



ORIGINAL ARTICLE

A prospective registry of European haemophilia B patients receiving nonacog alfa, recombinant human factor IX, for usual use

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Summary. Nonacog alfa, a recombinant factor IX (FIX) used for the treatment of haemophilia B, was approved in Europe in 1998. In accordance with European Medicines Agency requirements, a registry study was conducted from 2002 to 2009. A reformulated iso-osmotic version was approved for European use in 2007. This study was conducted to evaluate the safety of nonacog alfa in a usual care setting, and provide clinical trial and postmarketing surveillance data support. This open-label, non-interventional, prospective observational cohort study (registry) comprised 52 sites in nine European countries. Patients with haemophilia B receiving nonacog alfa in either formulation for prevention or treatment were followed on a usual care schedule. A total of 218 patients were enrolled, of whom 66 (30.3%) were <18 years of age. Haemophilia severity was evenly distributed, with baseline FIX

activity of <1%, 1–5% and >5% in 33.3%, 36.6% and 30.1% of patients, respectively. One hundred thirty-eight patients received the original formulation alone; 80 switched to or received only the new formulation. There was a low incidence of events of special interest (ESIs), with less-than-expected therapeutic effect in five patients (2.2%), inhibitor development in two (0.9%), thrombosis in one (0.5%) and allergic events in eight (3.7%). These accounted for the majority of the 15 serious AEs reported in six patients. Six patients discontinued because of AEs, primarily related to hypersensitivity. Nonacog alfa was shown to be safe for the treatment of haemophilia B, with a low incidence of serious AEs and ESIs.

Keywords: Europe, factor IX, haemophilia B, nonacog alfa, registry, safety

Introduction

Haemophilia B is an X-linked disorder caused by a congenital deficiency of coagulation factor IX (FIX) clotting activity. Patients with haemophilia B are usually

treated by replacing the missing or defective FIX for treatment or prevention of haemorrhage. Highly purified concentrates derived from pooled human plasma have been available for this purpose for many years, but are associated with a potential risk of transmitting blood-borne pathogens [1,2]. Nonacog alfa (BeneFIX; Pfizer Inc, PA, USA), the only recombinant source of blood coagulation FIX, is not derived from human plasma and does not contain human or animal proteins, therefore not carrying this risk. Nonacog alfa was licensed in the United States in 1997 and in Europe in 1998 for the control and prevention of haemorrhagic episodes and for routine and surgical prophylaxis in previously treated patients with haemophilia B. To date, nonacog alfa has been commercialized in more than 49 countries.

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In order to comply with requirements of the European Medicines Agency (EMA), a registry of patients treated with nonacog alfa was initiated in March 2002 by Wyeth Pharmaceuticals, which was acquired by Pfizer Inc in October 2009.

In July 2007, a reformulated nonacog alfa was approved for use in the European Union (US approval was granted in March 2007); this reformulation was developed to minimize the risk of red blood cell agglutination into the tubing or syringe. The original and reformulated versions differ in that the diluent used for original nonacog alfa was sterile water, whereas the diluent used for reformulated nonacog alfa is 0.234% sodium chloride, and the diluent volume was reduced to 5 mL for the reformulated product; pharmacokinetic parameters are not different between the two formulations [3]. As reformulated nonacog alfa is more concentrated than the previously marketed formulation, smaller infusion volumes can be used.

Following the approval of reformulated nonacog alfa in Europe, the registry protocol was amended in January 2008 to allow patients using reformulated nonacog alfa to participate in addition to those treated with the original formulation. The purpose of the registry was to evaluate the safety of nonacog alfa in a usual care setting, with a focus on particular events of special interest (ESIs) regarding FIX replacement: less than expected therapeutic effect, inhibitor formation, thrombosis, red blood cell agglutination and allergic reactions [4–7]. The information gathered was to be used to support the safety findings of clinical trials and postmarketing surveillance of nonacog alfa [3,8–10].

