Introduction

Hemophilia B is an underrecognized disease, with research efforts primarily directed at hemophilia A, owing to the latter disorder's greater prevalence and frequency of inhibitors. One-fifth as common as hemophilia A, hemophilia B is estimated to affect approximately 10% to 20% of hemophilia patients. The incidence of inhibitors is 5 to 10 times less common than for hemophilia A (1.5% to 3% versus 15% to 30%, respectively). Despite its rare occurrence and lower frequency of inhibitors compared to hemophilia A, hemophilia B is associated with greater morbidity. More than 80% of the inhibitors that develop to factor IX (FIX) are of the high-responder type and it is not uncommon for severe anaphylaxis or allergic reactions in connection with the administration of FIX-containing products to accompany the development of an inhibitor. Nevertheless, what is known about hemophilia B remains largely derivative. Most information concerning standards of care for the treatment of bleeding in the presence of inhibitors is based on extrapolations from hemophilia A clinical data. Few retrospective analyses or prospective studies examining the treatment or prevention of bleeds in inhibitor patients have historically involved patients with FIX alloantibodies.

Besides lacking defined standards of care, hemophilia B lacks established guidelines for FIX antibody surveillance. The disorder has remained underappreciated by researchers until the mid nineties, when registry databases were first created. The advent of such registries enabled collaborative efforts to be made in the collection of information about hemophilia B. One such registry, the ISTH-SSC international FIX inhibitor registry, was developed by Dr. Indira Warrier under the auspices of the FVIII/IX Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) to gather information on hemophilia B patients with inhibitors and complications related to inhibitor development. Through the clinical surveillance of FIX inhibitors and subsequent documentation of complications associated with their development, researchers and clinicians involved in the ISTH-SSC registry initiative have been able to further understanding within the scientific community about a neglected disease.

Clinical Experience That Gave Rise to the ISTH-SSC International FIX Inhibitor Registry

Providing impetus to the creation of the ISTH-SSC international registry was a small-scale analysis conducted in 1996 by Warrier and colleagues. Investigators examined clinical and laboratory data on children with hemophilia B who had severe allergic reactions to infused FIX in association with the development of an inhibitor (Table 1). Twelve hemophilia care centers from the United States, Canada, and Europe provided information on 18 patients.

Study Results

- Study population comprised various ethnic and racial groups
- FIX inhibitor was detected simultaneously with first sign of anaphylaxis in 12/18 patients
Considerations
The Warrier study raised questions that remain speculative, given what little is known about hemophilia B. A primary question concerned the high incidence of anaphylaxis at the time of inhibitor development. Anaphylaxis in children with the disorder was only newly discovered, and study investigators questioned whether the purity of FIX concentrates was a factor in the severe reactions observed in their cohort of patients. Additionally, there was no standardized protocol in place to manage bleeding. rFVIIa demonstrated excellent results but was only available on a compassionate use basis in the United States for the treatment of life- or limb-threatening bleeding episodes, which left FIX-containing PCCs or aPCCs as the only readily available treatment choice. However, the degree to which the amount of FIX in the agent induced anaphylactic reactions remained a question. These questions aside, the Warrier study was instrumental in illuminating the complications of anaphylaxis and allergy with simultaneous inhibitor development and introduced issues that would be addressed several years later as part of the ISTH-SSC registry report.

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ISTH-SSC International FIX Inhibitor Registry

Collecting information via questionnaire from 1997 through 2006 on hemophilia B patients, the registry focused on patients who had severe allergic or anaphylactic complications associated with inhibitor development. Questionnaire recipients were either affiliated with hemophilia treatment centers in North America, Europe, Japan, and Australia, or attendees at the annual meeting of the SSC's FVIII/IX Subcommittee.

