An observational study of sucrose-formulated recombinant factor VIII for Japanese patients with haemophilia A

Jean-Christophe Delumeau[1], Chiho Ikegawa[1], Chisato Yokoyama[1], Verena Haupt[2]
[1]Bayer Yakuhin Ltd., Osaka, Japan; [2]Bayer Vital, Leverkusen, Germany

Summary
The safety and efficacy of sucrose-formulated recombinant factor VIII (rFVIII-FS; Kogenate® FS) under usual clinical practice were evaluated for 12 months in an observational, postmarketing surveillance study conducted at 214 treatment centres throughout Japan. The study included 631 patients with haemophilia A, 80% of whom had severe or moderately-severe disease (≤2% FVIII:C). Most patients (n=477; 75.6%) had >100 prior exposure days (EDs), but the study also included 62 (9.8%) patients with <20 EDs who were at high risk for inhibitor development. A total of 71,240 infusions were administered during the observation (mean, 113 ± 108 per patient). Physicians rated efficacy and tolerability of rFVIII-FS as "very good" or "good" in >99% of patients. FVIII inhibitors were observed in seven patients (5 *de novo*; 1 persistent/fluctuating; 1 recurrent). The overall *de novo* inhibitor incidence was 0.8% (5/631; or 5/599 among the subgroup of patients with negative baseline titre and no known inhibitor history). *De novo* cases represented 3.2% (2/62) of patients with <20 EDs at enrollment (2/57 in the no inhibitor subgroup) and 0.2 % (1/477) of patients pretreated with >100 EDs (1/452 in the no inhibitor subgroup) at enrollment. The results of this large observational study demonstrate that rFVIII-FS is both safe and efficacious as used in the usual clinical setting for the treatment of Japanese patients with mild to severe haemophilia A. This study supports the efficacy of rFVIII-FS with an incidence of inhibitor formation no greater than in a comparable European study or previous phase III clinical studies.

Keywords
Haemophilia A, Kogenate, recombinant factor VIII, inhibitors

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Introduction

Haemophilia A is a blood coagulation disorder characterized by a deficiency of functional blood coagulation FVIII. Treatment consists of conventional FVIII replacement therapy, which originally relied on pooled donor plasma as a source of FVIII (1). Advances in recombinant gene technology and protein purification techniques have minimized the risk of blood-borne pathogen transmission, permitting the development of highly purified recombinant factor products (2).

Recombinant FVIII-FS is a full-length recombinant FVIII (rFVIII) formulated with sucrose as a stabilizer in place of added human albumin and includes viral inactivation steps during manufacture (3, 4). The efficacy and safety of rFVIII-FS was demonstrated by clinical studies with previously treated patients (PTPs) and with previously untreated (PUPs) or minimally treated patients (MTPs) in North America and Europe (3, 5, 6). In these studies, haemostasis was satisfactorily achieved in approximately 90% of bleeding episodes after one or two infusions of rFVIII-FS, and rFVIII-FS had an excellent safety profile. Clinical studies have also demonstrated the efficacy and safety of rFVIII-FS in haemophilic patients during surgical procedures, both as bolus or continuous infusion (7, 8).

A potentially serious complication of haemophilia A treatment is the development of inhibitory antibodies to replacement FVIII. Inhibitor formation generally affects 20%-30% of PUPs and 1%-3% of PTPs treated with other rFVIII products (9–11). These antibodies usually develop following therapy onset after a median of 10–15 exposure days (EDs) (12). Patients of African or Hispanic ethnic backgrounds are known to be more susceptible than other ethnic groups to inhibitor antibody formation (13). Specific genetic variants within the major histocompatibility complex (14, 15) or of genes involved in the immune response (e.g. interleukin [IL]-10) (16) are also associated with increased risk for inhibitor formation.

Correspondence to:
Jean C. Delumeau, MD, PhD
Mikuni Office, Bayer Yakuhin Ltd.
Osaka, Japan
Tel.: +81 6 6398 2861, Fax: +81 6398 1079
E-mail: jdelumeau@bayerhealthcare.com

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In previous clinical evaluations of rFVIII-FS, the incidence of *de novo* inhibitor formation was zero among 71 PTPs and low (15%) in 60 PUPs/MTPs with severe haemophilia A (3, 5). However, these trials used North American and European study populations and enrolled only small numbers of patients, as is typical for a rare bleeding disorder such as haemophilia A. We report the results of a postmarketing surveillance (PMS) study designed to evaluate the efficacy and safety of rFVIII-FS as used in routine clinical practice for a 12-month observation period in a large Japanese haemophilia A patient population.

