A multicenter, real-world experience with recombinant FXIII for the treatment of patients with FXIII deficiency: from pharmacokinetics to clinical practice. The Italian FXIII Study

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Background - Congenital factor XIII (FXIII) deficiency is a rare coagulation disorder characterized by muscular or mucocutaneous bleeding with life-threatening intracranial hemorrhages (ICHs), especially in cases with severe disease. The best treatment is the use of prophylactic plasma-derived or recombinant FXIII (rFXIII). Few data on the use of rFXIII in the real-world scenario are available. The main goal of this study was to assess the efficacy and safety of catridecacog (NovoThirteen®) in a population of patients with FXIII deficiency. Other objectives were to compare the different pharmacokinetic (PK) profiles of each patient and to use them to create a tailored prophylaxis regimen.

Materials and methods - We collected and analyzed all pharmacokinetic and clinical data in our registry of the patients with congenital FXIII deficiency treated with rFXIII at eleven Italian hemophilia centers. Data were collected from January 2019 to December 2020.

Results - Overall, data on 20 patients with FXIII deficiency were collected, 16 of whom presented with severe disease. Pharmacokinetics was assessed in 18 cases before starting prophylaxis. Prophylaxis was subsequently started in these patients using a wide range of dosages (25.0-80.0 IU/kg; mean 33.8 IU/kg) and infusion intervals (3.0-8.0 weeks). During a mean follow up of 47 months, two minor bleeds and one ICH in a severe patient who had remained under on-demand treatment were reported.

Discussion - Efficacy and safety of rFXIII were proven in all patients. The dosage and infusion timing for the treated patients sometimes differed to those reported in the MENTOR pivotal studies, thus underlying the importance of tailored management in a real-world scenario.

Keywords: *FXIII deficiency, recombinant FXIII, NovoThrirteen, rare bleeding disorders, pharmacokinetics.*

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INTRODUCTION

Congenital factor XIII (FXIII) deficiency is an autosomal recessive disorder that affects males and females equally, with a prevalence of about one per 1 million people. Prevalence

can vary greatly according to geographical area, with the highest in societies in which consanguine marriage is frequent[1-3]. Coagulation FXIII is a pro-transglutaminase present in plasma as hetero-tetramers (FXIII- A2B2) composed of two catalytic subunits (FXIII-A2) and two carrier subunits (FXIII-B2). This pro-enzyme is a multi-functional complex with an important role in different biological processes such as pregnancy, angiogenesis, bone metabolism, wound healing, and cardio protection[4]. The clinical manifestations of FXIII deficiency are extremely heterogeneous, and range from mucocutaneous bleeds of little concern to life-threatening intracranial hemorrhages. Depending on plasma FXIII levels, these bleeding episodes may occur spontaneously within the first months of life or even at birth from the umbilical cord, or in adulthood when the hemorrhagic event follows surgery or a traumatic event[5]. As reported by the European Network of Rare Bleeding Disorders (EN-RBD), and confirmed by others, patients with very low plasma levels of FXIII activity have a higher risk of developing severe spontaneous bleeding, while patients with low but measurable levels of activity usually remain asymptomatic[6]. These results enabled the FVIII/FIX Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis to develop a new classification system for FXIII deficiency; this was used in this study[7]. When diagnosis of this coagulation disorder occurs following the onset of a severe bleeding episode, prophylaxis with a FXIII concentrate is recommended to prevent further hemorrhages. In the past, fresh frozen plasma (FFP), cryoprecipitate or plasma-derived FXIII had been used for prophylaxis, but in 2014 the new recombinant FXIII (rFXIII) catridecacog NovoThrirteen® (Novo Nordisk A/S, Bagsværd, Denmark) became available. The data obtained in the pivotal MENTOR program[8-11] showed that the catridecacog,

