The pharmacokinetics of recombinant FXIII (catridecacog) from the MENTORTM2 trial to a real-world study: a head-to-head comparison

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The pharmacokinetics of recombinant FXIII (catridecacog) from the MENTOR™2 trial to a Real-World study: a head-to-head comparison

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Conflict of Interest

All authors declare no conflict of interest

Abstract

Background: FXIII deficiency is a very rare coagulation disorder that can affect equally males and females with an estimated incidence of 1 in 2 million persons worldwide. Due to this rarity, there are only few clinical and pharmacokinetic (PK) data deriving from the real-world.

Aim: The aim of this report is to compare head-to-head the pharmacokinetic data of catridecacog derived from the MENTOR™2 trial with our real-world (RW) study.

Methods: The PK-profiles of all patients with FXIII deficiency treated with catridecacog at eleven Italian Hemophilia Centers were compared with PK data obtained by Kerlin et al. in the MENTOR™2.

Results: Overall 18 real-world PK were compared with 23 PK derived from the pivotal study. In the RW 55.6% of patients were females, 26.2% in the MENTOR™2 ($p<0.05$). The mean dosage of drug used for the PK assessment was 35 IU/kg in the MENTOR™2, and 33.9 IU/kg in the RW study.

The mean achieved plasma Cmax was higher in the MENTOR™2. The mean of clearance was lower in the RW patients (0.12 vs 0.15 ml/h/kg) with a $p<0.05$; while the half-life of catridecacog in this group was nearly two days longer than that obtained in the MENTOR™2 (15.7 vs 13.9 days).

Conclusion: The obtained PK parameters of the RW study are similar of the MENTOR™2 in case of mean drug used or timing of administration, but differ in case of Cmax, clearance, and half-life thus allowing to hypothesize a possible modification of the use of rFXIII in the real-world.

Key words

FXIII deficiency, FXIII treatment, recombinant FXIII (rFXIII), MENTOR program, pharmacokinetics of rFXIII

Brief Communication

FXIII deficiency is a very rare coagulation disorder that equally affects males and females, the incidence in the general population is estimated about 1 in 2 million persons worldwide, more frequent in countries where consanguineous marriages are common [1].

Coagulation FXIII is a pro-γ-transglutaminase circulating in plasma as a hetero-tetramer (FXIII-A2B2) comprising two catalytic subunits (FXIII-A2) and two carrier subunits (FXIII-B2), it is activated by thrombin and calcium. The transglutaminase thus obtained binds the α2-antiplasmin to fibrin, stabilizing the fibrin clots. The FXIII plasma level is often not detectable in patients with severe FXIII deficiency due to limitations of the laboratory assay, whereas factor activity is only 50-70% of the normal range in those with a heterozygous defect. Heavy menstrual and umbilical cord bleeding, recurrent miscarriages, muscle hematomas, and intracranial hemorrhages are often reported in patients with severe FXIII deficiency and therefore patients require regular factor replacement therapy or treatment [2].

In the past, prophylaxis was performed with fresh frozen plasma (FFP) or cryoprecipitate, later replaced by plasma-derived FXIII concentrates, while more recently the recombinant FXIII (rFXIII) concentrate (Catridecacog; NovoThirteen®, Novo Nordisk HealthCare AG, Switzerland) is commonly used in children and adults, at the recommended dosage of 35 IU/kg every four weeks, following the pharmacokinetic (PK) results obtained by the MENTOR^{TM} trials. But these data are confirmed in a real-world population of patients with FXIII deficiency?

Here, we compared the PK data obtained by Kerlin et al. in the MENTOR^{TM}2 [3] with the results of our retrospective, multicenter, Real-World (RW) study.

Data of twenty patients with FXIII deficiency were collected at eleven Italian Hemophilia Centers, 85% of them had a severe disease, 9/20 were males. Population PK was assessed in 18/20 patients following a PK model created at the Clinical Pharmacology of Bologna [4]. A non-compartmental (NCA) pharmacokinetic analysis was performed with PKAnalix2020.R1, an application of the

Monolix Suite for compartment and non-compartment analysis. Drug concentrations were obtained after a single intravenous dose of rFXIII. Each patient received a single 5-min intravenous infusion of rFXIII. Blood samples for monitoring FXIII activity were collected at different times. rFXIII activity was measured with the Berichrom_FXIII chromogenic assay (Marburg, Germany) having the lower limit of quantification equal to 0.05 IU/ml [5].

The settings for NCA parameter calculation included the linear trapezoidal linear as the integral method for area under the curve (AUC) calculation, and the adjusted R2 criteria for calculation of $lambda_z$, namely the constant first-order rate constant associated with the terminal portion of the curve.

