU/kg with four patients achieving sustained remission with no treatment-related complications; one of these patients had previously suffered from

an allergic reaction. Two patients were not considered for ITI because of allergic reactions.

Successful use of the Malmö protocol (FIX + cyclophosphamide + IVIg) was described in a single case (9) and a case series (13), in which six of seven patients could be tolerated. While one patient relapsed after six months, three needed several courses of immunosuppressive therapy.

Several case reports have been published describing the use of immunosuppression in addition to ITI in patients with haemophilia B and inhibitors. The monoclonal CD20 antibody rituximab, mycophenolate mofetil (MMF), IVIg, dexamethasone and cyclophosphamide were used in different combinations. In most cases, complete or partial remissions were achieved (1–4, 7, 14, 15, 17).

In patients with haemophilia B who have acquired an inhibitor and who experience allergic reactions upon replacement therapy, addition of immunosuppressive agents to high-dose FIX seems to be a promising strategy with a favourable risk-to-benefit ratio, but the efficacy of this strategy in patients with recurrent FIX inhibitors is currently unclear.

Case report

We report the case of an 18-year-old patient. Severe haemophilia B was diagnosed at the age of 10 months, and a high-risk mutation for inhibitor development was detected (ins/del 6379–6384delAATTCAinsG in exon B of the FIX gene).

The patient's previous medical history revealed a first allergic skin reaction at the age of 22 months after his sixth exposure day while being treated on demand (4). At that time, no FIX inhibitor was detectable and on demand treatment was continued using a different plasma-derived FIX product with no further reactions. A FIX inhibitor with a maximum titre of 6.2 Bethesda units (BU) was detected at 5 years of age after start of prophylactic FIX infusions with concomitant allergic reactions to FIX and activated prothrombin complex concentrate. He was therefore treated with recombinant human activated factor VII (rFVIIa) and experienced multiple joint

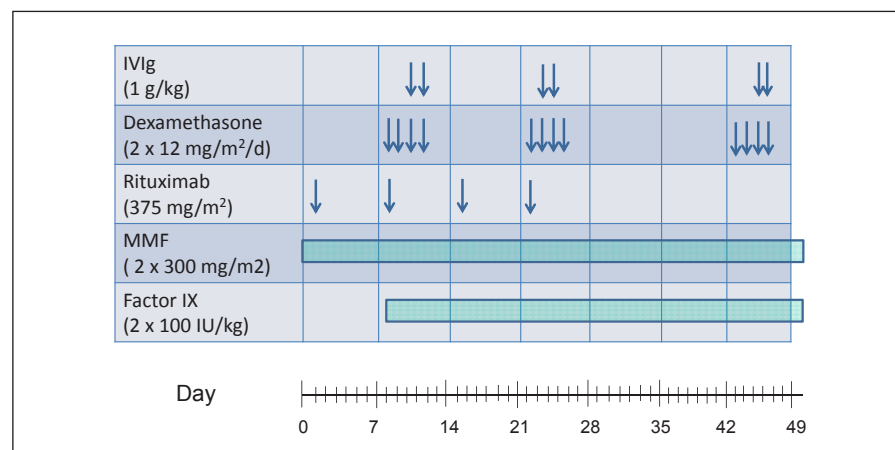


Fig. 1 ITI protocol 2012 (IVIg: intravenous immunoglobulins, MMF: mycophenolate mofetil)

bleeds during the following years. At eleven years of age, ITI with high-dose FIX, dexamethasone, rituximab, MMF and IVIg was initiated after the inhibitor level had dropped to undetectable levels. No further allergic reactions occurred and no nephritic syndrome developed. Success of ITI was sustained over the following seven years until the current presentation (4).

The patient presented in January 2012 at age of 18 with increasing bleeding symptoms despite regular prophylaxis. He had a major joint bleed into the left knee six months earlier with intensive FIX treatment and long lasting synovitis. FIX trough level 24 hours after the injection of 50 IU/kg FIX concentrate was $<0.2\%$, but at that time no inhibitor was detectable by a Nijmegen-modified Bethesda assay. Acute bleeds were controlled by increasing the FIX doses. Two months later, allergic skin reactions upon FIX infusions occurred, and a FIX inhibitor with a maximum titre of 2.6 BU was measured 7 years after first ITI.

