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LETTER TO THE EDITOR

Tailored prophylaxis with rFXIII (NovoThirteen®) in a young girl with severe FXIII deficiency and previous cephalohaematoma

Factor XIII (FXIII) deficiency is a rare coagulation disorder that affects about one in two million persons in the general population.[1] The diagnosis is often difficult because traditional coagulation tests such as activated partial thromboplastin time (aPTT), prothrombin time (PT), bleeding time, thrombin time or platelet count are normal. Therefore, the FXIII activity assay should be performed as soon as FXIII deficiency is suspected.[2,3] Coagulation FXIII is a pro-γ-transglutaminase found in plasma as a heterotetramer (FXIII-A2B2) comprising of two catalytic subunits (FXIII-A2) and two carrier subunits (FXIII-B2). The FXIII plasma levels are often not quantifiable in patients with severe FXIII deficiency (homozygous), whereas they are about 50%-70% of normal in those with a heterozygous defect. Patients with severe FXIII deficiency often present with a history of recurrent miscarriages, umbilical cord bleeding, muscle haematomas and intracranial haemorrhages.[4] Due to the potential severity of bleeding, continuous prophylaxis is paramount. [5]In the past, prophylaxis consisted of fresh frozen plasma (FFP) or cryoprecipitate, long before plasma-derived FXIII concentrates were licensed. The latter are widely used nowadays at a prophylactic dosage of 40 IU/kg every 4 weeks, adjustable to maintain trough levels of FXIII activity of approximately 5%-20%. Up till now, replacement FXIII concentrates were the sole therapeutic option for the treatment of severe FXIII disorder with proven efficacy and safety. [5,6] In early 2016, a novel recombinant FXIII (rFXIII) concentrate (Catridecacog; NovoThirteen®, Novo Nordisk HealthCare AG, Switzerland) was licensed with a recommended dosage of 35 IU/kg every 4 weeks.

Here we describe the prospective study of a young female patient with severe FXIII deficiency and prior cephalohaematoma who initially received prophylaxis with plasma-derived FXIII, which was later replaced by a tailored prophylactic regiment of rFXIII (NovoThirteen®). Our patient was born in December 2009, through natural delivery and she developed umbilical cord bleeding 24 hours after birth. Fresh frozen plasma and red blood cells were transfused. No coagulation tests were performed at that time except for PT and aPTT, which were normal. In June 2011, she developed a cephalohaematoma after a traumatic occipital head injury. Coagulation analyses performed upon admission showed PT, aPTT and haemoglobin within normal range, while FXIII activity was <1% (range 70%-140%). The patient's father and mother presented with a FXIII activity of 55% and 63%, respectively. Commercially available chromogenic assay (Behrichrom FXIII, Siemens, Milan, Italy) was used to detect FXIII activity (within-run and day-to-day CVs <5%). The laboratory pattern was consistent with a diagnosis of severe inherited FXIII deficiency in the proband. Genetic analysis performed later revealed the presence of a lesion in the F13A1 gene affecting the synthesis of FXIII-A-subunit (manuscript under submission).