A similar number of patients was evaluated, 18 in our RW study and 23 in the MENTOR™2 trial, but in the first the females were almost twice as many as there were in the second (55.6% vs 26.2%, $p<0.05$); the mean age was 36.4 and 30.7 years, respectively, without a statistically significant difference ($p=0.31$). The mean body mass index (BMI) was very similar in the two considered patient populations, as well as the dosage of NovoThirteen™ used for the PK assessment, 35 IU/kg in the MENTOR™2, 33.9 IU/kg in our RW study. The mean achieved plasma peak of rFXIII (C_{max}) was higher in the MENTOR™2, but the difference between the two patient populations was not statistically significant ($p=0.11$). The mean clearance was lower in the RW study (0.12 vs 0.15 ml/h/kg) with a $p<0.05$; while the half-life of rFXIII in this group was nearly two days longer than that obtained in the MENTOR™2 (15.7 vs 13.9 days). The median AUC was similar in the two studies, while the median V_{ss} was higher in the RW population (65.9 vs 57.4 ml/kg). The through level assessed at 28 days was slightly higher in the RW study population (0.20 vs 0.17 IU/mL), which however included only eight patients in the analysis. In fact, as this was a retrospective study, no indication was given on the timing of the PK sampling which was therefore at the discretion of the clinicians involved in the trial.

A complete summary of demographics and PK data were reported in table 1.

Table 1

The comparison of PK data obtained in the MENTOR™2 and in the RW study offered interesting insights into the use of rFXIII in clinical practice.

Although no specific indications were given in the RW study, the mean of rFXIII used for the PK assessment was very similar to that used in the MENTOR™2 and subsequently recommended by the drug manufacturer, however, with a very wide range, from 25 IU/kg to 50 IU/kg. The higher dosage was used in a young girl with severe FXIII deficiency and presenting cephalohematoma at diagnosis. Based on her PK profile, this patient was subsequently put on prophylaxis with rFXIII 80 IU/kg every eight weeks [6], this also made it possible to avoid wasting drug since the vials currently available contain 2500 IU of concentrate, and to guarantee greater hemostatic coverage to the girl without increasing the thrombotic risk. The plasma C_{max} initially highlighted during the PK assessment (1.09 IU/ml) was maintained even at a higher dosage of rFXIII, without ever exceeding 1.30 IU/ml. The fact that the mean Cmax in the RW study was lower than that of the MENTOR™2 allows us to hypothesize that the dosage of the drug used in prophylaxis can be increased without incurring a greater thromboembolic risk, possibly also lengthening the administration times, such as occurred in the previously described case of our young girl [6].

Today, no clear correlation between high plasma levels of FXIII and venous thromboembolism (VTE) are found [7], four cases of VTE were reported after plasma-derived FXIII administration [8], but no cases were associated with rFXIII use. Some data, on the other hand, seem to correlate high levels of FXIII with an increased risk of peripheral arterial disease and myocardial infarction, especially in females. [9]. In our RW study the highest peak (1.77 IU/ml) was obtained in a mild patient with a basal level > 0.30 IU/ml, while in the severe patients the peaks remained significantly within the normal range (0.70-1.40 IU/ml), never exceeding 1.0 IU/ml, therefore no risk for arterial or venous thromboembolism was found. The data relating to the clearance of the drug and its half-life also allow us to hypothesize a possible modification of the dosage and the timing of NovoThirteen™ administration. An intracranial hemorrhage was reported only in one severe adult

patient in the RW study who decided not to undertake prophylactic treatment, quickly resolved without complications after rFXIII administration.

Although the two study populations have a very similar mean BMI, with a different male/female ratio, a significantly reduced drug clearance ($p < 0.05$) was found in patients included in the RW study compared to those in MENTOR™2, this assessment contrasts with what has been described by Brand-Staufer et al. [10] in their report, in which the sum of the PK data of the patients participating in the MENTOR™1, MENTOR™2 and MENTOR™4 studies shows that clearance is certainly influenced by weight difference, but not by sex difference.

Overall, the mean t½ in the RW study was more similar to that found in the pediatric population of MENTOR™4, (15.7 vs 15.0 days), compared to that obtained in the other patient groups analyzed in the MENTOR™ program [3.10], in which it was noticeably lower.

A limitation of our RW study is its retrospective nature. The data collected represent the clinical practice of each Center and can therefore differ from each other in terms of patients' characteristics (age, disease degree, etc) or drug dosage or samples collection. A comparison between the trough level values at 28 days, which represent the timing of administration of MENTOR™2, was also made difficult by the fact that only a few Centers had carried out an evaluation of the plasma level of FXIII on that day. As well as the lack of some values such as mean and range of AUC or V_{ss} limited other comparative analyzes, but what is a limitation can also be seen as a resource.

