Real-life clinical experience of 117 previously untreated patients (PUPs) treated with antihemophilic factor (recombinant), plasma/albumin free method in Japanese post authorization safety surveillance

Poster # P-M-51

Masashi Taki[1], Hideji Hanabusa[2], Katsuyuki Fukutake[3], Tadashi Matsushita[4], Keiji Nogami[5], Akira Shirahata[6] and ADVATE J-PASS Study group[7]

[1]Department of Pediatrics, St. Marianna University School of Medicine, Yokohama City Seibu Hospital, Kanagawa, Japan, Japan; [2] Department of Hematology, Ogikubo Hospital, Tokyo, Japan; [3] Department of Laboratory Medicine, Tokyo Medical University, Tokyo, [4] Department of Transfusion Medicine, Nagoya University Hospital, Aichi, Japan; [5]Department of Pediatrics, Nara Medical University, Nara, Japan; [6] Kitakyushu Yahata Higashi Hospital, Fukuoka, Japan; [7]Baxter, Medical Affairs & Clinical Development, Tokyo, Japan

Introduction

The treatment of hemophilia A patients has been improved by the availability of safe FVIII products and the adoption of routine prophylaxis, but inhibitors to FVIII remains one of the most significant complications. Data on previously untreated patients (PUPs) is valuable in delineating the natural history of hemophilia treatment. The real-life clinical practice during the early treatment phase of hemophilia A in Japan has been documented by ADVATE (rAHF-PFM) PUPs study since 2007 under Japanese ordinance Good Post-Marketing Study Practice (GPSP).

Objective

To investigate safety, i.e. adverse events namely inhibitors in PUPs treated with rAHF-PFM, and influence factors including inhibitor development.

Methods

This prospective, multicenter, observational surveillance study was conducted at 63 sites from February 2007 to June 2013 investigating PUPs of any age and disease severity with ≤ 3 exposure days (EDs) at study entry who were prescribed rAHF-PFM. Data were collected every 6 months for over two years using the electronic data-capture system (EDC) and reviewed March 2014.

- Inhibitor was assayed in institute or local laboratories and cut-off index was based on their standard.
- Cumulative probability of inhibitor risk were analyzed with Kaplan-Meier analysis using developed inhibitor.

Results

Subjects Characteristics

- Of 119 subject enrolled at 63 sites, data of 117 receiving the rAHF-PFM more than once were collected.
- The FVIII severity are < 1%:74%, 1 - 2%: 7%, > 2-5%: 7% and > 5%:12%.
- Forty nine (42%) had a family history of hemophilia and 9 (8%) had a family history of inhibitors.

Treatment

- A total 14M IU (prophylaxis :13.1M IU, on demand 0.9M IU) with 28,664 infusions (prophylaxis: 26,116 infusions, on-demand: 2,548) were administered.
- Ninety five (81%) had undergone a greater than two-year observation period (median: 36.1 months, range: 0.2-67.5). Twenty-two dropped out within two years (adverse events:9, lost to follow up:5, death:1, others:7).
- Total infusions per subjects was 172 (median), 248 ±308 (mean ±SD), 1-2562 (min-max).
- Eighty three (71%) had over 50 infusions (median:171). Ninety seven (83%) started on-demand and 69(59%) moved to prophylaxis.

Safety

- Serious adverse events :meningitis pneumococcal (product relation: unknown 1), inhibitor development (21).
- Acute subdural hematoma was reported to cause a death. The event was reported to be not related to rAHF-PFM by the investigator. However, due to insufficient information, this case was assessed by Baxter.
- There were no non-serious ADRs reported.

Inhibitor development

- The median age of diagnosis of hemophilia A was 0.3 in subjects who developed inhibitors (Inh) and 0.7 in subjects with no inhibitor (no Inh).
- The median age of first bleeds was 0.5 (Inh), 0.6 (no Inh) and the median age of severe bleeds was 0.3 (Inh) and 1.1 (no Inh).
- The median age of first exposure to rAHF-PFM was 0.9 (Inh) and 0.9 (no Inh).
- The adjusted odds ratio in inhibitor development was significantly higher in subjects with a family history of inhibitor.