Materials and methods

Study design

This was an open-label, multicentre, non-interventional, prospective observational cohort study carried out at 52 sites in Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden and the United Kingdom. The study was conducted in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. All investigators provided written commitments to comply with GCP standards and the study protocol. Signed informed consent of each patient and/or a parent or legal guardian was obtained or agreement was granted to allow for the collection of data from medical records, per local regulations.

Patients

Eligible patients were those with haemophilia B scheduled to begin treatment with original or reformulated

nonacog alfa. Previously treated, as well as untreated, patients were eligible. Those who initiated treatment with reformulated nonacog alfa prior to enrollment in the registry and who provided complete previous medical record information from the start of therapy were also included. Patients with prior FIX inhibitor history or history of allergic reactions to FIX products were not excluded as long as complete medical history and demographic information was provided.

Treatment and assessments

Patients received original and/or reformulated nonacog alfa according to the direction of their haemophilia physicians (i.e. investigators). Patients followed their usual visit schedule as determined by their physician, which, in the absence of traumatic events or spontaneous bleeding, was infrequent (e.g. biannually or annually).

Registry data were collected from medical record reviews conducted by the investigators. Although the initial intent of the registry was to collect data prospectively, data were also collected retrospectively to assess adverse events (AEs) in those patients receiving nonacog alfa in the period prior to the initiation of the registry.

Baseline data collected for all patients included demographics, medical and medication histories, date of haemophilia B diagnosis, disease severity, individual and family haemophilia B history, FIX inhibitor history including characterization of known FIX molecular defect, known allergies, and a list of prior FIX concentrate and other FIX-containing blood products, including estimated number of exposure days. Baseline FIX level and Bethesda assay for FIX inhibitor, when available from patient records, were recorded prior to starting treatment with nonacog alfa.

The dates of initiation and completion of treatment with nonacog alfa were documented. When analyzing data for patients who reported use of both formulations of nonacog alfa, but when specific dates of therapy were unknown, the date of commercial availability of reformulated nonacog alfa in the patient's country was used as the start date of treatment with reformulated nonacog alfa.

For patients who had surgery during participation in the registry, the following information was collected: diagnosis for which surgical intervention was required, type of surgery, estimated intraoperative blood loss and whether it was higher than expected, red blood cell transfusion requirement and number of units, unplanned FIX infusion(s) during surgery and details of the infusion(s), and postoperative clinical status.

An investigator reviewed each patient's medical records at least quarterly to obtain treatment data and any relevant safety information not collected through other means (e.g. verbal communication with patient).

Any AEs were reported on the appropriate forms. All data for serious AEs, ESIs (whether serious or non-serious) and product-related non-serious AEs were collected and reported to Wyeth Pharmaceuticals; investigators were instructed not to report non-serious AEs that they considered definitely or probably not related to nonacog alfa. A total of 19 periodic reports were prepared for the EMEA that detailed ESIs and AEs for all patients, according to local regulatory guidelines.

Statistical analysis

Data from all patients in the registry were included in the analyses. Data from patients taking original nonacog alfa formulation and/or reformulated nonacog alfa were pooled. The analyses were done using descriptive statistics.

Results

Patients and treatment

The registry was open from March 2002 to June 2009. A total of 218 patients were enrolled, received at least one dose of nonacog alfa, and were included in the safety population. A total of 103 patients participated in the registry through its completion date, and 115 discontinued prior to study conclusion (Table 1). Of these 115 discontinuations, 99 discontinued because either the patient ($n = 33$) or the investigator ($n = 66$) decided not to participate further, primarily because of lack of interest in continuing with extension of the planned duration of this registry. A total of six subjects, all of whom received the original formulation of nonacog alfa only, discontinued due to AEs [non-specific hypersensitivity ($n = 3$), non-specific hypersensitivity/pruritic rash ($n = 1$), non-specific hypersensitivity/urticaria ($n = 1$) and decreased therapeutic response ($n = 1$)].

Table 1. Patient disposition.

Parameter	<i>n</i> (%)
Enrolled	218
Completed	103 (47.2)
Withdrawals	115 (52.8)
Discontinued participation – investigator decision*	66 (30.3)
Discontinued participation – patient decision†	33 (15.1)
Event of special interest/serious adverse event	6 (2.8)
Death	4 (1.8)
Lost to follow-up	2 (0.9)
Withdrew consent	1 (0.5)
Switched to another FIX product	1 (0.5)
Moved to another country	1 (0.5)
Discontinued FIX therapy after liver transplantation	1 (0.5)

FIX, coagulation factor IX.