Materials and methods

Patient selection

The study enrolled patients of any age with mild, moderate, or severe haemophilia A seen at 214 participating centres throughout Japan. These are mostly local hospitals and practices where general physicians implement treatment strategies for patients that were designed in consultation with a haemophilia specialty centre. Aside from the contraindications described in the product information for rFVIII-FS (17), there were no restrictions on enrolling patients with additional underlying diseases or chronic infections.

Study design

This observational study, conducted as a Drug Use Investigation according to the definition of the Pharmaceutical Affairs Law of Japan, was aimed at collecting efficacy and safety data in the clinical practice setting. It was designed as a prospective, non-interventional, uncontrolled multi-centre PMS study. The planned observation period for each patient was 12 months and included an initial visit at the start of the observation period and a final safety and efficacy assessment. The treatment dose and regimen were selected by the treating physician. Regular prophylaxis was defined as ≥2 prophylactic infusions per week for at least 80% of the observation period. Throughout the study, rFVIII-FS (Kogenate® FS; Bayer HealthCare Pharmaceuticals, Hematology/Cardiology, Berkeley, CA, USA) was used as the sole source of FVIII for prophylaxis and on-demand treatment for all patients. Data were collected in case report forms (CRFs) and whenever possible, follow-up information subsequent to the period covered by the CRF was also collected.

The efficacy analysis was based on summarized data on infusions (number of infusions with average daily dosage by reasons) as well as a general efficacy assessment by the physician at the end of the observation period. The safety analysis comprised demographic data, clinical history, adverse events (AEs) during the study period, and drug tolerability as assessed by the physician at the end of the study period. An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure. An AE that resulted in any positive detection of FVIII inhibitor titre was systematically handled as a causally associated serious adverse event (SAE), irrespective of the titre or presence/absence of any clinical symptom.

Data analysis

All patients with at least one documented infusion were included in the data analysis. Descriptive analysis of the data was performed using summary statistics for categorical and quantitative data. Continuous data were described by mean, standard deviation (SD) minimum, 1, 5, 25, 75, 95, and 99 percent quantiles, median, maximum, and number of non-missing values. Moreover, continuous data were categorized in a clinically significant way, including categories of continuous data presented in frequency tables.

The incidence rates of AEs, adverse drug reactions (ADRs), SAEs, and serious adverse drug reactions (SADRs) were calculated and defined as the number of events divided by the number of patients at risk, where number of events equals the number of patients reporting the event and the number at risk equals all patients valid for safety analyses. For multiple occurrences of an event within a patient, the event was counted only once.

Results

Patients

A total of 701 patients from 214 Japanese haemophilia centres were enrolled and observed for 12 months. The study lasted from July 22, 2002, through September 28, 2005. Seventy patients were excluded from the study analysis for the following reasons: no drug administered (n = 46); lost to follow-up (n = 21); and double enrollment (n = 3). Thus, 631 eligible patients (mean age, 23.7 years) were included in the analysis. FVIII activity was <1% in 426 (67.5%) patients, 1%-2% in 79 (12.5%) patients, >2%-5% in 64 (10.1%) patients, and >5% in 56 (8.9%) patients; no information was available for six (1.0%) patients. A target joint was specified for 365 (57.8%) patients; the knee was the most frequently affected joint (n = 108). Information for all types of infusions was available for 570 (90.3%) patients, and 583 (92.4%) patients had reports about prophylactic infusions. Table 1 shows the demographics and baseline characteristics of the study population.