The patient underwent neurosurgery to evacuate the cephalohaematoma, and bleeding was prevented by administering plasma-derived FXIII (Fibrogammin®, CSL Behring GmbH, Germany) at a dosage of 40 IU/kg immediately before surgery. Subsequently, the patient received a second infusion of replacement concentrate one month after surgery. The secondary prophylaxis with plasma-derived FXIII at a dosage of 40 IU/kg every 4 weeks was continued, and no other bleeding events occurred thereafter. In May 2016, with prior authorization from our health regulatory agency, we administered the new recombinant FXIII concentrate NovoThirteen® to the by then six-year-old patient. FXIII activity was measured in plasma by using chromogenic assay (Behrichrom FXIII, Siemens, Milan, Italy—see above). The pharmacokinetic profile was then evaluated after the administration of 50 IU/kg of rFXIII, equal to 1125 UI (half a vial), using the Phoenix® WinNonlin® V6.4 (Certara USA Inc, Princeton, NJ, USA) by a single assay. Non-compartmental analysis and single subject non-linear model fitting were used. The pharmacokinetics showed a biological half-life of 26 days, and a trough level of 5.5% FXIII activity on the fifty-eighth day (Figure 1). Our decision to forego the usually recommended protocol in favour of a more tailored treatment was based on the pharmacokinetic results, the young age of the patient, the need to establish an effective and safe prophylaxis to provide a better quality of life for the child and her parents, and not least, to try to minimise product waste seeing as the manufacturer only provides vials of 2500 IU available. Upon explaining to the parents the specific of this new therapeutic regiment and receiving their informed consent, we initiated the prophylaxis with NovoThirteen® 80 IU/kg every eight weeks. To date, the peak of plasma FXIII activity measured after each infusion has always remained within normal range, namely between 110% and 130% with trough levels between 5% and 15%. The total number of assays performed from the start of prophylaxis to date is shown in Table 1. Periodical controls to assess any adverse events or bleedings occurred during prophylaxis were conducted at our centre at each visit, and before each planned infusion of rFXIII. So far, no bleeding episodes or thromboembolic events have occurred, and high compliance has been achieved thanks to the lower number of annual infusions which were reduced by about 25% with our tailored protocol. At this time, no other pharmacokinetic assessments have been performed.

Currently, the best prophylactic treatment consists of FXIII replacement concentrates to guarantee FXIII levels between 3% and 10% to prevent spontaneous bleeds. For this purpose, trough levels

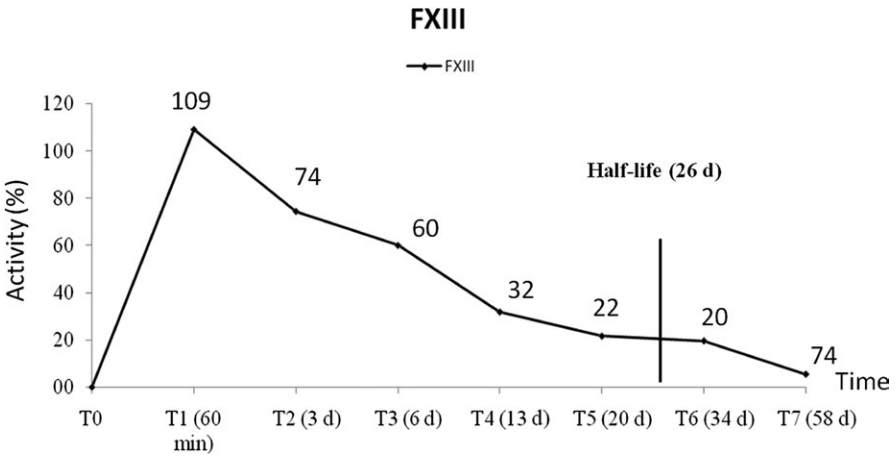

FIGURE 1 Pharmacokinetic profile after administration of rFXIII 50 IU/kg using the Phoenix® WinNonlin® V6.4 (Certara USA Inc, Princeton, NJ, USA) (see also text). *X*-axis represents time after rFXIII administration. *Y*-axis shows FXIII activity levels in plasma expressed in % of the normal value (normal ranges: 70%-140%)

TABLE 1 Number of assays performed from the start of prophylaxis with NovoThirteen 80 IU/dL every 8 wk, actual days between two consecutive FXIII infusions, trough level and peak reached at each check

Assays	Date (dd/mm/yyyy)	Interval between two consecutive FXIII infusions (d)	Through level (IU/dL)	Peak (IU/dL)
1	17/10/2016	70	10.5	NA
2	12/12/2016	56	5.5	110
3	03/04/2017	54	7	NA
4	29/05/2017	56	14	NA
5	24/07/2017	56	8.5	NA
6	18/09/2017	56	10	NA
7	13/11/2017	56	15	131.5
8	15/01/2018	63	11	NA
9	19/03/2018	63	5	NA
10	14/05/2018	56	7	121
11	02/07/2018	49[a]	9	NA
12	13/08/2018	42[a]	7	132.5

