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ORIGINAL ARTICLE *Rare bleeding disorders*

Prophylactic therapy with Fibrogammin® P is associated with a decreased incidence of bleeding episodes: a retrospective study

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Summary. Congenital factor XIII (FXIII) deficiency is an extremely rare, yet potentially life-threatening, bleeding disorder, with a 30% rate of spontaneous intracranial haemorrhage. Routine prophylactic management is recommended for all individuals with clinically relevant (FXIII) deficiency and for all symptomatic individuals with congenital factor deficiency. Fibrogammin® P is a purified, pasteurized concentrate of FXIII that appears to carry negligible risk of viral transmission, unlike other unprocessed products containing FXIII. An ongoing Phase II/III study of Fibrogammin® P in patients with congenital FXIII deficiency is being conducted to evaluate the prophylactic efficacy and long-term safety of this product. Using retrospective chart review data from subjects enrolled in the Phase II/III study, the current analysis was designed to compare spontaneous bleed-event rates prior to and after the initiation of Fibrogammin® P prophylaxis. Seven subjects were evaluable for comparison, having received no other prophylactic FXIII-containing product during the 24 months prior to study entry. The mean annual number of spontaneous bleeds was 2.5 events per year prior to Fibrogammin® P prophylaxis and 0.2 events per year during Fibrogammin® P prophylaxis (P = 0.01). Patients reported no severe bleeds during Fibrogammin® P therapy. This small sample supports a consistent and clinically meaningful reduction in spontaneous bleeding with prophylactic use of Fibrogammin® P.

Keywords: blood coagulation factors, factor XIII, factor XIII deficiency, genetics, prophylaxis, retrospective studies

Introduction

Congenital deficiency of factor XIII (FXIII, fibrin stabilizing factor) is an extremely rare, but severe and potentially life-threatening hereditary bleeding disorder [1]. The estimated incidence is approximately one affected person per million population [2–5]. Factor XIII deficiency was first clinically identified in 1960 in a child born of a consanguineous marriage [2,6]. Genetic inheritance is autosomal recessive in nature, and a higher incidence of compound heterozygosity is observed among non-consanguineous families [5].

Delayed umbilical haemorrhage is a presenting feature in 80–90% of FXIII deficiency cases and should arouse strong suspicion for the disorder [1]. Standard coagulation tests (prothrombin time, partial thromboplastin time) are usually normal for age. Specialized testing, including a clot solubility and FXIII activity assay, are required to make an accurate diagnosis [1]. Factor XIII deficiency is also characterized by a particularly high frequency of potentially fatal intracranial haemorrhage (~30% of cases), often occurring spontaneously or following very minor trauma [7]. This feature alone makes FXIII deficiency one of the most serious bleeding disorders. It also provides a basis for widely accepted recommendations that all patients with clinically relevant deficiency receive routine FXIII replacement therapy

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[1,6]. These patients also have a life-long propensity for subcutaneous bleeding into the skin, subcutaneous tissues, muscles, and joints. In the absence of effective treatment, most patients with FXIII deficiency continue to manifest repeated and prolonged bleeding episodes leading to various degrees of debilitation and potentially death [8]. Recently published questionnaire data from the International Registry on Factor XIII Deficiency reflect the experiences of 104 patients worldwide and confirm high rates of subcutaneous (57%), umbilical cord (56%), muscle (49%), joint (36%), and central nervous system (34%) bleeds among individuals with this deficiency [8]. While the majority of persons with FXIII deficiency are severely affected, the specific alterations of the FXIII protein show a high degree of heterogeneity and clinical manifestations can be highly variable from patient to patient [2]. As a consequence, individual bleeding patterns, tendencies, and severity will differ among affected patients [8,9]. The extent of bleeding inversely correlates with patients' FXIII level. For example, patients who experience only mild bleeding have a low mean FXIII level of 0.9 ± 0.6% of normal, whereas patients with severe bleeding have a much higher mean FXIII level of 4.6 ± 16.7% of normal [9].

The greatest risk of severe spontaneous bleeding occurs when FXIII levels are below 1 U dL^{-1}, and routine replacement therapy with FXIII concentrate is recommended for such patients from the time of diagnosis. Individuals with FXIII levels between 1 and 4 U dL^{-1} are still prone to moderate to severe bleeding, and FXIII replacement therapy should also be strongly considered [2].

Unlike most coagulation factors, FXIII has a long circulating half-life (7–12 days) and full haemostatic activity even at low concentrations, making it particularly suitable for routine prophylactic replacement [10]. In the past, replacement had been achieved using fresh-frozen plasma (FFP) or cryoprecipitate. However, the usefulness of these products for lifelong prophylaxis is hindered by the potential risk of hepatitis and other blood-borne diseases.

