Individual thrombin generation and bleeding rate during personalized prophylaxis with Nuwiq® in previously treated patients with severe haemophilia A

Y. Dargaud (1), R. Klamroth (2), L. Rusen (3), J. Windyga (4), J. Bichler (5), S. Knaub (5), C. Negrier (1)

(1) Université Lyon I - UFR Laennec, Lyon, France, (2) Vivantes Clinic Friedrichshain, Berlin, Germany, (3) Sanador SR, Bucharest, Romania, (4) Institute of Hematology and Transfusion Medicine, Warsaw, Poland, (5) Octapharma AG, Lachen, Switzerland

MP-74-W

Introduction

Nuwiq® is a 4th generation recombinant factor VIII concentrate without chemical modification or fusion with any other protein[1]. It is produced in a human cell line that adds only human-specific post-translational modifications[2]. Nuwiq® is approved in Europe, USA, Canada, Australia, Russia and some Latin American countries for the prevention and treatment of bleedings in haemophilia A patients based on clinical studies in 135 adult and paediatric previously treated patients (PTPs) with severe haemophilia A.

PK-guided personalized prophylaxis with Nuwiq® was validated in 66 adult PTPs with severe haemophilia. In the NuPreviq study (GENA-21), 73% of patients were bleed-free, the median dosing interval was extended to 3.5 days, and 58% of patients were treated with two or fewer infusions per week.

In the NuPreviq study also the thrombin generation assay (TGA) was performed to evaluate its relationship with the clinical bleeding phenotype of the patients.

Study Design, Material and Methods

This prospective, open-label, multicenter study included adult PTPs with severe haemophilia A. After the previously given FVIII concentrate was washed out, patients received a Nuwiq® dose of 60 ± 5 IU/kg for PK evaluation. Individual PK data were analyzed to determine the dose and injection interval which would theoretically result in a trough FVIII level of ≥1%. Personalized prophylaxis lasted 6 months.

For the TGA, blood was drawn in trisodium citrate tubes (0.106 M) containing 1.45 µM corn trypsin inhibitor (in whole blood), centrifuged twice to obtain platelet poor plasma which was stored frozen until analysis. Thrombin generation was initiated by adding tissue factor (1 pM) and endogenous thrombin potential (ETP) was measured using the calibrated automated TGA.

TGA and FVIII:C (automated APTT from Trinity Biotech, Siemens BCX-XP) were measured at the beginning of the study during the PK evaluation as well as after 2 months, 4 months and 6 months after start of the personalized prophylaxis (Figure 1).

Figure 1: NuPreviq – patients with FVIII:C / TGA measurements

Schematic representation of the GENA-21 study design:

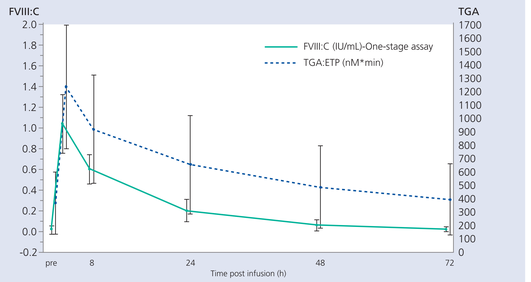
Study phase	Study Visits	No. of patients	
		NuPreviq	TGA cohort
Screening	Screening Visit		
Initial PK Evaluation Phase Duration: 72 hours Dose: 60 ± 5 IU FVIII/kg	**Initial PK Visit** (may coincide with the Screening Visit)	66	32*
Standard Prophylactic Treatment – Phase I **Duration:** 1–3 months **Dose and dosing interval:** 30–40 IU/kg every other day or 3×/week	Monthly compliance check(s) **End-of-Phase-I Visit**		
Personalized Prophylactic Treatment – Phase II **Duration:** 1–3 months **Dose and dosing interval:** individually PK tailored • Trough levels (FVIII:C and TGA) at 2 months • Trough levels (FVIII:C and TGA) at 4 months • Trough levels (FVIII:C and TGA) at 6 months	Monthly compliance check at 1 month **2-Month Visit** Monthly compliance check at 3 months **4-Month Visit** Monthly compliance check at 5 months **Study Completion Visit**	66 65 65	57 53 58

* FVIII:C & TGA measured: pre-inf., 0.5 h, 1 h, 3 h, 6 h, 9 h, 24 h, 30 h, 48h, 72 h

octapharma®

For the safe and optimal use of human proteins

Figure 2: ETP and FVIII:C before and after PK infusion (60±5 IU/kg) of Nuwiq® - Mean (± SD)



OS: Automated APTT from Trinity Biotech, Siemens BCX-XP

ETP and bleeding rate during personalized prophylaxis

Baseline ETP and bleeding rate

Baseline ETP was available for 32 patients. 21 patients did not experience any bleeding episode and 25 patients had no spontaneous bleeding during the personalized prophylaxis phase. The mean baseline ETP not differ between patients with and without any bleeding (373 ± 334 vs. 367 ±168 nmol*min, Figure 3). However, the mean baseline ETP but was considerably lower in patients who had spontaneous bleeds vs. those without spontaneous bleeding episodes (164 ± 66 vs. 426 ± 231 nmol*min, Figure 4).

Individual baseline ETP reflected the spontaneous bleeding tendency during prophylaxis (Figures 5, 6).

Characteristics of patients with and without bleeds are comparable to each other (Table 1).