Table 1: Subject Characteristics in inhibitor developed and no inhibitor developed

		All		Inhibitor developed		No inhibitor	
		N	%	N	%	N	%
		117	100.0	21	100.0	96	100.0
Age (y) of the first infusion of rAHF-PFM	Median	0.9		0.9		0.9	
	min-max	0-81		0-63		0-81	
	25%-75% IQR	0.9-1.9		0.9-0.9		0.1-2.0	
EDs at entry	0	95	81.2	17	81.0	78	81.3
	1-3	22	18.8	4	19.0	18	18.8
Reason of diagnosis	family history	27	23.1	10	47.6	17	17.7
	bleeding	92	78.6	14	66.7	78	81.3
Age (y) of diagnosis	Median	0.7		0.3		0.7	
FVIII (%)	<1	87	74.4	18	85.7	69	71.9
	1≦≦2	8	6.8	1	4.8	7	7.3
	2 <≦5	8	6.8	2	9.5	6	6.3
	5 <	14	12.0	0	0.0	14	14.6
Allergy	yes	7	6.0	1	4.8	6	6.3
Age (y) of the first bleeding	Median	0.5		0.5		0.6	
Treatment at the first bleeding	yes	61	52.1	12	57.1	49	51.0
Severe bleedings	yes	31	26.5	9	42.9	22	22.9
Age (y) of severe bleeding	Median	0.7		0.3		1.1	
	min-max	0-13		0-0		0-13	
	25%-75% IQR	0.3-1.3		0.1-0.6		0.4-1.5	
Site of severe bleedings	Intracranial hemorhage	19	16.2	7	33.3	12	12.5
Surgery	Yes	15	12.8	6	28.6	9	9.4
Age (y) of surgery	Median	1.3		1.2		1.3	
Cathertel	yes	17	14.5	9	42.9	8	8.3
Continous infusion	yes	14	12.0	5	23.8	9	9.4
Prophylaxis (including after inhibiter development)	yes	89	76.1	18	85.7	71	74.0
family history of hemophilia	yes	49	41.9	12	57.1	37	38.5
family history of inhibiotr	yes	9	7.7	6	28.6	3	3.1

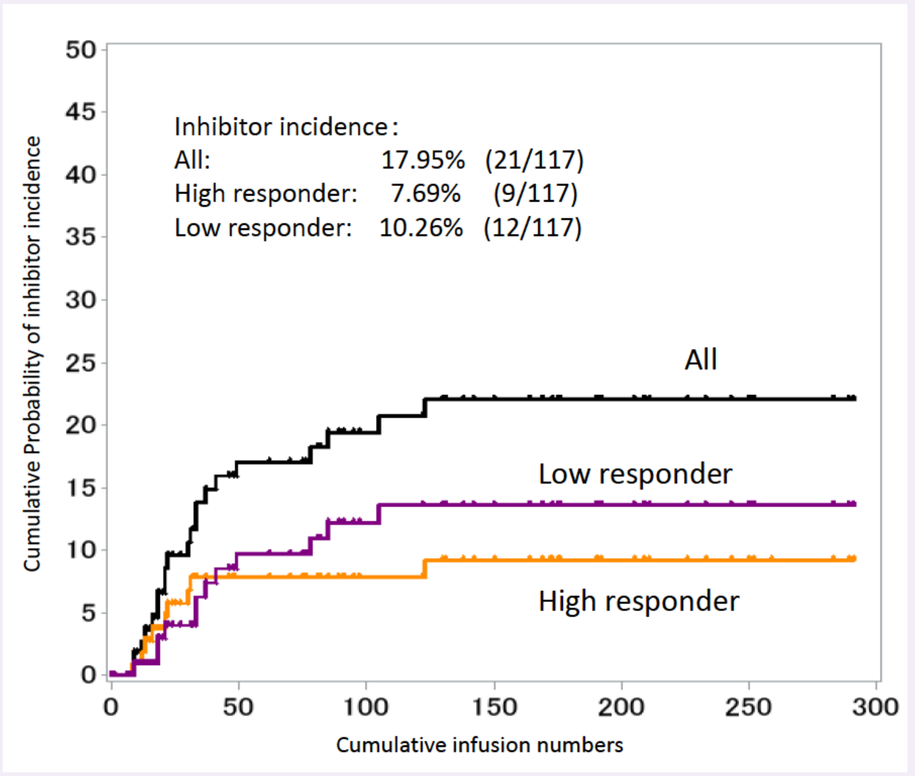
- 21 patients (17.95%) developed an inhibitor (7 high, 14 low titer at inhibitor diagnosis). (Table 2)
- In 10 of 21, inhibitors have disappeared during the study.