*Investigator did not continue to participate in the extension of the planned duration of this registry, primarily due to lack of interest.

†Patient did not agree to participate in the extension of the planned duration of this registry.

Patients were primarily white males; mean age was 30.1 years (median 29.2, range <1–79 years) (Table 2). Sixty-six patients (30.3%) were <18 years of age, 33 (15%) were <6 years and 15 (7%) were ≤1 year. Mean baseline FIX activity was 7.2%. The numbers of patients were approximately evenly distributed among categories of baseline FIX activity of <1%, 1 to 5% and >5% (33.3%, 36.6% and 30.1%, respectively). A total of 15 (6.9%) patients enrolled in the registry were females, with a mean age of 40.7 years (range, 3–76). Thirteen females had mild haemophilia B (baseline FIX:C range, 17–45%) and 2 females had moderate haemophilia B with FIX:C of 1% and 2%, respectively. One female had a nonsense mutation (baseline FIX:C, 2%), while 2 other females also were found to have a missense mutation – baseline FIX:C for these each of these two patients was 40% and 32%. Additional characteristics of the enrolled patients are described in Table 3.

During the registry period, 138 patients received only the original formulation of nonacog alfa, 36 received only reformulated nonacog alfa and 44 switched to reformulated nonacog alfa from original nonacog alfa.

Table 2. Baseline characteristics.

Parameter	<i>N</i> = 218
Sex, <i>n</i> (%)	
Male	203 (93.1)
Female	15 (6.9)
Mean age, years (range)	30.1 (<1–79)
<18 years, <i>n</i> (%)	66 (30.3)
<6 years, <i>n</i> (%)	33 (15.2)
≤1 year, <i>n</i> (%)	15 (6.9)
Ethnic origin, <i>n</i> (%)	
White	201 (92.2)
Black	7 (3.2)
Asian	5 (2.3)
Other	5 (2.3)
FIX activity, (%)*	7.2
FIX activity, <i>n</i> (%)*	
<1%	72 (33.3)
1–5%	79 (36.6)
>5%	65 (30.1)
Genotype, <i>n</i> (%)	
Missense mutation	59 (27.1)
Nonsense mutation	7 (3.2)
Frameshift mutation	4 (1.8)
Partial gene deletion	5 (2.3)
Total gene deletion	1 (0.5)
Other	34 (15.6)
Unknown	108 (49.5)
Prior FIX treatment, <i>n</i> (%)	
Yes	150 (68.8)
No	66 (30.3)
Unknown	2 (0.9)
Cumulative exposure days, patients with prior FIX, <i>n</i> (%)†	
1–25	33 (22.0)
26–50	9 (6.0)
51–100	6 (4.0)
>100	85 (56.7)

FIX, coagulation factor IX.

*Data available for 216 patients.

†Data available for 133 patients.

Table 3. History of allergic reaction to blood, fresh frozen plasma or FIX concentrates and history of inhibitors to any FIX product prior to study entry.

	N = 218 n (%)
Allergic reaction*	
No	205 (94.5)
Yes	12 (5.5)
Product	
Fresh frozen plasma	4 (33.3)
Other blood product/FIX concentrates	8 (66.7)
Type of reaction†	
Dermal	7 (58.3)
Class I	4 (33.3)
Class II‡	2 (16.7)
Class III§	0
History of inhibitors	
No	213 (97.7)
Yes	5 (2.3)
Product used at time of inhibitor development	
Nonacog alfa	1 (20.0)
Original nonacog alfa	1 (20.0)
Plasma-derived/NHS FIX	2 (40.0)
Preconativ (PCC)	1 (20.0)
Immune tolerance therapy/outcome	
Yes/successful	4 (80)
Yes/not successful	0
No	1 (20.0)

FIX, coagulation factor IX; PCC, prothrombin complex concentrate.

