



LETTER TO THE EDITOR

Induction of immune tolerance using rituximab in a child with severe haemophilia B with inhibitors and anaphylaxis to factor IX

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Anaphylaxis to factor IX (FIX) in patients with haemophilia B is a rare and life-threatening complication that occurs in association with the development of inhibitors to FIX [1]. The preferred management of patients with haemophilia and inhibitors is to induce immune tolerance with frequent high-dose factor replacement but this is difficult in patients with inhibitors to FIX and anaphylactic reactions. A more recent approach in the management of patients with haemophilia and inhibitors includes the use of the anti-CD20 monoclonal antibody, rituximab (Mabthera®; Roche, Deewhy, Australia). We report the case of immune tolerance induction in a patient with severe haemophilia B and inhibitors and anaphylaxis to FIX.

The patient is a 10-year-old child diagnosed with severe haemophilia B (FIX <1%) at the age of 8 months. At 9 months of age he developed recurrent anaphylactoid reactions following exposure to plasma-derived FIX concentrate manifest by shortness of breath, wheeze and widespread urticaria. There was no evidence of significant haemodynamic instability. A low-titre inhibitor to FIX was detected (1.0 BU) and FIX recovery was absent 2 h after infusion of FIX. At 18 months of age, immune tolerance using simple plasma exchange and high-dose FIX (130 units kg⁻¹ day⁻¹) was commenced and successful in eradicating the inhibitor for a total of 40 months. A further two attempts at immune tolerance induction using high-dose FIX were unsuccessful in improving the FIX recovery and were complicated by repeated anaphylactoid reactions. There was no biochemical evidence of nephrotic syndrome at anytime during the immune tolerance regimes.

Over the subsequent 5 years, the patient was managed with recombinant factor VIIa which was effective in limiting the bleeding episodes. However, the patient continued to experience frequent haemarthroses particularly into his right knee eventually resulting in the development of a 110° fixed flexion deformity. He subsequently became wheelchair bound. His management was impeded by poor intravenous access requiring insertion of multiple central venous access devices complicated by recurrent infection and thrombosis. Eventually, he required creation of a femoral artery to saphenous vein fistula using polyurethane (Thoratec®, Thoratec Corp, Pleasanton, CA, USA) graft.

A fourth attempt at immune tolerance was commenced with rituximab (375 mg m⁻² week⁻¹) for 4 weeks. A FIX inhibitor screen prior to commencement was negative. The first infusion of rituximab was associated with facial swelling but no other allergic manifestations. Premedication for the following three infusions included a corticosteroid and antihistamine. One week following completion of rituximab, high-dose exposure to plasma-derived FIX (Monofix; CSL, Parkville, Australia) was commenced (100 units kg⁻¹ day⁻¹) with antihistamine cover only. Two weeks after the commencement of FIX the inhibitor titre peaked at 27 BU but decreased over the following 2 weeks and was negative for 4 weeks after the commencement of FIX infusions. The patient did not experience any symptoms of anaphylaxis. A FIX recovery study performed 1 month following the final rituximab infusion confirmed normal FIX recovery [0.88 (units kg⁻¹)/ (units mL⁻¹)]. A formal FIX half-life study was not performed. Serum IgG levels have remained within the normal range and the patient did not receive supplemental intravenous immunoglobulin. Lymphocyte subset analysis performed at 10 months following rituximab infusion was normal with

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normal levels of CD20+ lymphocytes (11.7%). The patient has remained FIX inhibitor free for 12 months and this has allowed surgical correction of the fixed flexion deformity with an extensive open release of the knee joint and Ilizarov frame followed by an intensive physiotherapy programme. The procedure was managed with a preoperative infusion of 100 units kg⁻¹ FIX, followed by an infusion of 3 units kg⁻¹ h⁻¹ for 72 h and was not complicated by bleeding and at no time did the patient experience bleeding from the frame pin sites. Unfortunately, because of the extensive damage to the joint, knee flexion was limited to a few degrees only. The patient is now ambulant with a knee and ankle foot orthosis and is using one or two forearm crutches for walking longer distances. He is currently managed on prophylaxis and is self-infusing the FIX concentrate using the Thoratec graft.

The association of anaphylaxis and inhibitor development in patients with haemophilia B has been well described but remains poorly understood [1]. Induction of immune tolerance for patients with haemophilia B and FIX inhibitors is recognized to be particularly difficult with successful immun thrombocytopenia purpura (ITT) occurring in five of 16 patients (31%) with FIX inhibitors and anaphylaxis described in the North American Immune Tolerance Registry [2]. Allergic reactions to FIX infusions were the reason for ceasing immune tolerance in five of 11 unsuccessful course of immune tolerance.

Rituximab is a chimaeric murine-human monoclonal antibody directed against the CD 20 antigen that is present on mature B lymphocytes. After treatment with rituximab, mature B lymphocytes are depleted and this property suggests that rituximab may be effective in auto-immune conditions. Thus far, rituximab has been used with varying success in a number of autoimmune diseases including autoimmune haemolytic anaemia and immune thrombocytopenia [3].

A number of case reports and small case series have described the successful use of rituximab in patients with haemophilia A and inhibitors to factor VIII (FVIII) and haemophilia B with inhibitors to FIX [4,5]. The reported duration of affect in these case series ranges from 11 to 24 months. A suggested protocol for the use of rituximab in patients with haemophilia and inhibitors has been suggested [5], and a prospective study investigating the safety and

effect of rituximab in patients with haemophilia A and inhibitors to FVIII has been proposed. Included in the suggested protocol, co-administration of clotting factor concentrate and rituximab is recommended on the speculation that this may lead to recruitment of further CD20+ B cells responsible for inhibitor production. In patients with haemophilia B and inhibitors and anaphylaxis to FIX this may be difficult in the setting of recurrent allergic reactions.

We describe the successful use of rituximab in the difficult management scenario of FIX inhibitors associated with anaphylaxis. Treatment with rituximab in our patient has been associated with very limited morbidity and importantly has provided a critical window of opportunity to correct a disabling lower limb contracture. Although we are hopeful treatment with rituximab will be associated with long-term eradication of the inhibitor in our patient, we believe that the patient will have benefited significantly from a period of being free of inhibitor which enabled surgical correction of the contracture. Longer term follow-up to monitor for the potential future side effects of mature B lymphocyte depletion are required to accurately assess the risk and benefit relationship of rituximab in patients with haemophilia and inhibitors.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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