The majority of patients with available infusion data (n = 477, 75.6%) had been extensively treated in the past, with >100 previous EDs accumulated before study entry. An additional 59 (9.4%) patients had 20–100 previous EDs, 62 (9.8%) had <20 previous EDs (of whom 17 were considered PUPs), the number of previous EDs could not be determined for 12 (1.9%). No information was available for 21 (3.3%) patients. Of the 593 patients with at least one documented prior exposure to any kind of FVIII, 355 (59.9%) had previously been treated with one or more rFVIII products and 194 (32.7%) with a plasma-derived FVIII product. Information for the remaining 44 (7.4%) patients was incomplete. A history of inhibitors to FVIII was reported in 32 (5.1%) patients enrolled in the study.

Infusion and consumption summary

Patients were observed over a median of 401 days (range 16–893 days). During this period, a total of 71,240 infusions were administered for any reason to 631 patients with a mean of 113 (± 108) infusions per patient. Patients received a mean (± SD) of 72,800 ± 79,000 IU rFVIII-FS during the year (median 54,800 IU; range <1,000–777,900 IU). Reasons given for rFVIII-FS infusions, in

Table 1: Patient demographics and baseline characteristics (n = 631).

Mean age (SD), years[a]	23.7 (16.6)
Gender, n (%)	
Male	628 (99.5)
Female	1 (0.2)
No information	2 (0.3)
FVIII activity, n (%)	
<1%	426 (67.5)
1%-2%	79 (12.5)
>2%-5%	64 (10.1)
>5%	56 (8.9)
No information	6 (1.0)
Exposure days (EDs) prior to study, n (%)	
0 (PUPs)	17 (2.7)
1–19	45 (7.1)
20–100	59 (9.4)
>100	477 (75.6)
No information	33 (5.2)
Previous treatment product, n (%)[b]	
Recombinant FVIII	355 (59.9)
Plasma-derived FVIII	194 (32.7)
Non-FVIII product	2 (0.3)
Missing	42 (7.1)
History of inhibitors, n (%)	
Positive history (total)	32 (5.1)
Peak level ≤5 BU	19 (3.0)
Peak level >5 BU	11 (1.7)
No peak-level information	2 (0.3)
Inhibitors at baseline, n (%)	
Positive at baseline (total)	8 (1.3)
Low titre (<5 BU)	4 (0.6)
High titre (≥5 BU)	2 (0.3)
No titre information	2 (0.3)
Known seropositive status, n (%)	
Hepatitis A	9 (1.4)
Hepatitis B	112 (17.7)
Hepatitis C	311 (49.3)
HIV	86 (13.6)
Target joint specified, n (%)	365 (57.8)

SD, standard deviation; BU, Bethesda units; PUPs, previously untreated patients. [a]n = 629, [b]n = 593.

order of mean frequency per patient per year, were prophylaxis, joint bleeds, other bleeds, or surgery (Table 2). The mean number of infusions and mean total consumption of rFVIII-FS per patient for each of these reasons, for the total population as well as for the 111 (17.6%) subjects who received regular prophylaxis, are summarized in Table 2.

Bleeding events

On average, the mean number of follow-up treatments (± SD) required to manage joint bleeding episodes was 1.1 (± 1.5) and for other bleeding episodes, 1.2 (± 3.3). The results of follow-up treatments of bleeding episodes for patients on regular prophylaxis did not significantly differ from those of the total sample.

Efficacy assessment

At the end of the observation period, the efficacy of rFVIII-FS was globally evaluated for each patient by the physician; assessment data was available for 630 of 631 evaluable patients. Efficacy of treatment was rated "very good" in 409 (64.8%) patients, "good" in 219 (34.7%) patients, and "sufficient" in two (0.3%) patients. No cases were rated "insufficient"; an efficacy assessment was not available for one (0.2%) patient. Overall, the efficacy of rFVIII-FS was rated "very good" or "good" in 99.5% (628/631) of evaluable patients.

Safety evaluation

The safety analysis included data for the 631 eligible patients. Fifteen AEs were reported in 15 different patients. These included seven cases of inhibitor development, one non-serious case of a drug-related allergy, and seven serious non-drug-related SAEs. Four deaths occurred during the observation period due to lymphoma, cerebral haemorrhage, hepatic embolization, and ruptured liver carcinoma, respectively. All patient deaths were assessed as unrelated to rFVIII-FS by the investigator.