Study Results

- 94 individuals reported to registry as of May 2006
- Patients received variety of FIX concentrates, including complex concentrates and high-purity recombinant or plasma-derived concentrates
- Anaphylaxis was reported in 56 patients
- Severe allergic reactions occurred in 38 subjects comprising another cohort
- Reactions occurred concurrently with inhibitor detection in some patients and occurred weeks...
REFERENCES


6. Culling information via questionnaire from 1997 through 2006 on hemophilia B patients, the registry databases were first created. The disorder has remained underappreciated by researchers until the mid nineties, when increasingly anecdotal reports emerged of severe allergic reactions to FIX concentrates. The International Registry for Hemophilia B (http://www.kcl.ac.uk/ip/petergreen/haemBdatabase.html) was established in 1995. 12


8. Immune tolerance induction (ITI) attempted in 12 patients, with generally poor responses. Patients received variety of FIX concentrates, including complex concentrates and high purity derivatives. "Historically, ITI has met with poor success in hemophilia B patients, and results obtained from the ISTH registry accord with results documented elsewhere. An alternative ITI strategy for the treatment of FIX inhibitors involves use of a regimen comprising mycophenolate-mofetil, and dexamethasone and IV immunoglobulin together with high-dose FIX; however, reports of success are anecdotal and further studies are warranted to determine the most appropriate treatment course.

Risk factors for inhibitor development and the clinical course associated with them have also been well characterized. The National Hemophilia Foundation's (NHF) Registry (http://www.nationalthemophiliafoundation.org) and the World Federation of Hemophilia (WFH) Hemophilia B registry are two major databases that exist for hemophilia B patients. The NHF registry was established in 1997 and has since been supplemented with data from the WFH registry. Crawford et al. and colleagues 22 used data from these registries to study inhibitor development in hemophilia B patients. They found that large or complete gene deletions were associated with inhibitor development as well as anaphylaxis, consistent with earlier research findings. 12, 13

• 32/94 patients underwent genotyping for mutations in FIX gene, which subsequently revealed that large or complete gene deletions were associated with inhibitor development as well as anaphylaxis, consistent with earlier research findings 12, 13

• 39 patients underwent ITI, with successful inhibitor eradication noted in only 5

Table 2. FIX Inhibitor Characteristics in Patients With Allergic Reactions

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<td>Median age at inhibitor detection</td>
<td>16 mo (6 mo-12 yr)</td>
<td>19.5 mo (9 mo-13 yr)</td>
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<td>Median exposure days</td>
<td>11 (2-54)</td>
<td>11 (2-180)</td>
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<td>Mean peak inhibitor titer</td>
<td>48 BU (4.5-800 IU)</td>
<td>30 BU (1-1156 IU)</td>
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Etiology of Severe Reactions Associated With Appearance of Inhibitors in Hemophilia B

Although the cause of the allergic comanifestation with inhibitors is unclear, several theories have been advanced, including the small molecular weight of FIX, which allows for its extracellular distribution. Another theory proposes that high plasma concentrations of FIX expose patients to large amounts of the exogenous protein with each infusion, thereby triggering an immune response. Finally, complete gene deletions have been observed to play a role in allergic reactions. In 32 ISTH registry patients who underwent genotyping for mutations in the FIX gene, it was observed that large gene deletions were associated with inhibitor risk and anaphylaxis. Patients with complete gene deletions were found to have the greatest risk for anaphylaxis, with a minimum risk of 26%.

Recommendations

Due to its rare occurrence and lack of evidence-based research, hemophilia B has received little attention within the scientific community. What is known about the disease has led to recommendations for this patient population, including the establishment of molecular diagnosis in all severe patients identified to be at greatest risk for anaphylactic complications and administration of the first 10 to 20 FIX infusions at a facility equipped to handle life-threatening complications. Immunomodulatory therapy is a possible ITI treatment option, based on anecdotal experience, and warrants further exploration, as does the role for gene transfer technology in achieving permanent tolerance to FIX. However, it is the continued collection of data from registries that may play the greatest role in spurring research endeavors so that, someday, individuals with the disease will no longer have to experience its potentially devastating complications.

REFERENCES