Table 2: Subject Characteristics at entry

Inhibitor at diagnosis		No of subject inhibitor developed	%	95%CI	
High titer	(>5 BU)	7	5.98	2.44	11.94
Low titer	(1-5 BU)	12	10.26	5.41	17.23
Other	(<1 BU)	2	1.71	0.21	6.04
Total		21	17.95	11.47	26.12

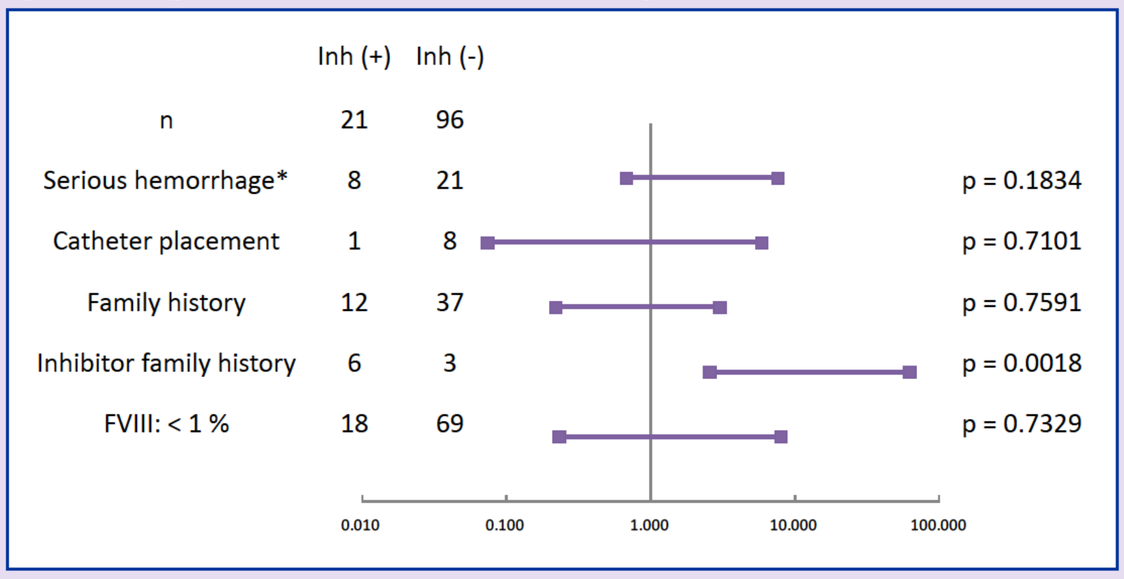
- The median infusion number to inhibitor formation was 30 (range: 8-123).
- The median infusion number to inhibitor development was 30 infusions in low titer (range: 8-123) and 21 infusions in high titer (range: 9-85).

Figure 1: Cumulative incidence of inhibitor development



- The risk factors of inhibitor development were compared using odds ratio in serious hemorrhage, catheter placement, family history of hemophilia, inhibitor family history and FVIII <1% (Figure 2)
- The adjusted odds ratio in inhibitor development was significantly higher in subjects with a family history of inhibitor

Figure 2: Subjects Odds ratio of inhibitor development risk factor



The adjusted odds ratio in risk of inhibitor development were serious hemorrhage: 2.271 (0.678-7.604), catheter insertion: 0.660 (0.074-5.887, family history of hemophilia: 0.815 (0.220-3.017), family history of inhibitors:12.662 (2.571-62.357), hemophilia severity:1.360 (0.232-7.959).
*: ICH were reported 6 in inhibitor developed subjects and 12 in non inhibitor developed subjects.

Conclusions

- 21 *de novo* inhibitors (7 high titer at diagnosis, 9 high responder) were reported in 117 treated subjects.
- The safety profile of rAHF-PFM in Japanese PUPs appears consistent with previous reports with an inhibitor rate of 17.95%.
- Odds ratio of inhibitor development was significantly higher in subjects with an inhibitor family history.

References

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Acknowledgment

We gratefully acknowledge all the investigators for ADVATE J-PASS study and Mr. N. Hoshii for biostatistics in this poster.

Presented at the WFH 2014 World Congress in Melbourne, Australia • May 11-15, 2014

If you have any additional questions, please feel free to contact Baxter Bioscience Medical Information at medinfo@baxter.com.

Conflicts of interest:

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DOI: 10.3252/pso.eu.WFH2014.2014