Inhibitor development

Positive inhibitor tests were detected and reported for seven patients during the study: five with *de novo* inhibitor formation, one with a persistent (fluctuating) inhibitor, and one with recurrent inhibitor development (Table 3).

Overall, there were five patients with *de novo* inhibitors in the total study population, giving an incidence of 0.8% (5/631). Data for 33 patients was insufficient to classify them among a particular pre-treatment group. Among all patients with <20 EDs at enrollment who were considered to be at highest risk for new inhibitor development, the *de novo* inhibitor rate was two in 62 (3.2%). Both cases occurred in severe haemophilia A patients (n = 35; 5.7% among patients with <1% FVIII:C) who were minimally treated at enrollment. No positive inhibitor titre was reported in any of the 17 PUPs. Among patients with 20–100 EDs at enrollment who are still at risk for inhibitor formation, two in 59 (3.4%) developed a *de novo* inhibitor (the inhibitors were transient in both patients). Both patients had severe haemophilia, making the rate in this subgroup two in 29 (6.9%). Among patients with >100 EDs at enrollment who are considered to be at low risk for new inhibitor development, *de novo* inhibitors were observed in one of 477 patients (0.2%) overall, and one in 344 (0.3%) of the severe patient subset.

Limiting the analysis to only the 599 patients with no known history of inhibitors and negative titre at baseline, the incidence is 0.8% (5/599) overall and 1.3% (5/399) among patients with <1% baseline FVIII:C. Within the no previous inhibitor group, the *de novo* inhibitor rate among the highest risk patients (<20 EDs at enrollment) was 3.5% (2/57) for all patients and 6.7% (2/30) excluding those with ≥1% FVIII:C. Among all patients

Table 2: Extent of exposure to rFVIII-FS during the study for the total population (n = 631).

	Total population (n = 631)	Prophylaxis population[a] (n = 111)
Mean no. of observation days (SD)	460 (142)	n/d
Mean no. of bleeds, surgeries, and prophylactic infusions (SD) per patient per year		
Prophylactic infusions	53.1 (60.4)[b]	148.9 (49.3)
Joint bleeds	10.5 (18.0)	3.1 (8.4)
Other bleeds	4.1 (16.5)	1.9 (4.3)
Surgeries	0.1 (0.8)	0.1 (0.3)
Mean consumption (SD) per patient per year, by reason (IU/kg)		
Prophylaxis[a]	1029 (1390)	2898 (1644)
Joint bleeds	551 (1020)	189 (384)
Other bleeds	252 (1102)	109 (209)
Surgery	24 (136)	21 (134)

SD, standard deviation; n/d = not determined. [a]Defined as regular treatment ≥2 prophylactic injections per week. [b]Patients who received treatment for any prophylactic reason, not limited to the subgroup of patients who received ≥2 injections per week.

with 20–100 EDs at enrollment, two in 57 (3.5%) developed a *de novo* inhibitor (2/28 [7.1%] patients with severe disease), and among patients with >100 EDs at enrollment, *de novo* inhibitors were observed in one of 452 (0.2%) patients (1/323 [0.3%] patients with severe haemophilia). The 447 extensively pretreated patients with no present or historical inhibitor titre were observed during this study for a sum total of 572 years, yielding a rate of 1.75 inhibitor cases per 1,000 person-years of observation. Among only the 323 extensively pretreated severe haemophilia A patients, there were 409 person-years of observation, yielding a rate of 2.44 cases per 1,000 person-years.

When considering the total number of EDs accumulated by the day of first inhibitor detection, all *de novo* FVIII inhibitors except for one (2 BU/ml) were detected in patients with <150 cumulative EDs to any FVIII preparation. High-titre inhibitors were detected in two patients, one with <20 EDs and the other with <40 EDs in total on the day of first detection. The overall rate of recurrent inhibitor formation was one in 32 (3.1%) patients with a history of inhibitors. No positive inhibitor titre was detected in the study in any patient with a documented switch from plasma-derived FVIII (pdFVIII) to rFVIII-FS. However, although not documented, one cannot definitely exclude that the 27-year-old patient who experienced inhibitor recurrence during this study may have received pdFVIII at some point in the past.

