Bleeding characteristics of patients with congenital hemophilia and inhibitors: data from a postmarketing study of recombinant activated factor VII (SMART-7)

P-W-79

K Kavakli;[1] F Demartis;[2] G Benson;[3] A Batorova;[4] K Cepo;[5] M Zak;[5] H Chambost[6]

[1]Ege University Children's Hospital, Izmir, Turkey; [2]A.O.U.C. Azienda Ospedaliero-Universitaria, Firenze, Italy; [3]Northern Ireland Haemophilia Centre, Belfast, Northern Ireland; [4]The National Haemophilia Centre, University Hospital, Bratislava, Slovakia; [5]Novo Nordisk A/S, Søborg, Denmark; [6]Hôpital de la Timone, Marseilles, France

Objective

- To explore differences in bleed characteristics between age cohorts of congenital hemophilia A or B patients with inhibitors, using real-world data from the SMART-7 study.

Conclusions

- SMART-7 was one of the largest prospective postauthorization safety studies conducted in congenital hemophilia with inhibitors, and provided important real-world data on bleeding characteristics in this patient population.
- Although the numbers of patients in each age cohort were small (half of the patients were aged 18–65 years), the data suggest that there is substantial heterogeneity between patients of different ages in the frequency, cause, and location of bleeding. Of note, the mean (and median) number of bleeds were lower in patients <2 years and in elderly patients, and the majority of bleeds occurred in joints.

Introduction

- The **S**tudy **M**onitoring **A**ntibodies against **R**oom **T**emperature stable factor **7** (SMART-7) investigated the safety of room temperature stable recombinant activated factor VII (rFVIIa) in congenital hemophilia A or B patients with inhibitors, based on real-world clinical practice.[1]
  - Primary endpoints were decreased therapeutic response and development of neutralizing antibodies against FVII.
- Secondary effectiveness data on the frequency, type, and location of bleeding episodes were also collected.

Methods

- SMART-7 was a prospective, observational, postauthorization, multi-national, non-interventional safety study.
- Study medication was not provided, and medication use was at the discretion of the treating physician according to the local label.
- Information on all bleeds requiring treatment was recorded in a patient diary and transferred to the clinical report form by the investigator at regular assessment visits.
- Patients were to remain in the study for ≥25 exposure days.
- Statistical analyses of categoric variables were based on regulatory specified age groups and were descriptive.

Table 1 Characteristics of the bleeds reported in SMART-7.

Bleed characteristic	Age (years)						
	<2	≥2 to <6	≥6 to <12	≥12 to <18	≥18 to ≤65	>65	All
Number of patients with bleeds	2	9	6	4	25	2	48
Total number of bleeding episodes	16	106	80	63	319	34	618
Bleeds per month							
Mean (SD)	0.2 (0.06)	1.7 (1.39)	1.2 (0.38)	1.6 (1.59)	1.0 (1.08)	0.7 (0.78)	1.2 (1.12)
Median (range)	0.2 (0.1–0.2)	1.5 (0.1–4.0)	1.2 (0.8–1.9)	1.1 (0.3–3.8)	0.5 (0.0–4.2)	0.7 (0.1–1.2)	0.7 (0.0–4.2)
Bleed cause, n (%)							
Spontaneous	9 (56.3)	35 (33.0)	18 (22.5)	60 (95.2)	249 (78.1)	21 (61.8)	392 (63.4)
Traumatic	7 (43.8)	65 (61.3)	51 (63.8)	3 (4.8)	55 (17.2)	12 (35.3)	193 (31.2)
Other	0 (0.0)	6 (5.7)	11 (13.8)	0 (0.0)	15 (4.7)	1 (2.9)	33 (5.3)
Bleed location, n (%)[a]							
Target joint	0 (0.0)	15 (14.2)	28 (35.0)	19 (30.2)	174 (54.5)	13 (38.2)	249 (40.3)
Nontarget joint	1 (6.3)	23 (21.7)	18 (22.5)	17 (27.0)	60 (18.8)	0 (0.0)	119 (19.3)
Muscle	4 (25.0)	28 (26.4)	17 (21.3)	19 (30.2)	52 (16.3)	13 (38.2)	133 (21.5)
Oral bleed	3 (18.8)	10 (9.4)	2 (2.5)	1 (1.6)	7 (2.2)	5 (14.7)	28 (4.5)
External/skin	1 (6.3)	6 (5.7)	3 (3.8)	4 (6.3)	5 (1.6)	2 (5.9)	21 (3.4)
Cranial (internal or external)	0 (0.0)	4 (3.8)	2 (2.5)[b]	2 (3.2)	1 (0.3)	0 (0.0)	9 (1.5)
Other	7 (43.8)	26 (24.5)	15 (18.8)	3 (4.8)	35 (11.0)	3 (8.8)	89 (14.4)

SD, standard deviation.
[a]A bleeding episode could have bleeds in more than one location. [b]Both of these bleeds were intracranial hemorrhages and occurred in one patient on two separate occasions (first being traumatic, and the second was spontaneous); the patient recovered with sequelae.

Results

Patients

- Fifty-one patients were enrolled in the study.
- Patient age ranged from 1.6 to 69.5 years, with a mean (standard deviation) age of 26.2 (20.86) years.
- Half the patients (n=25) were ≥18 to ≤65 years.
- The second largest age category included patients aged ≥2 to <6 years (n=9; 19%).

Bleed frequency

- Three patients did not report any bleeds.
- Forty-eight patients reported 618 bleeding episodes over 29,975 total study days (approximately 82 subject years). Bleed characteristics are shown in Table 1.
- Bleeding frequency varied across the different age groups.
  - The median number of bleeds was highest in patients aged ≥2 to <6 years (1.5 bleeds/month) (Table 1).

Cause of bleeding

- Overall, most bleeds (63.4%) were spontaneous.
- However, the proportion of spontaneous versus traumatic bleeds differed between age groups (Table 1).
  - Adolescent patients (≥12 to <18 years) showed the highest proportion of spontaneous bleeds (95.2%) and the lowest proportion of traumatic bleeds (4.8%).

Bleed location

- Overall, target joints were the most common bleed location (40.3%); however, bleed location also varied across age groups (Table 1).
  - For children aged ≥2 to <6 years, the greatest proportion of bleeds occurred in muscles (26.4%).

Reference

1. Kavakli K, *et al*. *Haemophilia* 2016;22(Suppl 2):52.

Conflict of interest disclosure

KK is an advisory board member for Novo Nordisk, and has received grant/research support and honoraria from Baxalta and Novo Nordisk. **AB** has received grants from Novo Nordisk to support participation in the SMART-7 study. **HC** has received fees for lecturing and attending scientific advisory boards from Baxter, Bayer, CSL Behring, LFB, Novo Nordisk, and Pfizer, and is a consultant for Baxter, Bayer, CSL Behring, LFB, Novo Nordisk, and Pfizer. **HC** is also an investigator in studies sponsored by Novo Nordisk. **KC** and **MZ** are employees of Novo Nordisk. **FD** and **GB** have no conflicts of interest to declare.

This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT01220141).
The authors acknowledge the medical writing assistance of Sharon Eastwood (PAREXEL).
Presented at the World Federation of Hemophilia (WFH) World Congress, July 24–28, 2016, Orlando, FL, USA.