*Data available for 217 patients.

†Patients may have experienced both a dermal and/or class I/II allergic reaction.

‡Class II reactions defined as respiratory symptoms such as dyspnea and hypoxia accompanied by generalized hypersensitivity.

§Class III reactions defined as severe anaphylaxis with hypotension.

The availability of reformulated nonacog alfa coincided with the commercial launch of this product in each patient's country. This launch began in Europe in September 2007 and concluded in 2008. As a result, there was a longer observation period of patients using the original formulation of nonacog alfa (≥ 6 years) than of patients using reformulated nonacog alfa (≤ 1.5 years).

Safety

A total of 16 (7.3%) patients experienced ESIs; all were reported in patients receiving only the original formulation of nonacog alfa, with seven patients receiving on-demand treatment and nine receiving prophylaxis treatment (five of whom received surgical prophylaxis) (Table 4). Of the 16 ESIs, eight were considered serious and deemed possibly, probably, or definitely related to nonacog alfa. Serious AEs (SAEs) were reported in 46 (21.1%) patients. Of these 46 SAEs, 15 SAEs (reported in six patients) were considered probably, possibly, or definitely related to original nonacog alfa (Table 4). Four patients died during the registry, with causes of death being complications of liver transplantation, drug overdose not related to nonacog alfa, colon cancer and bronchopneumonia/cardiac failure/hepatic cirrhosis.

Table 4. Events of special interest and serious adverse events possibly, probably or definitely related to nonacog alfa.

Event of special interest, n (%)	Serious N = 218	Non-serious N = 218
Less than expected therapeutic effect	2 (0.9)	3 (1.4)
Inhibitor development	2 (0.9)	0
Thrombosis	1 (0.5)	0
Red blood cell agglutination	0	0
Allergic events	3 (1.4)	5 (2.3)
Serious adverse events possibly, probably or definitely related to nonacog alfa, n (%)		
Hypersensitivity NOS/allergic event*	3 (1.4)	
FIX inhibitor*	2 (0.9)	
Drug ineffective*	2 (0.9)	
Thrombosis*	1 (0.5)	
Urticaria NOS	1 (0.5)	
Abdominal pain NOS	1 (0.5)	
Malaise	1 (0.5)	
Burning sensation NOS	1 (0.5)	
Dizziness	1 (0.5)	
Dyspnea NOS	1 (0.5)	
Hot flushes NOS	1 (0.5)	

FIX, coagulation factor IX; NOS, not otherwise specified.

*After 2007, events of special interest were also required to be reported as serious adverse events. A single patient could have more than one adverse event.

None of the deaths were considered to be related to nonacog alfa.

Twenty product-related non-serious AEs were reported in a total of 10 (4.6%) patients (nine taking the original formulation, one who switched from original to reformulated nonacog alfa). Events occurring in more than one patient were non-specific hypersensitivity in four patients (1.8%), paresthesia in three (1.4%) and infusion-site phlebitis in two (0.9%).

In this registry, a 71-year-old man receiving original nonacog alfa for FIX deficiency experienced distal deep venous thrombosis considered possibly related to nonacog alfa therapy. The patient's medical history was significant for a history of spinal column stenosis, spinal stenosis surgery, moderate haemophilia B (baseline activity 5%) and a missense factor gene mutation. The patient received nonacog alfa via continuous infusion prior to orthopaedic surgery for spinal stenosis, with FIX level maintained at approximately 80% until the fourth postoperative day, upon which the dose was decreased (total exposure, 12 days). During a postoperative ultrasound as part of a local study, a distal deep venous thrombosis was found in the right calf. The patient, who had not received any postsurgical thrombosis prophylaxis, was asymptomatic and was treated with low-molecular-weight heparin while maintained on FIX therapy; the thrombus resolved 2 weeks later.