Tolerability assessment

At the conclusion of the observation period, the tolerability of rFVIII-FS was globally evaluated for each patient by the physician. The tolerability of rFVIII-FS treatment was rated "very good" or "good" in 627 of 631 evaluable patients (99.4%) with available assessment data; tolerability was rated as "sufficient" for three (0.5%) patients, and for one (0.2%) patient there was no available assessment of tolerability; no patient received a rating of "insufficient tolerability". Physicians recorded patient ratings of their acceptance of the treatment during the observation period. A total of 619 of 631 evaluable patients (98.1%) rated their acceptance of the treatment as "very good" or "good." Of the remaining 12 patients, eight (1.3%) rated their acceptance as "sufficient", three (0.5%) as "insufficient", and one (0.2%) patient had no assessment available.

Discussion

This non-interventional study was designed to evaluate the safety and efficacy of full-length rFVIII-FS, as used in routine clinical practice, during a 12-month observation period in a Japanese haemophilia A patient population. With over 700 patients enrolled, this trial is one of the largest studies performed in haemophilic patients. Furthermore, the design of this Japanese study was similar to that of another large, recently completed PMS study of full-length rFVIII-FS that enrolled over 230 European patients (18). The results of both studies support the very good safety and efficacy profile of rFVIII-FS for the treatment and prevention of bleeding episodes in routine clinical practice.

On average, joint bleeding episodes in this study required 1.1 follow-up infusions of rFVIII-FS to achieve adequate haemostasis, and other (non-joint) bleeding episodes required 1.2 follow-

Table 3: Patients with positive inhibitor tests during the study (n = 7).

Inhibitor type	Patient age, years	Disease severity[a]	No. of EDs prior to enrollment	No. of cumulative EDs prior to detection	Titre at first detection (BU)	Peak level during study (BU)	Titre at end of study (BU)
De novo	1	Severe	<20	<20	16	27	27
De novo	1	Severe	<20	<40	46.1	183[b]	103.4[c]
De novo	0.1	Severe	20–100	27	2	2	1
De novo	2	Severe	20–100	100–150	1	2	2
De novo	1	Severe	>100	150–200	2	2	0
Persistent (fluctuating)	8	Severe	>100	>150	1	3	3
Recurrent	27	Severe	>100	>150	1	3	2

EDs, exposure days; BU, Bethesda units; ND, no data available. [a]Disease severity defined by baseline FVIII:C levels as follows: severe (<1%), moderately severe (1–2%), moderate (>2–5%), or mild (>5%). [b]After initiating immune tolerance therapy. [c]Titre decreased to 7.8 BU/ml on last follow-up data available after completion of study.

up infusions. The efficacy of rFVIII-FS was rated by physicians as "very good" or "good" in 99.5% of patients. No treatment with rFVIII-FS was rated "insufficient". These findings are very similar to those observed in the European study, where 85.4% of haemorrhages were controlled using one or two infusions of rFVIII-FS, and 98.7% of physicians assessed efficacy as "very good" or "good" (18). By comparison, in a recently published interim analysis of an ongoing observational study of a B-domain-deleted rFVIII product in Germany, the overall physician assessment of efficacy was "very good" or "good" in 77.0% of treated cases (19).

When considering the extent of rFVIII-FS exposure, an average of 6,066 (± 6,583) IU were administered per patient per month in the current study (including patients on prophylaxis). Interestingly, patients in the European observational study consumed more than twice the amount of FVIII (mean 14,000 IU per patient per month) (18). The comparatively lower rFVIII consumption in this Japanese study may be related to the slightly smaller proportion of severe and moderately severe haemophilia A patients (<2% FVIII:C) enrolled (80.0% of patients) compared to 99.5% of patients in the European rFVIII-FS surveillance studies. The disparity between consumption rates may also be indicative of differences in body weight, culture, and/or medical practices between Japan and Europe, which would emphasize the importance of performing confirmatory studies in a Japanese patient population.