Fibrogammin® P (CSL Behring GmbH, Marburg, Germany) is a purified concentrate of FXIII obtained from HIV-negative, pooled human plasma screened for common viruses. The manufacturing process includes rigorous viral inactivation and elimination techniques, including pasteurization at 60°C for 10 h, adsorption of AL(OH)3/Vitacel and defibrinization, as well as ion exchange chromatography, making viral disease transmission highly unlikely. This high margin of safety is supported by the absence of any proven cases of virus transmission due to Fibrogammin® P administration during clinical trials or reported via postmarketing surveillance. Due to its long half-life (7–12 days), Fibrogammin® P can be conveniently administered for prophylactic treatment once every 3–4 weeks. Scheduled monthly treatment with 10–30 units kg^{-1} of Fibrogammin® P is considered sufficient in most cases to maintain FXIII levels above a critical threshold to prevent bleeding episodes [2,11]. It is provided in lyophilized vials containing 250 units or 1 250 units, and is reconstituted with Sterile Water for Injection USP. Fibrogammin® P is licensed in several countries in Asia, Europe, and South American, but not in the United States.

An ongoing investigational new drug (IND) study is evaluating the prophylactic efficacy and long-term safety of Fibrogammin® P [11]. The study is currently being conducted at 39 sites in the United States and has enrolled 61 subjects, who are thought to represent approximately two-thirds of US patients with FXIII deficiency based on incidence. Response to therapy has been good to excellent in these patients, who have been followed for up to 9 years, with no inhibitor development and no seroconversions. No major intracranial or life-threatening bleeds have been reported in patients on study while receiving continual prophylaxis.

Due to the high rate of spontaneous intracranial haemorrhage, there is no control group in the prophylaxis follow-up study. Therefore, to generate a meaningful 'control' data set, historical records of bleeding events were reviewed for some study subjects and used to compare bleed frequencies prior to and during Fibrogammin® P prophylaxis. Adequate historical data were not available for all subjects because of early diagnosis or other factors. The findings for seven eligible patients are nonetheless of clinical value in relation to managing this rare disorder.

Materials and methods

This was a retrospective, chart review analysis of selected participants in an ongoing Phase II/III study (hereafter, 'main study') of Fibrogammin® P prophylaxis. An overview of the methodology for this main study is being provided as relevant background information.

Methodology of main study

Any patient with congenital FXIII deficiency was eligible to enrol in the main study, including children

and newborns. Individuals with acquired FXIII deficiency were not eligible. A total of 61 patients have been enrolled at 37 study sites. An FXIII pharmacokinetic analysis was performed in each subject following a 4-week washout period (no FXIII or other blood-product infusion), preferably prior to the first Fibrogammin® P infusion. The first dose of Fibrogammin® P for pharmacokinetic analysis was 20 U kg^{-1} given over a 5-min period. The circulating half-life of FXIII was determined for each subject (data to be reported elsewhere) and used to calculate an individualized dosing regimen to maintain FXIII levels within a protective range. Patients continued to receive Fibrogammin® P infusions at 3–4 week intervals. Further descriptions of the study methodology, as well as some preliminary findings, have been published elsewhere [11].

Methodology for historical control analysis of bleeding frequency

When the mean length of treatment with Fibrogammin® P in the main study was 22 months, patients' medical records were retrospectively reviewed for the 24 months prior to study entry to generate an historical comparison database. The criteria for gathering useful historical control data excluded many of the subjects enrolled in the main study. First, data collection was limited to subjects from study sites that had enrolled two or more subjects. Second, subjects could not have received routine prophylactic infusions of cryoprecipitate, FFP, or FXIII from any other sources during the historical review period. Finally, historical data was sought for a 24-month period prior to the start of Fibrogammin® P prophylaxis. For some patients, especially very young children, the interval between FXIII deficiency diagnosis (or date of birth) and start of Fibrogammin® P prophylaxis was often less than 6 months, rendering many subjects ineligible for retrospective comparison.

The number of bleeding episodes was recorded for each subject before and during Fibrogammin® P prophylaxis. Bleeding frequency per year was calculated for each subject. Mean bleeding frequencies before and during Fibrogammin® P prophylaxis were compared using a two sided paired *t*-test with $\alpha = 0.05$.

Results

Thirteen patients at four study sites were eligible for chart review for historical and on-treatment bleeding data. Subjects ranged between the ages of 10 months and 29 years. Of the 13 cases reviewed, two had incomplete historical information (medical records inaccessible or missing the required data). Four additional subjects had received prophylactic treatment with cryoprecipitate or FFP during the 24 months prior to starting Fibrogammin® P prophylaxis and were also excluded from the current analysis. The remaining seven patients had received no prior prophylaxis with FXIII or other blood products during the historical assessment period, allowing a true comparison of bleeding frequency with and without Fibrogammin® P prophylaxis. Table 1 provides a summary of dosing and bleeding-episode data for these subjects prior to study entry (pre-Fibrogammin® P therapy) and while receiving Fibrogammin® P prophylaxis. Patients were dosed on a unit basis. Variability in weight and vial size led to a range of doses per kilogram.

