

ORIGINAL ARTICLE

Inhibitors in factor IX deficiency a report of the ISTH-SSC international FIX inhibitor registry (1997–2006)*

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Summary. Haemophilia B is an X-linked disorder resulting in coagulation factor IX deficiency. Patients with severe deficiency (<1% factor IX activity) may have significant bleeding complications similar to patients with haemophilia A or factor VIII deficiency. The development of inhibitory antibodies to the missing coagulation factor is a major complication in patients with haemophilia. While the incidence of inhibitors in patients with haemophilia A is higher than that in haemophilia B, the occurrence of allergic and or anaphylactic reactions with the development of inhibitors is unique to haemophilia B patients. Since haemophilia B is a rare bleeding disorder and the incidence of inhibitors is an even

rarer entity, a registry was established by Dr Indira Warriar under the auspices of the FVIII/FIX subcommittee of the International Society of Thrombosis and Haemostasis, to gather information on the occurrence and characteristics of patients with inhibitors and also the incidence of allergic and anaphylactic reactions in this group of patients. This is the first report from this registry and helps us to gather some insight on haemophilia B patients with inhibitors and complications related to inhibitor development and difficulties with immune tolerance.

Keywords: anaphylaxis, haemophilia B, immune tolerance, inhibitor antibodies, nephrotic syndrome

Introduction

Haemophilia A and haemophilia B are X-linked recessive, inherited bleeding disorders characterized by specific coagulation factor deficiencies. Factor VIII (FVIII) deficiency (haemophilia A) is seen in approximately 80% of patients, while factor IX (FIX) deficiency (haemophilia B) occurs in approximately 20% of patients. Based on the activity of the coagulation factor detectable in the patient's plasma, haemophilia may be classified as mild (>5%), moderate (1–5%) or severe (<1%). In persons with haemophilia B, approximately 30–45% have severe haemophilia B, whereas 60% of those with haemo-

philia A have severe disease. With the advent of highly purified, virally attenuated, plasma derived coagulation factor products and then recombinant FVIII and FIX concentrates, the complications from severe bleeding such as haemophilic arthropathy and transmission of infectious agents have almost been obscured, leaving the development of inhibitory antibodies as the most serious and important complication seen. The development of inhibitory antibodies (which result in the neutralization of coagulation factor activity following infusion of FVIII or FIX) is seen in about 30% of patients with severe haemophilia A and in 1–3% of those with haemophilia B [1].

A 1970 survey of United States Hemophilia Treatment Centers (HTCs) showed that 44% of haemophilia B patients had severe disease, while 60% of haemophilia A patients were classified as severe [2]. A later US survey by Katz, concerning 1967 patients with haemophilia B being followed at 82 HTCs, indicated that 37% were classified as severe, 33% as moderate and 30% mild [3]. A survey conducted by Warriar in 1997–98 (which included some of the patients initially reported by Katz) showed a similar breakdown of severe, moderate and

*Report of the ISTH-SSC FIX inhibitor registry. Registry of severe allergic/anaphylactic reactions to FIX in hemophilic patients with FIX inhibitors.

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Table 1. Factor IX deficiency: US survey data.

	Years 1997–98 (Warrier)	Year 1995 (Katz)
Responding HTC's	97	82
Total # patients	1900	1967
Severe (<1%)	573 (30%)	735 (37%)
Moderate (1–5%)	680 (36%)	644 (33%)
Mild (>5%)	647 (34%)	590 (30%)

HTC, Hemophilia Treatment Centers.

mild haemophilia B. Data were obtained from 97 HTCs and 1900 patients, 573 (30%) with severe, 680 (36%) with moderate and 647 (34%) with mild haemophilia [4] (Table 1).

An inhibitor antibody is a polyclonal high affinity immunoglobulin that neutralizes the procoagulant activity of a specific coagulation factor. Inhibitor levels, measured using Bethesda units (BU), are classified as high titre (≥ 5 BU) or low titre (<5 BU). Although the incidence of inhibitors in patients with haemophilia B is low most are 'high titre'. Certain genetic mutations are associated with an increased incidence of development of inhibitors in haemophilia A and haemophilia B. Haemophilia B patients with complete deletions or rearrangements of the FIX gene have a risk of inhibitor development of approximately 50%, whereas those with nonsense or frame shift mutations have a risk of approximately 20% [5]. For those with mis-sense mutations the risk of inhibitor development is almost zero [6]. Immune Tolerance Induction (ITI) therapy is the most effective method for management of patients with inhibitors to FVIII. However, in patients with haemophilia B and a FIX inhibitor, this has not been as successful, reported success rates being 40% or less [4,6,7].