In the safety evaluation, seven cases of FVIII inhibitor formation accounted for all AEs considered related to treatment (by definition, inhibitors were to be considered drug-related). Because they interfere with the haemostatic efficacy of infused FVIII, inhibitor development is a serious concern for the management of patients with haemophilia. The risk of inhibitor formation is related to numerous endogenous factors (e.g. FVIII gene mutation, severity of haemophilia) and exogenous factors (e.g. intensity of treatment, surgeries, on-demand treatment versus prophylaxis) (20, 21). The risk for inhibitor development decreases with additional exposure to infused FVIII; therefore young patients with a limited number of previous EDs are at highest risk. In this study, the rate of *de novo* inhibitor formation in high-risk patients (<20 previous EDs at enrollment) was 2/62 (3.2%). This figure compares favourably to the rate reported in the European observational study (2/25; 8.0%) (18), although the difference in the incidence rates may be related to the greater number of mild and moderate haemophilia patients included in the Japanese cohort, as these patients are at lower risk compared to severe haemophiliacs. In the subgroup of only severe haemophilia A patients at high risk in our study, the inhibitor rate was 5.7% (2/35). The findings of both these PMS studies are supportive of the inhibitor incidence reported in a phase III clinical trial with rFVIII-FS in PUPs and MTPs with severe haemophilia A (9/60; 15%) (5). Because the incidence of inhibitor development among previously untreated severe patients is generally considered to be in the range of 20%-30% (10), these findings suggest that full-length rFVIII-FS has a low incidence of inhibitor formation in these patients. Moreover, reports of patients with positive inhibitor tests suggest a positive correlation between the number of EDs prior to and after enrollment before the onset of inhibitor development.

In contrast to high inhibitor risk patients, PTPs (those with at least 100 or 150 EDs to infused FVIII), are generally considered to be at low risk for inhibitor formation. This makes pretreated patients the ideal population in which to assess the immunogenicity of new FVIII products (11, 22). In the Japanese cohort studied here, the rate of *de novo* inhibitor formation in patients with >100 EDs at enrollment was 0.21% (1/477), which is consistent with reported rates in the European observational study (0/181, or 0%) (18) and a phase III study of patients with >150 previous EDs at enrollment (0/71, or 0%) (3). Notably, there were no reports of inhibitor formation in patients with a documented switch from a pdFVIII concentrate as a previous therapy to rFVIII-FS in this study. A retrospective study of a cohort of 838 PTPs with haemophilia A in the US determined an incidence of 2.14 inhibitor cases per 1,000 person-years assessed (2.26 cases per 1,000 person-years among only those with severe disease) (23). In our population of extensively pretreated (>100 EDs at enrollment) Japanese patients with no evidence of prior or current inhibitor, we calculated a rate of 1.75 inhibitor cases per 1,000 person-years of observation (2.44 cases per 1,000 person-years among only those with severe disease). Although these rates appear comparable, the US report excludes patients without a confirmation inhibitor test, which was not done in our observational study. One would expect this methodological difference to bias the incidence rates in the Japanese study higher relative to that of the US study. Collectively, the inhibitor safety findings in our study suggest that rFVIII-FS may have a low immunogenic potential.

There are a number of caveats to the interpretation of inhibitor incidence within the context of a surveillance study such as the one described here. One is that FVIII genotyping could not be specified within the design of the study; therefore, the proportion of high inhibitor risk (e.g. large deletion) compared to low inhibitor risk (e.g. single nucleotide substitution) subjects who were included in the analyses is not known. Two, the frequency of inhibitor testing also could not be specified by study protocol. Since in normal clinical practice routine inhibitor testing may only occur once or twice annually, unless an inhibitor is suspected, it must be considered that transient inhibitors and low-titer inhibitors that do not have a clinical impact may be missed. This would lead to a lower inhibitor incidence in a surveillance study compared to an interventional trial. Third, the lack of centralised inhibitor testing during this study leaves open the possibility for variation in the quality of testing performed at individual centres that may either lead to false positive or, more critically, false negative results that could depress the determined incidence. For these reasons, surveillance studies are best compared to other non-interventional, observational trials, and the comparability of the findings in our study to those of the large epidemiological study in the US (23) described above, suggests that the results are valid when such caveats are taken into consideration. Surveillance studies do, however, provide critical insight into the use of a product within the usual practice setting. The surveillance study described here would be expected to identify the occurrence of clinically relevant inhibitors (i.e. inhibitors that would require medical intervention) within the Japanese haemophilia population studied, and therefore would be of relevance to treating physicians.