While being treated on demand with rFVIIa, the patient experienced multiple major joint bleeds, resulting in high-dose and long-term treatment with rFVIIa and only slow resolution of a major knee joint bleed. He was therefore restarted on the same ITI regimen with high-dose FIX and aforementioned immunosuppressants (► Fig. 1) a few weeks after inhibitor detection. Rituximab and MMF were initiated one week before re-exposing the patient to FIX. Rituximab was administered using the standard regimen for lymphoproliferative or autoimmune diseases with four weekly doses of 375 mg/m^2 body surface area; MMF was used at a dose of 300 mg/m^2 twice daily for 50 days. Dexamethasone pulses were given at 12 mg/m^2 twice daily on days 8–11, 22–25 and 43–46 in parallel to two infusions of IVIg at 1 g/kg each. The first five infusions of FIX at 100 IU/kg twice daily were administered under close monitoring on an intermediate care unit. Urine analysis was initially performed daily and then weekly during the first seven weeks of ITI. No allergic reactions and no anamnestic response, nephrotic syndrome or serious infection occurred during ITI. The FIX trough levels increased rapidly and the FIX inhibitor was already unde-

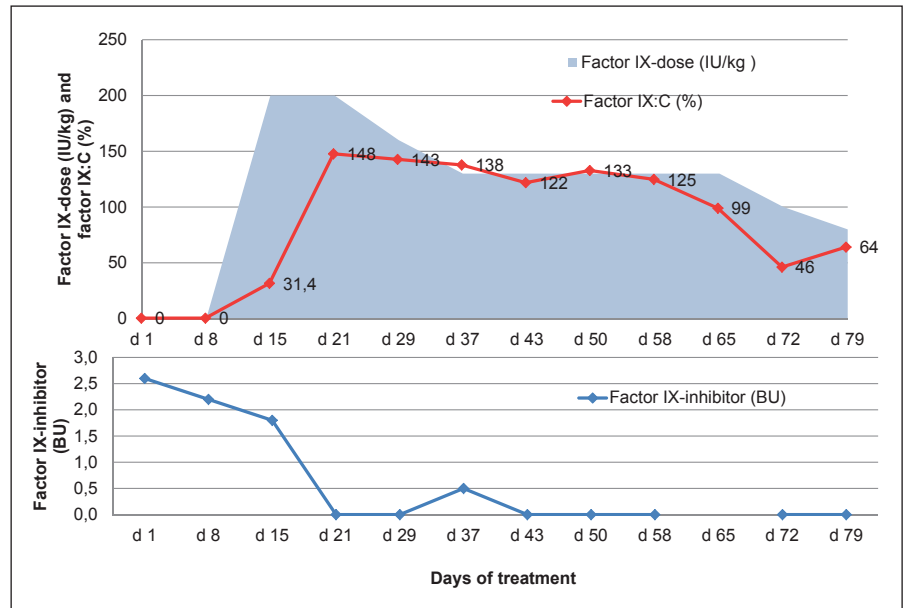


Fig. 2 Laboratory results during ITI

tectable after five weeks of treatment (► Fig. 2). FIX trough levels of $>150\%$ allowed early dose reduction. During ITI no further bleeding occurred. FIX doses were tapered slowly to 50 IU/kg every second day six months after ITI initiation. At ten months, the patient experienced another major knee joint bleed with synovitis requiring radiosynoviorthesis. At that time, FIX trough levels and FIX recovery were adequate, and no inhibitor was detected. After resolution of synovitis, no further major joint or soft-tissue bleeding occurred.

Intensive immunosuppressive treatment resulted in complete B-cell depletion and severe deficiency of CD4+ T-cells. Neutrophil counts were unaffected. Pharmacological prophylaxis against pneumocystis jirovecii and herpes simplex virus was carried out with cotrimoxazole and aciclovir, respectively. Twelve months after treatment with rituximab, the B-cell count was still reduced to 4.2% (reference range $7.9\text{--}18.7\%$). Complete recovery of B-cells was observed 16 months after the initiation of rituximab therapy. No bacterial, viral or opportunistic infection occurred during this long period of immunosuppression. At 19 months of follow-up after the initiation of his second ITI, the patient has still no signs of inhibitor recurrence.

Discussion, conclusion

In a young adult patient with severe haemophilia B and late recurrence of an inhibitor, we attempted a second ITI, although the outcome in this particular situation appeared to be poor because of the patient's allergic phenotype. An ITI regimen with high-dose FIX and concomitant immunosuppressive therapy was used that was identical with the patient's previous ITI regimen as described by Beutel et al. (4). The ITI course was uneventful without occurrence of further allergic reactions, nephrotic syndrome, bleeding events or infectious complications and resulted in complete remission of the inhibitor. Since the normal half-life of FIX is not clearly established (8), a definition of complete remission according to haemophilia A (negative inhibitor titre, recovery of $>0.6\%/ \text{IU/kg}$ and half-life of $>6 \text{ h}$) is not established for haemophilia B. In our patient, the inhibitor titre was negative after five weeks of treatment, and we observed a FIX trough level of 23% 72 hours after the infusion of 64 IU/kg as well as a recovery of $0.97\%/ \text{IU/kg}$ 100 days after the initiation of ITI, which is compatible with normal FIX pharmacokinetics.