In the 1990s, as high purity FIX concentrates became available and prelicensure clinical trials with these included periodic FIX inhibitor assays, a few inhibitors were detected which were associated with severe allergic reactions on infusion of such products [7]. As a result, some physicians treating patients with haemophilia B worried that these high purity FIX products were more immunogenic than the 'older' intermediate purity FIX products. As the occurrence of inhibitors in patients with Haemophilia B is uncommon and developing a better understanding of the characteristics of inhibitor development in these patients has been difficult, an International Registry of patients with FIX Inhibitors was established under the auspices of the FVIII/FIX subcommittee of the International Society on Thrombosis and Hemostasis (ISTH), Scientific and Standardization Committee (SSC) by Dr Indira Warrier in 1997. Data on the occurrence of inhibitors in

haemophilia B, as well as complications associated with them and their management, were collected until 2006; here we present a report of the information collected from this database. Current research efforts are being directed towards a better understanding of the epidemiology and immunological aspects of inhibitor development.

Materials and methods

The ISTH-SSC FIX Inhibitor Registry (1997–2006)

This registry focused on patients with FIX inhibitors who had complications associated with the inhibitor development, mainly severe allergic (clinical reaction following exposure to the FIX concentrate manifesting with pruritis, urticaria, erythema, angioedema without respiratory or cardiovascular compromise) or anaphylactic reactions (clinical reaction following exposure to the FIX concentrate manifesting with pruritis, urticaria, erythema, angioedema with respiratory or cardiovascular compromise). The registry data were obtained by questionnaire. The questionnaire was sent to haemophilia centres in North America, European countries, Japan and Australia, and was also distributed at the annual meeting of the SSC's FVIII/FIX Subcommittee, and later appeared on the SSC website. Completed questionnaires were returned to Dr Indira Warrier in Detroit, MI. While periodic oral reports were presented at the SSC's FVIII/FIX Subcommittee meetings, this is the first published report of data from this registry.

Results

As of May, 2006, 94 individuals with inhibitors had been reported to the registry, 55 from the US and 30 from other countries. Many of them were receiving FIX complex concentrates at the time, while others were receiving a high-purity FIX concentrate (either recombinant or plasma-derived). There was no evidence that a particular type of FIX concentrate caused these reactions.

Anaphylaxis was reported in 56 patients; of these, 29 were from the USA and 27 from other countries. Another cohort of 38 subjects had severe allergic reactions. In the 94 patients, the median age at

Table 2. FIX inhibitor characteristics in patients with allergic reactions.

Median age at inhibitor detection	19.5 months (9–156)
Median exposure days	11 days (2–180)
Peak inhibitor titre	30 BU (1–1156)

Table 3. Registry data on treatment of FIX inhibitors with ITI.

Number of patients (N = 39)	ITI modality
25	FIX product
14	FIX + immune modulation (CTX, IVIG, prednisone)
7/14	Plasmapheresis & filtration immune adsorption

CTX = cyclophosphamide; IVIG = IV immunoglobulin; ITI, Immune Tolerance Induction; FIX, Factor IX.

Table 4. Nephrotic syndrome (NS) and ITI.

Number of patients developing NS	13
Total NS with history of anaphylaxis	11
NS developing while on ITI regimen	13/13 (100%)
NS when FIX alone used for ITI	11/13 (84%)

ITI, Immune Tolerance Induction; FIX, Factor IX.

detection of the inhibitor was 19.5 months (range 9–156 months) and the median number of exposure days until inhibitor detection was 11 (range 2–180 days) (Table 2). The mean peak inhibitor titre reported was 30 BU (range 1–1156 BU). In some of these patients, anaphylaxis or severe allergic reactions occurred concurrently with inhibitor detection, whereas in others, these events occurred weeks or months apart. In view of the real possibility of developing anaphylaxis with exposure to any FIX containing product after relatively few exposure days to FIX, it was recommended that the first 20 doses of FIX concentrate be given in a hospital prepared to deal with this severe complication [8–10].

Thirty-two of the 94 patients had undergone genotyping for mutations in the FIX gene causing their haemophilia B; it was observed that large gene deletions such as null mutations and complete gene deletions were associated with inhibitor development as well as anaphylaxis. Patients with complete gene deletions were found to have the greatest risk for anaphylaxis, with a minimum risk of 26%, while nonsense, frame shift and partial gene deletions had a 2.4% risk [5].