Two patients developed FIX inhibitors; one event was a recurrence and the other was a de novo inhibitor. The first patient was a 29-year-old with severe haemophilia B and a history of inhibitor to plasma-derived FIX products. This patient developed a low-titer (1.2 BU) inhibitor after several hundred exposure days to

plasma-derived FIX, and was switched to nonacog alfa in January 2005. Subsequent testing showed an inhibitor titer of 0.65 BU and 1.7 BU in October 2006 and in October 2007, respectively. The nonacog alfa dose was increased and administration of cortisone was initiated. The inhibitor resolved in September 2008. The FIX gene defect for this patient was not known. The second patient was an 11-month-old, previously untreated patient with severe haemophilia B, no previous history of inhibitor development, and a stop mutation in the FIX gene (C31118T, R333X). The patient had received nine exposure days to nonacog alfa, at which time a FIX inhibitor was detected (inhibitor level <0.3 BU). Two days later, the patient developed a subsequent life-threatening allergic reaction immediately after the administration of nonacog alfa and had an inhibitor level of 1.6 BU. Nonacog alfa treatment was discontinued, and the patient was switched to recombinant Factor VIIa. Upon follow-up 2 weeks later, the inhibitor level was 10.3 BU. Ten months later, the patient was started on immune tolerance therapy (with Malmo regimen) and began nonacog alfa prophylaxis therapy. Six weeks after starting immune tolerance therapy, the Bethesda assay was negative (a more sensitive inhibitor screen becoming negative after 10 weeks). The patient has been on nonacog alfa prophylaxis since this time.

A total of eight patients experienced allergic reactions; of these, six had severe haemophilia B while one patient each had moderate and mild haemophilia B. Of these allergic events, two patients experienced reactions considered to be serious. The first patient was a 61-year-old male with severe FIX deficiency and a history of FIX inhibitors and allergic reactions to plasma-derived FIX replacement products. The subject was known to have a nonsense FIX gene mutation and had previously received successful FIX immune tolerance therapy. Approximately 1 month after beginning nonacog alfa therapy, the patient developed an allergic reaction (rash starting on the legs). The patient was switched to plasma-derived FIX for prophylaxis, and the allergy and rash resolved 1 month later. The second patient was a 28-year-old male with severe haemophilia B and hepatitis C, with a frameshift gene mutation, no history of allergic reactions or inhibitors and previous treatment

with a plasma-derived FIX. Twelve hours after the initial dose of nonacog alfa, the patient experienced shortness of breath, dizziness, hot flushes and abdominal cramps, but did not seek medical treatment. Symptoms resolved after 3 h. Four days later, he self-administered nonacog alfa and experienced similar symptoms and time to resolution. Upon informing the clinic, discontinuation of treatment was recommended, and he was examined at the clinic and found to be clinically well. The events were presumed to be allergic reactions, probably related to nonacog alfa treatment. Treatment was switched to a plasma-derived product, with no further symptoms.

Discussion

The objective of this registry was to evaluate the overall safety of nonacog alfa in usual care, with a focus on product-specific ESIs. Overall, the incidence of ESIs in nonacog alfa therapy and of serious AEs was low, and the safety profile was consistent with the prescribing information. Among the 218 patients enrolled, serious ESIs were reported in eight patients (3.7%), and non-serious ESIs were also reported in eight patients. All reported ESIs occurred in patients receiving the original formulation of nonacog alfa. Fifteen SAEs at least possibly related to nonacog alfa occurred in six patients (2.8%). There was a low incidence of registry discontinuation attributable to AEs (six patients; 2.8%), with five owing to allergy-related events (urticaria, pruritic rash, non-specified hypersensitivity); one discontinuation because of AEs was inhibitor-related. No ESIs, including inhibitor development, thrombosis or red cell agglutination were observed in patients receiving reformulated nonacog alfa, and no ESIs were reported in the females enrolled in this registry. No new safety signals, regardless of which formulation a patient had received, were noted during the registry period.

The registry data reported herein for reformulated nonacog alfa supports the safety of nonacog alfa as reported in previous clinical trials in adults and children [8–10] and in a retrospective safety analysis [11]. As can be seen in Table 5, adverse events reported in those studies were similar in type and incidence to those reported in this registry.