Several single cases have been reported in the literature suggesting that ITI in com-

ination with immunosuppressive therapy is safe and efficacious in patients with haemophilia B and inhibitors.

Registry data indicate that patients with an allergic phenotype are at particularly high risk for treatment complications and ITI failure. Therefore, ITI should be carefully considered, and a weak recommendation for the combined use of FIX and immunosuppressive therapy is provided (8).

The positive results of the single cases in contrast to the registry data are suggestive for a publication bias, but can also be due to the use of immunosuppressive agents in most of the case reports and only 36% and 47% in the ISTH-SCC and NAITR registries, respectively. Infectious complications with immunosuppressive therapy seem to be low in this young patient cohort, leading to a perceived benefit of this strategy for haemophilia B inhibitor patients with an allergic phenotype. Our data further support this strategy even in the setting of late inhibitor recurrence. However, multicentre studies or registries are needed to confirm these findings and to avoid the potential publication bias of single case reports.

Conflict of interest

KH and FL have received travel support, research funding, lecture fees, and/or hon-

oraria for consultancy from Baxter, CSL Behring and Novo Nordisk.

References

- Alexander S, Hopewell S, Hunter S, Chuksey A. Rituximab and desensitization for a patient with severe factor IX-deficiency, inhibitors and history of anaphylaxis. *J Pediatr Haematol Oncol* 2008; 30: 93–95.
- Barnes C, Davis A, Furmedge J et al. Induction of immune tolerance using rituximab in a child with severe haemophilia B with inhibitors and anaphylaxis to factor IX. *Haemophilia* 2010; 16: 840–841.
- Batorova A, Morongova A, Tagariello G et al. Challenges in the management of hemophilia B with inhibitor. *Semin Thromb Hemost* 2013; 39: 767–771.
- Beutel K, Hauch H, Rischewski J et al. ITI with high-dose FIX and combined immunosuppressive therapy in a patient with severe haemophilia B and inhibitor. *Hämostaseologie* 2009; 29: 155–157.
- Castaman G, Bonetti E, Messina M et al. on behalf of Italian Association of Haemophilia Centers. Inhibitors in haemophilia B: the Italian experience. *Haemophilia* 2013; 19: 686–690.
- Chitlur M, Warrier I, Rajpurkar M, Lusher JM. Inhibitors in factor IX deficiency: a report of the ISTH-SSC international FIX inhibitor registry (1997–2006). *Haemophilia* 2009; 15: 1027–1031.
- 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.
- Collins PW, Chalmers E, Hart DP ET AL. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th ed). UK Haemophilia Centres Doctors Organisation. *Br J Haematol* 2013; 160: 153–170.
- Curry NS, Misbah SA, Giangrande PL, Keeling DM. Achievement of immune tolerance in a patient with haemophilia B and inhibitory antibodies, complicated by an anaphylactoid reaction. *Haemophilia* 2007; 13: 328–330.
- DiMichele D, Kroner BL. The North American Immune Tolerance Registry: Practices, outcomes, outcome predictors. *Thromb Haemost* 2002; 87: 52–57.
- DiMichele. The North American Immune Tolerance Registry: contributions to the thirty-year experience with immune tolerance therapy. *Haemophilia* 2009; 15: 320–328.
- Ewenstein BM, Takemoto C, Warrier I et al. Nephrotic syndrome as a complication of immune tolerance in hemophilia B. *Blood* 1997; 89: 1115–1116.
- Freiburghaus C, Berntorp E, Ekman M et al. Tolerance induction using the Malmö treatment model 1982–1995. *Haemophilia* 1999; 5: 32–39.
- Gameran S, Singh AM, Makhija M, Sharathkumar A. Successful eradication of inhibitor in a patient with severe haemophilia B and anaphylaxis to factor IX concentrates: is there a role for Rituximab and desensitization therapy? *Haemophilia* 2013; 19: e382–e385.
- 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.
- Oldenburg J, Pavlova A. Genetic risk factors for inhibitors to factor VIII and IX. *Haemophilia* 2006; 12 (Suppl 6): 15–22.
- Verghese P, Darrow S, Kurth M et al. Successful management of factor IX inhibitor-associated nephrotic syndrome in a hemophilia B patient. *Pediatr Nephrol* 2013; 28: 823–826.
- Warrier I, Ewenstein BM, Koerper MA et al. Factor IX inhibitors and anaphylaxis in haemophilia B. *J Pediatr Hematol Oncol* 1997; 19: 23–27.