Table I - *Hemorrhagic events recorded at diagnosis and at first treatment*

Patient number	Sex	Age at diagnosis (years)	Severity of FXIII defect	Hemorrhagic event at diagnosis	Major or minor bleeding*	Type	First treatment
1	F	1.5	Severe	Cephalohematoma	Major	Traumatic	pdFXIII
2	M	15	Severe	Upper limb hematoma	Major	Spontaneous	pdFXIII
3	F	NA	Severe	None	/	/	None
4	F	19	Severe	Hemoperitoneum	Major	Spontaneous	Fresh frozen plasma
5	M	74	Mild	Subdural hematoma	Major	Concomitant use of DOACs	Fresh frozen plasma
6	M	14	Moderate	Lower limb hematoma	Major	Spontaneous	rFXIII
7	F	32	Mild	Ileo-psoas hematoma	Major	Spontaneous	Arterial embolization
8	M	17	Severe	Ileo-psoas hematoma	Major	Spontaneous	Fresh frozen plasma
9	M	12	Moderate	Ileo-psoas hematoma	Major	Spontaneous	Fresh frozen plasma
10	M	16	Severe	Ileo-psoas hematoma	Major	Spontaneous	Fresh frozen plasma
11	F	11	Severe	Follicular hematoma on abortion	Major	Spontaneous	Fresh frozen plasma
12	M	17	Severe	Not specified hematoma	Minor	Spontaneous	Fresh frozen plasma
13	F	3	Severe	Previous umbilical cord bleeding	Minor	Spontaneous	Unknown
14	M	1	Severe	Supracostal hematoma	Minor	Spontaneous	Not specified
15	F	At birth	Severe	Umbilical cord bleeding	Major	Spontaneous	pdFXIII
16	F	7	Severe	Bleeding after adenotonsillectomy	Minor/ Major	Post-surgery	pdFXIII
17	M	15	Severe	Intracranial hemorrhage	Major	Spontaneous	Fresh frozen plasma
18	F	9	Severe	Intracranial hemorrhage	Major	Spontaneous	Cryoprecipitate
19	F	19	Severe	Multiple muscular hematomas	Major	Spontaneous	Cryoprecipitate
20	F	NA	Severe	NA	NA	NA	pdFXIII

pdFXIII: plasma-derived FXIII; rFXIII: recombinant FXIII (catridecacog); NA: not available; DOACs: direct oral anticoagulants. *ISTH Classification[14].

produced by recombinant DNA technology, is structurally identical to the human A subunit of FXIII, and binds to the free FXIII subunit B, resulting in a hetero-tetramer with a half-life similar to that of the endogenous FXIII. Following the pivotal MENTOR program, the prophylactic dosage recommended to reduce the bleeding risk in patients with severe FXIII deficiency was established at 35 IU/kg every 4 weeks[8-11]. However, real-world data are lacking. Therefore, this study aimed to report the results of the Italian registry. In addition to data on clinical treatment, pharmacokinetic data were also collected.

Study aims

The primary goal of this study was to assess the efficacy and safety of rFXIII (NovoThirteen®) in a population of Italian patients with various degrees of FXIII deficiency. Secondary goals were to compare the different pharmacokinetic profiles of each patient and explore how these could be used to design a tailored prophylaxis regimen.

MATERIALS AND METHODS

Patients

The Italian FXIII Study is a registry that includes all patients with FXIII deficiency of any degree treated with catridecacog at eleven Italian hemophilia centers. Data collection began in January 2019 and ended in December 2020. The study protocol was approved by each institution's Ethics Committee, and data were collected in accordance with the principles of the Declaration of Helsinki and with local laws and regulations.

Methods

At each participating center, the following data were collected for treated patients: 1) demographic and baseline characteristics, such as sex, age at diagnosis, body mass index (BMI); 2) descriptive characteristics of bleeding events at diagnosis; 3) laboratory findings (baseline factor XIII activity and creatinine clearance); 4) genetics (when available); 5) treatment of acute events; 6) PK data, (i.e., FXIII activity at different timepoints); 7) data concerning prophylaxis (onset, dosage, timing); 8) clinical results (bleeding, surgery); 9) any adverse event (e.g., inhibitor development, thromboembolic events, etc.).