Events of special interest, n (%)	Current study N = 218	Roth <i>et al.</i> [9] N = 56	Shapiro <i>et al.</i> [10] N = 63	Monahan <i>et al.</i> [8] N = 25	Recht <i>et al.</i> [11] N = 180 n = 163 (rFIX) n = 88 (pdFIX)
Inhibitor formation	2 (0.9)	1 (1.8)	2 (3.0)	1 (4)	3 (1.8) rFIX 4 (4.6) pdFIX
Thrombosis	1 (0.5)	0 (0)	0 (0)	0 (0)	NR
Red blood cell agglutination	0 (0)	NR	2 (3.0)	0 (0)	NR
Allergic reactions	8 (3.7)	4 (7.1)	5 (7.9)	1 (4)	4 (2.5) rFIX 3 (3.4) pdFIX

NR, not reported; pdFIX, plasma-derived factor IX product; rFIX, recombinant factor IX product.

Table 5. Events of special interest in current and previous FIX studies.

One patient in the registry had an asymptomatic distal deep venous thrombosis postoperatively in the right calf which resolved after 2 weeks. A recent report examined the occurrence of subclinical deep venous thrombosis in haemophilic patients undergoing major orthopaedic surgery and found that in approximately 10% of these patients, a subclinical deep venous distal thrombosis was identified [12].

Of all of the AEs associated with FIX therapy, inhibitor formation is considered the most important and the most challenging to manage [5,13,14]. FIX inhibitor development occurs in 1–3% of haemophilia B patients, and it is known to commonly occur in close temporal association with allergic manifestations and anaphylactoid reactions [7,15]. Certain FIX-encoding genetic mutations are known to predispose patients to inhibitor formation with FIX treatment [16,17]. Postulated non-genetic risk factors for FIX inhibitor development are similar to those in factor VIII deficiency, i.e. age at first exposure, bolus vs. continuous infusion, and immune system challenges such as infection [18,19]. However, given the relative rarity of FIX inhibitor development, the impact of these proposed non-genetic factors is still unclear and has not been definitively demonstrated [5,19]. Patients with a history of inhibitors were not excluded from this registry, and a baseline Bethesda assay was not required before registry entry.

Registries offer both advantages and disadvantages over prospective randomized clinical trials. Randomized controlled trials are considered the gold standard in generating high-quality efficacy and safety data; however, because of the rarity of haemophilia B, conducting such studies is difficult from a practical standpoint. As a result, clinical trials generally enroll small numbers of patients for a short duration and may not study the population in which the intervention will ultimately be used owing to strict inclusion/exclusion criteria. In a registry, there are no required procedures, no specified visit schedules, and treatment regimens and length of follow-up can vary according to clinical needs and judgment. While this may make data collection more difficult, registries have the advantage of providing a more realistic picture of usual clinical use.

The longer-term, observational nature of registry studies can often pose issues, particularly in terms of patient follow-up and discontinuations; this was the case in our study as well. This registry endeavor had a duration of more than 7 years; as a result, withdrawals by study centres, investigators or patients increased – primarily owing to lack of interest. Withdrawal in these instances does not imply discontinuation of treatment, only termination of study follow-up. While AEs or ESIs could not be recorded post-discontinuation, the overall safety data gathered on those completing the registry provided a more than sufficient picture of typical usage with nonacog alfa. In fact, because registries usually involve more patients for a longer duration than do

controlled clinical trials, they are typically more sensitive in detecting low-frequency AEs and atypical treatment reactions [20]. Thus, they provide valuable information regarding long-term safety that can be used to support the results of randomized clinical trials [21].

Conclusions

The data presented in this report indicate that nonacog alfa is safe in the treatment of haemophilia B in a usual care setting. Findings are consistent with the safety profile observed in previously reported clinical trials and the current product labeling.

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Author contributions

JB and RC contributed to the conception and design of this study; EB, DK, MM, AT, CM, EPM-B, RM, CAR and AH were study investigators and provided study materials and/or patients; JB, DK and RC collected and

assembled the data; PR and JB performed data analysis and interpretation; PR, CK, DK and RM contributed to the development of this manuscript; EB, DK, MM, AT, CM, EPM-B, RM, CAR, AH, CK, RC, JB and PR reviewed and granted final approval of this manuscript.

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