Data were also obtained concerning response to ITI in patients with FIX inhibitors. Several patients had to undergo a FIX desensitization regimen before they could be tried on ITI regimen. A total of 39 patients reported to the registry underwent some form of ITI. Twenty-five were treated with FIX concentrate alone, 14 with FIX concentrate in combination with immune modulation therapy (cyclophosphamide, IVIG and/or prednisone). Seven patients who received immunomodulation also underwent plasmapheresis in combination with

immunofiltration or immune adsorption (Table 3). Only five of these patients were successfully cleared of the inhibitor, two with FIX concentrate alone and three with FIX concentrate and plasmapheresis. Thirteen patients including 11 with a history of anaphylaxis to FIX developed nephrotic syndrome during ITI (Table 4). All 13 patients who developed nephrotic syndrome developed this complication 8–9 months into the ITI regimen with high dose FIX concentrate (100–325 IU kg⁻¹ per day). Clinically, patients presented with periorbital edema, proteinuria and hypoalbuminemia [11]. Eleven of 13 (84%) developed nephrotic syndrome while receiving a purified FIX product alone. As far as the treatment of bleeding episodes in the patients with FIX inhibitors reported via the registry, over 50% of those reported after the year 2000 were being treated with recombinant activated FVII.

Discussion

Despite the similarities between FVIII and FIX inhibitors, there are several important differences as well. In contrast to the severe allergic or anaphylactic reactions often seen in association with FIX inhibitors, anaphylactic reactions to FVIII in haemophilia patients with FVIII inhibitors almost never occur. Severe anaphylactic reactions occurring simultaneously with the appearance of inhibitors in haemophilia B patients were first reported in the 1990's [7–9,12,13]. It has been postulated that the smaller molecular weight of FIX (55 000 Daltons) allows its distribution in both the intra and extravascular space compared with FVIII, which complexed with von Willebrand factor (VWF) stays confined to the intravascular space [1]. The extravascular distribution may facilitate mast cell activation and IgE mediated hypersensitivity [11]. Most of the inhibitory antibodies are known to be polyclonal and predominantly of the IgG4 subclass [14]. Sawamoto *et al.* in 1996 reported six patients with haemophilia B who had allergic reactions to purified FIX concentrates. All samples were positive for IgG4, but three patients who were tested during the acute reaction also showed IgG1 antibodies indicating that this may be a transient phenomenon [14]. Another possible reason is that haemophilia B patients are exposed to much larger amounts of exogenous protein when treated with standard doses of FIX because of the higher normal concentration in plasma, FIX = 5 mcg mL⁻¹ vs. 0.1 mcg mL⁻¹ of FVIII, and the standard dosing of FIX replacement therapy is double that of FVIII deficiency to allow for increased volume of distribution [10]. However, immune

complex formation has not been documented in patients with allergic reactions to FIX [15].

With the development of high purity FIX concentrates, prelicensure clinical trials were conducted in both previously treated patients with severe haemophilia B and previously untreated patients (PUPS). The study cohorts were relatively small, but an occasional PUP developed not only a FIX inhibitor but also anaphylaxis on infusion of the high-purity FIX product. Many physicians of patients with haemophilia B were concerned that the new high purity product(s) were responsible for the occurrence. In view of such concerns, Warrior recommended that FVIII/FIX subcommittees of ISTH's SSC start a registry of these severe reactions in haemophilia B patients. As reported above, there were 94 patients on the registry with history of allergy or anaphylaxis to FIX containing products and 39 patients with inhibitors. It is noteworthy that only five of the 39 with inhibitors were successfully treated with immune tolerance therapy indicating a very poor response to ITI regimens. The other unique association was the occurrence of Nephrotic Syndrome (in patients with previous history of allergy/anaphylaxis) that was seen during ITI using FIX containing products. Of two known to the authors to have undergone renal biopsy, both had a membranous glomerulonephritis [11,16]. According to data reported to the registry, proteinuria and oedema resolved on decrease or discontinuation of FIX in most, but not in all patients.

Midway through the conduct of this registry, Professor P. M. Mannucci proposed to the FVIII/FIX subcommittee that an immunological study be conducted on patients with newly developed inhibitors and anaphylaxis. The study protocol was presented and posted on the ISTH website. However, it proved to be very difficult to accrue patient samples for these studies. In those infants or young children who developed anaphylaxis while being infused with FIX, medical management of the anaphylactic shock took precedence over looking up a study protocol.

The presence of certain mutations in the patients FIX gene is an important predisposing factor in the development of FIX inhibitors; mutations resulting in a loss of coding information are most frequently associated with inhibitor development. Thorland *et al.* reported that complete gene deletions confer the greatest risk for anaphylactic reactions [5]. It was postulated that deletion of neighbouring immunomodulatory genes contributes to anaphylaxis in these patients [5,16].

Clinical trials are difficult to conduct as these patients are few and far between. The establishment

of international registries has facilitated more accurate reporting of the incidence of the unique complications seen in this group of rare bleeding disorder patients. The long-term management of these patients with the potentially life threatening complications remains to be defined. Continued collection of information via registries may promote a better understanding of the pathophysiology and stimulate co-operative research and clinical trials, which are very much needed for these patients [17].

Disclosures

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

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