NA, not available.
[a]Reduced interval due to unavailability of parents on other dates.

should always be maintained >5 IU/dL although spontaneous bleeding may occur in a small percentage of patients. [7]Plasma-derived FXIII has a reported mean biological half-life of 6.6 days (range 5-12 days). Our patient has been treated with this concentrate for four years at a dosage of 40 IU/kg, based on periodic checks of trough levels. In patients younger than 16 yrs, the half-life of this drug can be shorter than in adults and dose adjustments may often be necessary. Although safety of plasma-derived products has been proven, 19 cases of pathogen transmission with plasma-derived FXIII were reported by Solomon et al [8]in their pharmacovigilance analysis covering the last twenty years. Of course, this risk is not present with recombinant drugs. The rFXIII (subunit A) NovoThirteen® is produced in yeast cells (Saccharomyces cerevisiae) by recombinant DNA technology. It is structurally identical to the human FXIII-A-subunit and binds to free human FXIII B-subunit resulting in a heterotetramer with a half-life of 15 days in the paediatric population, very similar to the endogenous FXIII.

The recommended prophylactic dosage to reduce bleeding risk in severe FXIII deficiency is 35 IU/kg every 4 weeks. In our case, the patient was switched to the recombinant concentrate at the age of six years. A pharmacokinetic assessment was performed before initiating the prophylaxis. The infused dose to estimate the pharmacokinetics was 50 IU/kg, and the biological half-life estimated was 26 days, higher than that previously reported. With the consent of the parents, we have administered a tailored prophylaxis of 80 IU/kg every eight weeks. Since then, the greatest risk in using such a high dose of coagulation factor concentrate was obtaining a very high post-infusion peak which could have increased the patient's thromboembolic risk. Although very high post-infusion peaks might predispose to thrombosis, a definitive correlation between high levels of FXIII and venous thromboembolism has not been established yet and the role of different FXIII-A and FXIII-B polymorphisms is still under investigation. [9]Nonetheless, four cases of deep vein thrombosis or pulmonary embolism were reported after administration

of plasma-derived FXIII, [8]whereas no thromboembolic events have been described so far during rFXIII treatment. Moreover, elevated FXIII levels also seem to correlate with an increased risk of myocardial infarction and peripheral artery disease, especially in the female patients, [10]which was also confirmed by pharmacovigilance analyses on the use of plasma-derived FXIII. [8]In our case, the peak reached between NovoThirteen® infusions remained within the safe range throughout. This is the first report on the use of high-dose rFXIII for prophylaxis to prevent bleeding and extend infusion time.

Although in our patient the prophylaxis with plasma-derived FXIII was effective, the new rFXIII was chosen due to its better pharmacokinetic profile. A biological half-life of 26 days allows for a tailored prophylaxis to our patient every eight weeks, thus improving compliance to treatment. We decided to increase the dose to 80 IU/kg each infusion to maintain a high trough level through the eighth week and also to reduce haemorrhagic risk in our patient. Further studies and registries are needed to confirm our results.

In conclusion, it is possible to administer a tailored prophylaxis of NovoThirteen® after careful evaluation of pharmacokinetics, genetics and needs of each patient with severe FXIII deficiency. The quality of life of patients can be improved but periodic clinical and laboratory checks are needed to ensure that proper regiment is followed.

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All of 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. The parents of our young patient signed the informed consent to participate in this prospective study and to publish the report. We thank Prof. Massimo Morfini who performed the pharmacokinetic analyses.

DISCLOSURES

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTION

E. Zanon, S. Pasca and P. Simioni were responsible for the study design and manuscript preparation. P. Simioni, S. Pasca and L. Spiezia were responsible for data acquisition. C. Radu and N. Scattolo performed laboratory tests. All the authors were responsible for the critical revision and for the approval of the manuscript.

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