Trough ETP and bleeding rate during personalized prophylaxis

Trough ETPs during personalized prophylaxis were available for 34 patients. Patients with lower trough ETPs tended to have more spontaneous bleedings (Figure 7).

Figure 3: ETP baseline and patients with / without any bleeds in Phase-II

ETP (nmol*min)	Pts with no bleeds (n = 21)	Pts with ≥ 1 bleed (n = 11)
Mean ± SD	366.9 ± 167.7	372.7 ± 333.7
Median (min, max)	342.3 (136, 795)	226.3 (78, 1084)

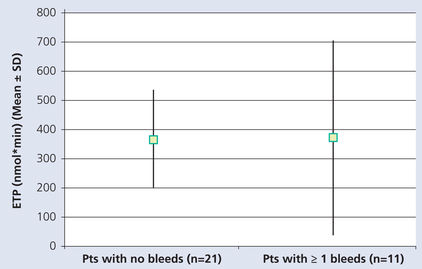
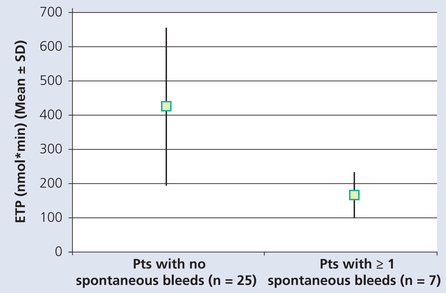


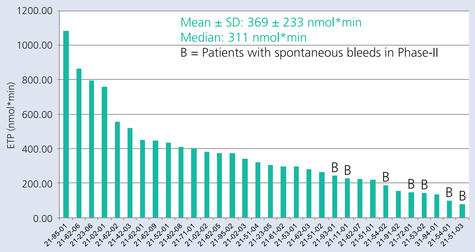
Figure 4: ETP baseline and patients with / without any spontaneous bleeds in Phase-II

ETP (nmol*min)	Pts with no spontaneous bleeds (n = 25)	Pts with ≥ 1 spontaneous bleed (n = 7)
Mean ± SD	426.1 ± 230.7	164.4 ± 65.6
Median (min, max)	373.3 (136,1084)	147.1 (78, 242)



p = 0.0002 (Wilcoxon two-sided Pr)

Figure 5: Individual ETP baseline values and occurrence of spontaneous bleeds in Phase-II (n = 32)



Reference ranges

Severe haemophilia A	394 ± 186 nmol*min
Moderate haemophilia A	657 ± 205 nmol*min
Mild haemophilia A	1083 ± 388 nmol*min
Normal	1429 ± 198 nmol*min

Figure 6: Baseline ETP (nmol*min) and FVIII:C (IU/ml)

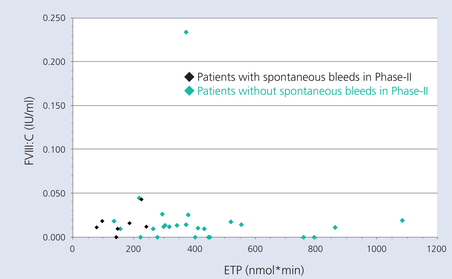
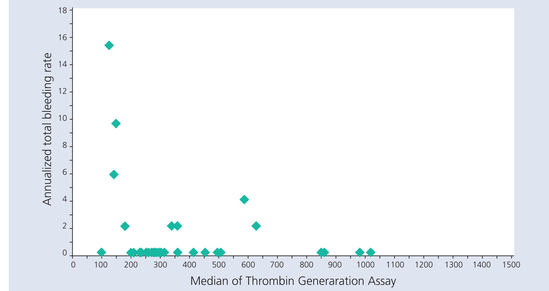
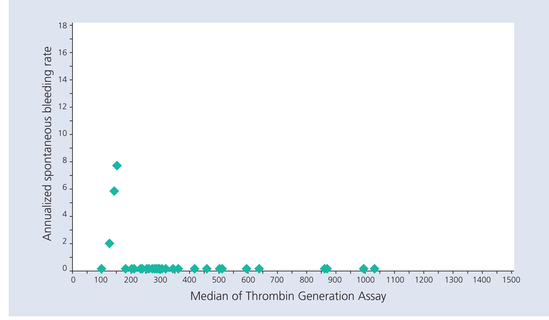


Table 1: Characteristics of patients with vs without any spontaneous bleeds (see Figure 5)

Mean ± SD (median)	Pts with no spontaneous bleeds (n = 25)	Pts with ≥ 1 spontaneous bleed (n = 7)
Half-life (hours)	15.9 ± 5.9 (15.3)	16.1 ± 3.8 (16.1)
Age (years)	30.6 ± 8.0 (32.0)	31.4 ± 9.0 (30.0)
Prophylactic injection interval (days)	3.2 ± 0.8 (3.5)	3.3 ± 1.0 (3.5)
Prophylactic dose (IU/kg/week)	100 ± 24.0 (102.0)	96.9 ± 15.6 (99.7)

Figure 7: Trough ETP (median of 2, 4 and 6 months*) vs. ABR during personalized prophylaxis (n = 34)





*Trough blood samples taken within 6 hours of planned time points

Conclusions

In patients with severe haemophilia A, ETP correlates with plasma FVIII:C. Patients with low thrombin generating potential tend to experience more frequent spontaneous bleedings.

References

1. FDA Memorandum to Octapharma dated 09 October 2014, reference STN 125555\0
2. Kannicht et al. Thrombosis Research 2013; 131: 78–88