Having a snapshot of what is happening in the real-world can help clinicians make the best use of what they have at their disposal.

In our case it has emerged that maybe the rFXIII can also be used in a slightly different way than recommended by the manufacturer, the dosage can perhaps be increased, and the infusion timing extended, all while maintaining a high efficacy and safety profiles.

Although FXIII deficiency is a very rare disease, further studies in the real-world are desirable to provide even more information on this drug to confirm or disprove what we have described.

Acknowledgments

All the authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval of the version to be published. S.P and E.Z. concepted and designed the study; P.C. and F.P. analyzed and interpreted the data; S.P. wrote the manuscript; all authors revised and approved the manuscript.

Thanks to all the Italian FXIII Study Group : Laura Banov (Gaslini Children Hospital, Genoa), Chiara Biasioli (Hospital of Cesena), Patrizia Di Gregorio (SS. Annunziata Hospital of Chieti), Antonietta Ferretti (Umberto I University Hospital, Rome), Angelo Claudio Molinari (Gaslini Children Hospital, Genoa), Lucia Dora Notarangelo (ASST Spedali Civili, Brescia), Roberta Palla (Haemophilia and Thrombosis Center, Milan University Hospital), Flora Peyvandi (Haemophilia and Thrombosis Center, Milan University Hospital), Michele Pizzuti (San Carlo Hospital, Potenza), Berardino Pollio (Regina Margherita Children Hospital, Turin), Gianluca Sottilotta (Hospital of Reggio Calabria), and Simona Maria Siboni (Haemophilia and Thrombosis Center, Milan University Hospital).

Ethical statements

The authors declare that the manuscript was not be submitted to other journal for simultaneous consideration; the results have been presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Table 1. Summary of demographic characteristics and rFXIII pharmacokinetic parameters derived from the MENTOR™2 trial and from the Real World (RW) study.

	MENTOR™2	**RW study**	**p-value**
Patients, *n*	23	18	/
Age, *yrs* - Mean (SD) - Median (Range)	 30.7 (15.1) 28.0 (7.0 – 58.0)	 36.4 (20.1) 34.5 (6.0 – 74.0)	 0.31* /
Male, *n (%)*	18 (73.8)	8 (44.4)	< .05**
Body Max Index (kg/m^2) - Mean (SD) - Median (Range)	 24.6 (5.5) 23.4 (12.8–36.5)	 24.3 (5.3) 24.5 (13.0 – 33.5)	 0.86* /
Dose for PK evaluation (IU/kg) - Mean (SD) - Median (Range)	 35.0 (NA) 35.0 (NA)	 33.9 (6.1) 32.5 (25.0 – 50.0)	 / /
C max*, (IU/ml)* - Mean (SD) - Median (Range)	 0.89 (0.20) 0.86 (0.57 – 1.24)	 0.71 (0.48) 0.80 (0.11 – 1.77)	 0.11* /
C trough – day 28*, (IU/ml)* - Mean (SD) - Median (Range)	 0.17 (0.06) 0.15 (0.06 – 0.32)	(^n=8 patients) 0.20 (0.15) 0.16 (0.08 – 0.58)	 0.42* /
Clearance, *(ml/h/kg)* - Mean (SD) - Median (Range)	 0.15 (0.03) 0.15 (0.10 – 0.21)	 0.12 (0.04) 0.13 (0.02 – 0.18)	 < .05* /
t½, *days* - Mean (SD) - Median (Range)	(^n=20 patients) 13.9 (3.5) 13.2 (10.1 – 24.6)	 15.7 (5.3) 12.7 (5.0 – 52.3)	 0.22* /
AUC – day 28, *(IUh/ml)* - Mean (SD) - Median (Range)	(^n=19 patients) 240.4 (49.0) 234.0 (168.6 – 355.9)	 NA 237.5 (NA)	 / /
V_{ss}, *(ml/kg)* - Mean (SD) - Median (Range)	(^n=19 patients) 73.2 (24.8) 65.9 (44.0 -150.3)	 NA 57.4 (NA)	 / /

*Unpaired t-test of continuous baseline variables, comparing patients from the MENTOR™2 trial with patients from the RW study. NA: data not available; C max: peak of plasma activity concentration; C trough: plasma activity at 28th day; AUC: area under the curve; t½: half-life; Vss, volume of distribution at steady state. ^n: patients with complete data for the parameter