The annual spontaneous bleeding rates in evaluable subjects decreased during Fibrogammin® P prophylaxis (Fig. 1). The majority of subjects (six of seven, 86%) had experienced one or more bleeding episodes during the historical assessment period. Five of the seven subjects (71%) experienced no spontaneous bleeding while receiving Fibrogammin® P therapy. The two bleeding episodes recorded in subject 3302 while on Fibrogammin® P prophylaxis were related to normal postpartum events, and as such, were not considered spontaneous bleeds or ineffectiveness of the prophylactic treatment. Disregarding these events, the mean number of spontaneous bleeds during Fibrogammin® P therapy was 0.2 per year, significantly less than the mean calculated for the prestudy interval (2.5 events per year; $P = 0.01$).

One severe bleeding event (intracranial bleed, subject 3 303) was documented during the 24 months prior to starting Fibrogammin® P prophylaxis. No intracranial bleeds or other severe bleeding events were observed during Fibrogammin® P administration.

Case summaries

Subject 504 was a male subject born in February 1998 and diagnosed with FXIII deficiency in September 2003 (FXIII level at diagnosis <10%). During the 24-month period prior to entering the Fibrogammin® P study in September 2003, this subject experienced two abnormal bleeding episodes: a haematoma on the right thigh and one involving the rib cage, neither of which required treatment. No bleeding events were recorded during 12 months of Fibrogammin® P prophylaxis.

Table 1. Bleeds before vs. during Fibrogammin® P therapy.

	Pre-Fibrogammin® P therapy					Fibrogammin® P therapy			
Patient	Age* (years, unless noted)	Observation period (months)	No. of bleeds	Type of bleed	Acute treatment	Observation period, months; (no. of infusions)	No. of bleeds	Type of bleed	Dose (units kg^{-1})
1	5	24	2	Haematomas, right thigh and rib cage	None	12 (12)	0		27
2	10 months	9	2	Umbilical cord; extensive bruising	FFP, vit K	25 (26)	1	Head trauma and bruising	29.7–44.9
3	17 months	6	3	Forehead bruise; frenulum bleed; forehead haematoma	FFP	26 (26)	2	Soft tissue bleed from trauma to foot; extracranial head	18.3–43.1
4	9	24	3	Lower lip; ankle; forehead haematoma	FFP	13 (12)	0		19.9–29.7
5	19	24	5	Various haematoma; forehead bruise	FFP	9.5 (11)	0		18.9
6	17	24	0	None	None	9.5 (12)	0		24.3
7	14	24	8	Intrancranial; mouth; forehead; gums; thigh	FFP	19 (11)	0		15.6
Mean no. bleeds per year			2.5 per year			Mean no. bleeds per year	0.2 per year†		

FPP, fresh-frozen plasma.
*Age at onset of Fibrogammin® P therapy.
†$P = 0.01$ vs. pretherapy.

Fig. 1. Calculated rates of spontaneous bleeding (events per year) for previously un-prophylaxed subjects, prior to and during Fibrogammin® P prophylaxis. Annual rates were extrapolated where necessary.

Subject 2703 was a 10-month-old female at the time of study enrollment. She had experienced an umbilical cord bleed approximately 2 weeks after birth in December 1999 and was treated with FFP and vitamin K, and was diagnosed with FXIII deficiency (categorized as 'severe'). She was enrolled in the Fibrogammin® P prophylaxis study in September 2000, and only one spontaneous bleed was recorded during 25 months of treatment.

Subject 2704 was diagnosed with severe FXIII deficiency in February 2000 following increased bleeding after circumcision (no treatment given). Three additional bleeding episodes occurred prior to enrollment in the Fibrogammin® P study in August 2000: bleeding gums/bruise on forehead, frenulum bleed, and a forehead haematoma, all of which were treated with FFP. Two bleeding events occurred in this subject over 26 months of Fibrogammin® P prophylaxis: one on the foot and one on the head.

Subject 2705 was a male patient born in 1994 and diagnosed with severe FXIII deficiency in 2002. During a surgery (umbilical hernia repair) in 1999, he had experienced increased bleeding, hypovolaemia, and anaemia and was given two units of packed red blood cells. Following diagnosis, this subject began Fibrogammin® P prophylaxis in January 2005. During the prior 24 months, three bleeding episodes had been recorded: lower lip, right ankle injury, and a forehead haematoma, all treated with FFP. No bleeding episodes occurred during 13 months of Fibrogammin® P prophylaxis.