According to the FVIII/FIX Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis[7], we considered FXIII deficiency to be severe when the plasma activity was undetectable (<0.05 IU/mL, lower limit of quantification[12] according to the Berichrom FXIII chromogenic assay), moderate deficiency when activity was <0.30 IU/mL, and mild deficiency when activity was ≥0.30 IU/mL (normal range 0.70-1.40 IU/mL). According to the ISTH definition[13], major bleeding episodes were symptomatic bleeding in an organ or critical area (i.e., intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) and/or bleeding causing a fall in hemoglobin levels of 2.0 g/L or more or leading to the transfusion of two or more units of whole blood or red cells.

Pharmacokinetics

A non-compartmental pharmacokinetic analysis for each patient was performed using PKAnalix2020.R1, an application of the Monolix Suite (Simulations Plus, Lancaster, CA, USA).

Statistical analysis

Due to the non-interventional nature of this study, all patients were included in the analysis and sample size definition was not required. All collected variables were summarized by appropriate descriptive statistics, such as mean, standard deviation (SD), median, range, percent.

All the PK statistical analyses included in this study were performed at the Clinical Pharmacology Units of the IRCCS Azienda Ospedaliero Universitaria Sant'Orsola, Bologna, Italy.

RESULTS

Overall, 20 patients with FXIII deficiency were included in this registry. Eleven were females. Sixteen had severe disease, 2 moderate and 2 mild (**Table I**). Genetic analysis was only available for 9 patients with severe disease (p.Gly562Arg: n=1; p.Gly563Arg: n=3; p.Gly216Arg: n=3; p.Ser404Arg: n=1; double mutation p.Gly420Ser/p.Tyr215X: n=1). Mean age at diagnosis was 10.6 years in the severe patients (range: at birth-74 years). In the 2 moderate patients, diagnosis was made at the age of 12 and 14 years, respectively, while in the 2 remaining mild patients, the diagnosis was made at the age of 32 and 74 years, respectively. **Table I** also summarizes the bleeding events recorded at diagnosis and their first treatment. Only one patient with severe deficiency had had no hemorrhagic event at the time of diagnosis.

Pharmacokinetic analysis was performed in 18/20 patients before starting rFXIII. Mean age at PK assessment time was 34.5 years (range: 6-74 years), mean weight was 71.5 kg (range: 19-98 kg) and patient BMI was 24.5 kg/m^2 (range: 13.0-33.5 kg/m^2); there were no significant differences between males and females. All patients had normal renal function which therefore did not affect the PK parameters. PK analyses were performed after the intravenous administration of a mean dose of 33.9 IU/kg (range: 25.0-50.0 IU/kg). A summary of PK results is reported in **Table II**.

Median interquartile (IQR) rFXIII concentrations before dosing was 0.06 IU/mL (0.0-0.54 IU/mL), and the highest concentration (1.77 IU/mL) was observed at 15 minutes post infusion for mild patients, whereas for severe patients the highest concentration (1.21 IU/mL) was observed in one woman one hour (h) after receiving 35.0 IU/kg of rFXIII. Although a large variability was observed for mean AUC_{inf} with a coefficient of variation (CV%) of 105.18%, inter-individual variability in clearance (CL) and volume of distribution associated with the terminal phase (V_z) were at acceptable levels. Mean terminal half-life was 15.7 days (range: 5.0-52.3 days).

Once PK results had been obtained, prophylaxis was started in 16/18 patients at a mean dosage of 33.8 IU/kg (range: 25.0-80.0 IU/kg) and with an average dosing interval of 4 weeks (range: 3-8.0 weeks). Overall, 4/16 patients with severe FXIII deficiency continued to receive treatment on-demand, while all 4 non-severe subjects were put on prophylaxis. The oldest patient, in spite of presenting a mild defect, received prophylaxis to prevent bleeding events owing to a concomitant treatment with a direct oral anticoagulant (DOAC) for atrial fibrillation. During a mean follow up of 47 months, only an ileo-psoas hematoma (that quickly resolved) and a post-traumatic muscular hematoma were observed. The ileo-psoas hematoma was observed in a severe patient treated with rFXIII 29.7 IU/kg every 4 weeks, while the post-traumatic hematoma occurred in a young severe patient on prophylaxis with this concentrate at a dosage of 35.0 IU/kg every 5-6 weeks. In both cases, a single dose of NovoThirteen® was administered to resolve the hemorrhagic event; no other data were available. Two minor surgeries (a pacemaker implant in a mild patient and surgery for wisdom tooth extraction in a severe patient) were performed without complications. NovoThirteen® was administered to these 2 patients once, 1 h before scheduled interventions at doses of 36.7 IU/kg and 31.0 IU/kg, respectively. A severe patient who chose to continue to receive on-demand treatment experienced an intracranial hemorrhage without sequalae. No thromboembolic events or inhibitors against FXIII were reported by clinicians either during the study period or during follow up, and therefore no further inquiries were made into this.

