Case Report

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

K. Beutel\textsuperscript{1}; H. Hauch\textsuperscript{2}; J. Rischewski\textsuperscript{3}; U. Kordes\textsuperscript{1}; J. Schneppenheim\textsuperscript{4}; R. Schneppenheim\textsuperscript{1}

\textsuperscript{1}Paediatric Haematology and Oncology, University Medical Centre Hamburg-Eppendorf, Germany; \textsuperscript{2}University Children’s Hospital Tübingen, Germany; \textsuperscript{3}Paediatric Haematology and Oncology, University Hospital Basel, Switzerland; \textsuperscript{4}Institute of Biochemistry, University of Kiel, Germany

Summary
Inhibitor development is a rare but serious event in haemophilia 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\textsuperscript{®}. 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.

Keywords
Haemophilia B, inhibitor, immune tolerance induction, immunosuppression

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, immunadsorption 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 637–638delAAATCInsG in exon B of the FIX gene). He was initially treated on-demand with a plasma-derived FIX product (Immune®).

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 there was 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.

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 topical 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.
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