Subject 3301 was a male patient enrolled in the Fibrogammin® P study at 19 years of age (June 2001). At the time of diagnosis in 1986, his FXIII level was <1%. During the 24 months prior to Fibrogammin® P prophylaxis, he experienced five spontaneous bleeding episodes characterized as haematomas on the thighs, back, buttock, or arms, and a

bruise on the forehead, all treated with FFP. During Fibrogammin® P prophylaxis in the main study, there were no spontaneous bleeds during 9.5 months (11 Fibrogammin® P doses) of observation.

Subject 3302 was diagnosed with FXIII deficiency (FXIII levels <1%) shortly after birth in 1983. Her history included four bleeding events requiring administration of FFP. Her historical assessment period was evaluated as the 24 months prior to February 1990, during which time she had no significant bleeding episodes. While enrolled in the Fibrogammin® P prophylaxis study, she experienced two episodes of normal postpartum bleeding.

Subject 3303, a 14-year-old male subject (FXIII levels <1%), started Fibrogammin® P prophylaxis in March 1990. During his 24-month historical assessment period, he was noted to have had eight spontaneous bleeding episodes: three episodes of bleeding gums, treated with aminocaproic acid (Amicar or FFP); two forehead haematomas (one treated with FFP, one not treated); an intracranial bleed treated with FFP every 3 days while hospitalized; bleeding following a MediPort placement, treated with FFP; and a haematoma on the thigh, treated with FFP. No spontaneous bleeding events were evident during 10 months (11 infusions) of Fibrogammin® P prophylaxis.

Discussion and conclusion

This review of historical bleed data in patients with congenital FXIII deficiency before and during Fibrogammin® P therapy provides a 'control' data perspective in a population for which traditional placebo-controlled protocols are problematic. There were no set parameters for follow-up interval, and this review was simply intended to provide a soft 'snapshot' of experience before and during Fibrogammin® P prophylaxis. The follow-up intervals are not indicative of discontinuation of therapy or patients being lost to follow-up. The results demonstrate a consistent and clinically meaningful reduction in spontaneous bleeding from mild trauma with prophylactic use of Fibrogammin® P from a mean of 2.5 episodes per year to 0.2 episodes per year compared to no treatment in a small group of patients with symptomatic congenital FXIII deficiency.

Although retrospectively gathered data formed the basis for this analysis, the on-treatment data were obtained as part of a carefully supervised prospective clinical trial; likewise, historical records of prior bleeding events were expected to be well-documented, considering the nature of the disorder and the management of these subjects at Hemophilia Treatment Centers. Ongoing findings from the larger IND study of Fibrogammin® P in congenital FXIII deficiency should continue to produce more rigorous scientific outcomes, especially as patient accrual continues. To date, no serious adverse events have been reported.

The first prospective study of Fibrogammin® P was carried out in France and involved 19 patients from 15 centers [12]. Sixteen patients were given regular prophylaxis with Fibrogammin® P ranging from 19 to 108 weeks without major bleeds. Response was defined as good to excellent, and no patients developed detectable antibodies. Published case report series have reported similar efficacy [1,13].

Fibrogammin® P is currently marketed in a number of countries, including Japan, Germany, and the United Kingdom. Marketing approval in the United States is being pursued. A new recombinant FXIII-A_2 product is also under investigation, one that involves no human or mammalian production elements. Preliminary research supports indications that it may be an effective alternative, although longer-term studies will be required to confirm immunogenicity risk and overall safety [14].

Other products have been used for the treatment of FXIII deficiency, including FFP and cryoprecipitate, although the limited data regarding prophylactic use in this population suggest efficacy inferior to experience with Fibrogammin® P. Garcia-Talavera *et al.* described the bleeding and treatment patterns of seven patients with FXIII deficiency from four families in Tenerife, Spain, over a 30-year period. Prior to 1983, six patients received FFP (250–500 mL every 4 weeks) prophylactic therapy [15]. Bleeding events reported during this period included four episodes of central nervous system bleeding, a newborn death, and a fatal bleeding diathesis related to high-titre inhibitor. Two patients also developed chronic VHC infection. Three patients have received prophylaxis with Fibrogammin® P (every 4 weeks) since 1983. Throughout an average observation period of 171 months, there were no reports of bleeding episodes in patients using prophylactic Fibrogammin® P, and one woman experienced an uncomplicated pregnancy using the product every 3 weeks. In addition, both FFP and cryoprecipitate carry potential risks of blood-borne disease transmission (e.g. hepatitis, HIV, West Nile virus). Fibrogammin® P is highly purified and heat-treated to minimize such risks.

The data from this small sample of subjects indicate a clinically significant reduction in spontaneous bleeding episodes among subjects receiving Fibrogammin® P for routine prophylaxis. These

recent data from the United States support previously published data from Europe and should be of interest to the readers of *Haemophilia*. This information is important to those involved in the management of patients with this rare and serious bleeding disorder.

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Disclosures

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