Table II - *Summary of non-compartmental pharmacokinetic analysis of rFXIII in the study population*

Parameter	Median	25th	75th	Mean	SD	CV	Min	Max
AUCinf(IUh/mL)	242.36	203.23	407.13	400.34	421.1	105.18	172.09	1570
AUClast(IUh/mL)	237.52	187.18	422.35	907.47	2449.78	269.36	106.31	10073.38
CL (mL/h/kg)	0.13	0.099	0.14	0.12	0.044	35.63	0.024	0.18
Clast (IU/mL)	0.11	0.074	0.17	0.18	0.14	91.13	0.019	0.58
Cmax (IU/mL)	0.8	0.17	0.99	0.71	0.48	68.53	0.11	1.77
HF_lambda_z (h)	304.9	176.74	377.95	377.87	127.39	86.64	142.08	1256.34
Lambda_z (h-1) **T1/2 (h)**	0.0023 12.7	0.0018 7.36	0.0039 15.75	0.0027 15.74	0.0014 5.3	51.91 3.61	0.00055 5.92	0.0049 52.35
Tlast (h)	672	672	984	754.67	272.68	36.13	168	1392
Tmax (h)	24	1	672	235.08	362.91	154.37	0.25	984
Vz(mL/kg)	47.01	41.49	59.01	49.7	12.65	25.45	29.86	66.96

AUCinf : AUC from the time of dosing extrapolated to infinity; AUClast : AUC from the time of dosing to the last measurable concentration; Clast : concentration of last time point with measurable concentration; CL: clearance based on observed Clast; Cmax : maximum observed concentration; CV: coefficient of variation; HF_lamda_z: terminal half-life; Lambda_z: first-order rate constant associated with the terminal portion of the curve; SD: standard deviation; T1/2: terminal half-life; Tlast : last time point with measurable concentration; Tmax : time of maximum observed concentration; Vz : volume of distribution associated with the terminal phase.

DISCUSSION

This is a study on a registry of the real-world use of NovoThirteen® in patients with FXIII deficiency. The study aimed to analyze the clinical and pharmacokinetic aspects of this drug. Today, prophylaxis with plasma-derived or recombinant FXIII concentrates is recommended in patients with FXIII deficiency to prevent spontaneous and/or life-threatening bleeding; fresh frozen plasma or cryoprecipitate are only used in the absence of the above-mentioned drugs[14]. The available data have demonstrated the efficacy of a plasma-derived concentrate both in prophylaxis and in on-demand treatment. However, although the safety of plasma-derived products has significantly improved over the years thanks to innovative viral inactivation techniques, a possible contamination cannot be completely excluded[15], as also shown by Salomon *et al.*[16] who reported 19 cases of pathogen transmission with plasma-derived FXIII in their 20-year pharmacovigilance analysis.

NovoThirteen® is the only FXIII of recombinant origin currently available. This characteristic means: 1) there is no risk of transmitting viral infections; 2) it is produced in yeast cells; and 3) it is structurally identical to the human FXIII-subunit A. The recommended prophylactic dosage to reduce the bleeding risk in patients with severe FXIII deficiency is that obtained from the pivotal MENTOR clinical trials[8-11]: 35.0 IU/kg every 4 weeks. However, data on a real-world experience are very limited. This registry was designed to try to reduce this gap.

Overall, we evaluated the pharmacokinetic and the clinical responses to treatment with NovoThirteen® in 20 patients presenting FXIII deficiency. A prophylaxis regimen was applied in two-thirds of them with a similar dosage regimen of 33.8 IU/kg every 28 days. Two patients on prophylaxis had bleeding events during follow up but without sequelae, while a severe patient, who decided to continue to receive on-demand treatment, had an intracranial hemorrhage which was resolved without sequalae after FXIII infusion. Thus, the results of our study highlight once again the fundamental role of early prophylaxis in patients with FXIII deficiency.

In our patients, the plasma peak of FXIII was 1.77 IU/mL, but no thromboembolic events related to high levels of this clotting factor were observed, whereas four thrombotic episodes were described by Solomon *et al.*[16] using a plasma-derived product. The MENTOR 2 study[8] described 12 minor surgeries performed in the 60 enrolled patients, all using rFXIII; none of them had any complication. Also in our cases, no spontaneous bleeding was reported in the 2 minor surgical interventions, that took place uneventfully.

The pharmacokinetic profile, assessed in 18/20 patients before initiating prophylactic treatment, showed a median geometric half-life and the geometric mean clearance of 12.7 days and 0.13 mL/h/kg, respectively. This is not very different from those obtained by Kerlin *et al.*[9] in the 23 patients from the MENTOR 2 trial included in the pharmacokinetic sub-analysis, while the mean terminal half-life was nearly 2 days longer than that of the pivotal study (15.7 *vs* 13.9 days). Timing of infusion and trough level in some of our patients were also very different. Based on these results, it is, therefore, possible to implement tailored prophylaxis with rFXIII after the evaluation of the pharmacokinetics, clinical conditions and needs of each patient with severe FXIII deficiency, thus improving quality of life; this is especially the case in children.

AFXIII coagulant activity of 0.15 IU/mL seems to be sufficient to protect against the risk of spontaneous bleeding events, as reported by Menegatti *et al.*[17]. However, unlike the MENTOR studies in which the trough level reached after 28 days was between 0.15 and 0.25 IU/mL, in our study, only 8/18 of patients exceeded 0.15 IU/mL in the same timeframe.

Thus, further study is needed to better explore what minimum trough level is required to prevent bleeding, as well as the dosage of NovoThirteen® that can be used in prophylaxis and the infusion time.

Study limitations

This is a retrospective registry that collected data on patients under treatment with different degrees of FXIII deficiency. Since this was an observational study, it was not possible to clearly define the times for sample collection for pharmacokinetic analyses, which were left to the discretion of the clinicians. For the same reason, it was not possible to establish a dosage to be used for PK determination and subsequent prophylaxis.

This is a Registry that includes only patients treated with NovoThirteen®. FXIII deficiency is an extremely rare disease. Therefore, we chose to include all patients under treatment, even those with mild or moderate disease, to ensure that no data relating to the efficacy and safety of the drug in a real-world scenario were lost.

CONCLUSIONS

Our study reports a population of patients with FXIII deficiency in a real-world scenario treated with NovoThirteen®. It provides information on efficacy and safety after a follow up of almost four years. Although this is a retrospective Registry, the results confirm those of the MENTOR studies, even though the dosages of the drug used and the infusion times sometimes differed from those recommended by the manufacturer. However, this allowed us to suggest some flexibility in the use of rFXIII according to patients' individual PK, lifestyle, and hemorrhagic history. Our registry further emphasizes the need to initiate prophylaxis in subjects with severe FXIII deficiency at birth or at the time of diagnosis. This is essential to avoid the risk of serious and potentially life-threatening bleeding, as was the case of our patient who chose to continue on-demand treatment and who then experienced an intracranial hemorrhage, fortunately resolved without consequences.

AUTHORS CONTRIBUTIONS

ZE contributed to study design, analyzed and interpreted data, and wrote the manuscript. PS collected data and wrote the manuscript. PF reviewed the entire content of the manuscript. PGC and FP performed the pharmacokinetics analysis. All Authors provided data, were involved in critically revising the manuscript, and approved the final version.

DISCLOSURE OF CONFLICTS OF INTEREST

PF has received speaker fees for education meetings for: Ablynx, Roche, Grifols, Takeda, Sanofi, Sobi, and Biomarin, and is a member of the Advisory Board of Sanofi, Roche, Takeda, Sobi, and Biomarin. The other Authors declare no conflicts of interest.

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